Gynecological Drug Therapy

Edited by
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Preface

In no other area has the speed of progress in medical therapeutics been faster paced, and nowhere in medicine have a greater number of patients been treated with relatively new pharmaceuticals than in the field of women’s health. Gynecology has traditionally been regarded as a largely surgical speciality. However, the place of surgery in the management of gynecological problems has been greatly reduced over the past two decades by the introduction of new and more effective means of treating many common gynecological disorders medically. Whole new subspecialty areas have appeared within the field, ranging from assisted reproduction to management of HIV/AIDS. Subspecialization has divided obstetrics and gynecology into several highly technical areas. The level of knowledge required to remain up-to-date in gynecological oncology, reproductive medicine, feto-maternal medicine, and urogynecology is expanding rapidly and can challenge full-time subspecialists as well as the generalist obstetricians and gynecologists who still comprise the majority of practitioners in the field.

It is therefore timely to produce a comprehensive review of the drug therapies available to gynecologists and others involved in the management of women’s health. Since most doctors will have female patients, it can serve as a ready reference when unfamiliar drugs or treatment regimes are encountered. Issues specific to women’s health begin before birth and continue well past menopause, and an understanding of the latest therapies available, and their advantages and side effects, is essential for optimum patient care. Patients are now better informed than ever, although information gleaned from the Internet and elsewhere may not always be accurate. Practitioners need reference material to hand out during and after consultation in order to reach evidence-based decisions on prescribing with their patients. This book should be a useful resource to busy clinicians, midwives, nurses, and other healthcare workers involved with female patients, and a revision
aid to those taking higher professional exams. We have deliberately interpreted the term “gynecology” widely, including comprehensive reviews of drugs used in genito-urinary medicine and in the subspecialties of obstetrics and gynecology, thereby hoping to provide an inclusive guide to drug therapy in this complex and burgeoning area of medicine.

William Leigh Ledger
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The wide range of fluctuating symptomatology associated with menstrual dysfunction can be enormously disruptive to the lives of many women. Indeed, these symptoms may impact health status as profoundly as do such chronic conditions as angina and arthritis (1). In this nationally representative random sample of 1744 American menstruating women (1):

- 67% reported one or more menstrual symptoms,
- women with menstrual symptoms had significantly worse scores for all domains of functioning (using the SF36 health status questionnaire),
- it was concluded that some types of active management may greatly improve functioning, but not all approaches have been appropriately and comprehensively studied for their effects on symptom improvement.

Many therapies described in the following sections have beneficial effects across a range of cyclical menstrual symptoms and underlying pathologies, and are therefore described in several sections. However, there is variation in the therapeutic regimens and the possible responses. Hence,
it has been decided to include separate discussion of similar therapies in each section.

REFERENCE
Medical conditions that are exacerbated by or occur in phase with the menstrual cycle vary from the common [premenstrual exacerbation of asthma and menstrual migraine (MM)] to the exceptionally rare (catamenial pneumothorax, autoimmune progesterone dermatitis, and cyclical thrombocytopenia). All cyclical syndromes require prospective symptom and menstrual charting to confirm their relationship with menstruation and to avoid recall bias. The triggers for the various syndromes are different; they are generally hormonal (late luteal estrogen fall in MM; high estrogen, low progesterone in catamenial epilepsy), but may also be physical (vicarious menstruation, possibly related to endometriosis) and in some conditions remain unknown. An understanding of the underlying pathophysiology of the relationship between symptoms and the menstrual cycle can aid in successful treatment of these cyclical conditions.

Drug management strategies vary from those specific to the medical conditions (which is beyond the scope of this text and often requires consultation...
across specialties) to hormonal manipulation. The drugs used for hormonal manipulation are mainly the commonly used estrogens and progestogens, anti-estrogens, and gonadotropin releasing hormone (GnRH) analogs. Hormonal manipulation needs to be tailored to the pathophysiology of the individual condition and aims to suppress hormone peaks, prevent precipitous declines in hormone serum levels, or prevent ovulation and the subsequent hormone responses. In general, the level of evidence for hormonal drug therapy use in prophylaxis against or amelioration of medical conditions exacerbated by the menstrual cycle is poor, with most evidence derived from case reports or case series and very little from double-blind placebo-controlled trials.

MENSTRUAL MIGRAINE

The adult prevalence of migraine has a female to male ratio of 3:1. The peak onset of migraine in women is in the second decade, often coinciding with menarche. The peak prevalence of migraine in women is in the fourth decade, with prevalence then decreasing corresponding to menopause (1). About 60% of female migraineurs experience a worsening of their headache in association with the menstrual cycle. Menstrually associated migraine (MAM) is defined as migraine occurring during the perimenstrual period (day 1 of menses ± 2 days) in addition to migraine occurring at other times of the month. True MM affects 7% to 14% of migrainous women, and such women experience migraine attacks exclusively in the perimenstrual period (2). The etiology of both MAM and MM is related to the late luteal fall in serum estradiol (3).

Management begins with the patient keeping a diary record of headache days, menstruation, and other triggers if recognized. Nonpharmacologic methods, particularly avoiding modifiable triggers, should be encouraged. Acute therapy of both MAM and MM is as for all migraine and includes tryptans, nonsteroidal anti-inflammatory drugs (NSAIDs), ergotamines, and antiemetics. In women with frequent migraines, especially those in whom abortive therapies are not adequately effective, prophylactic medication to reduce the frequency, duration, and/or intensity of migraine headaches may be required (1–3).

Nonhormonal prophylaxis with tryptans, NSAIDs, or ergotamines may be used throughout the cycle in women who suffer migraines at any time. Dosages may be increased perimenstrually in women who suffer exacerbation of migraines in association with menstruation (MAM). Intermittent prophylaxis should be instituted for women with true MM; the same medications can be used, with administration from two to three days before the onset of menses and continuing for a total of five days (2). Clearly, the success of intermittent therapy is largely dependent on the prediction of the timing of migraine by a regular menstrual cycle.

The knowledge that estrogen withdrawal is the primary precipitant for MAM and MM logically leads to hormonal manipulation for prophylaxis.
However, the use of synthetic contraceptive estrogens in migraineurs is controversial due to the small increased risk of stroke found in association with use of the older, higher estrogen dose contraceptive pills. It is generally accepted that the modern low-dose oral contraceptive pill may be used in women with migraine in the absence of aura. Any additional risk factors for arterial disease (smoking, hypertension, older age, or diabetes) should also be excluded (3).

There are three basic strategies of hormonal prophylaxis that can be employed to minimize estrogen withdrawal (2). Prescription of a low estrogen dose (20 μg) contraceptive pill formulation both reduces the dose of estrogen and the absolute estrogen drop from active pill to placebo. If migraines still occur during the pill-free week, add-back estrogen (oral 10 μg ethinyl estradiol or 0.625 mg estrone sulfate, or transdermal 25–50 μg estradiol) can be used to lessen the decline in estrogen that triggers the migraines. Alternatively long-cycle oral contraceptive therapy can be employed, with only active pills being taken for 9 to 12 weeks (or for as long as breakthrough bleeding does not become a problem). Again this minimizes the frequency of estrogen withdrawal.

**CATAMENIAL EPILEPSY**

Catamenial epilepsy lacks a standard definition. It is generally regarded as epileptic seizures occurring exclusively or significantly more often during a seven-day period of the menstrual cycle beginning three days before menstruation and ending four days after its onset. Catamenial epilepsy is reported to occur in 10% to 70% of reproductive aged women with epilepsy (largely determined by the degree of magnitude of increased seizures during the perimenstrual period required in its definition) (4). Animal studies have shown that seizures might be linked to menses because sex hormones alter neuronal excitability, with estrogen increasing seizure activity and progesterone reducing seizure activity (5,6).

There are at least three distinct patterns of seizure exacerbation in relation to the menstrual cycle (7). The hormonal features of these periods (relatively high estrogen and low progesterone) support a biologic basis for these seizure patterns. The first two patterns occur in ovulatory cycles. As above, classically described catamenial epilepsy is seizure exacerbation perimenstrually, from three days before until four days after the onset of menstruation. This is triggered by the rapid progesterone decline that also triggers menstruation. The second form of menstrual-related epilepsy is preovulatory, corresponding to elevated estrogen levels. The third pattern is seizure exacerbation during the second half of the cycle. This tends to occur in anovulatory cycles, where progesterone remains low for the luteal phase, resulting in an ill-defined pattern of increased seizures throughout the second half of the menstrual cycle because of unopposed
estrogen. Of note, about 10% of menstrual cycles in healthy women are anovulatory, whereas in women with temporal lobe epilepsy, 35% are anovulatory (4).

Treatment strategies again begin with a prospective record of menses and seizures, with an aim to identify the pattern of seizure exacerbation. A supplemental daily dose of the patient’s usual maintenance antiepileptic drug (AED) at the time of the expected seizure exacerbation may promote control. Generally, an increase in daily dose may be commenced two to three days before the expected exacerbation and continued for two days after the usual exacerbation (4).

Although unconventional, AED treatment may be supplemented by hormonal therapy. Strategies targeting increasing progesterone effect with intramuscular depot-medroxyprogesterone acetate or oral progestogen have been reported with variable success (5,6). In case reports and a case series, intermittent clomiphene citrate (25–100 mg days 5–9) has been reported to improve refractory epilepsy associated with anovulatory cycles (8). The mechanism may be through inducing ovulation, and thus increasing progesterone in the luteal phase or by antiestrogenic effects centrally. A combined oral contraceptive pill relatively low in estrogen and high in progestogen may also be trialed (with continuous therapy if necessary) (6). It should also be remembered that the metabolic interactions between some AEDs and oral contraceptives impair contraceptive efficacy, and result in an increased frequency of spotting and breakthrough bleeding. Most current research centers on use of progestogen therapy.

PREMENSTRUAL ASTHMA

Up to 40% of women with asthma experience worsening of symptoms premenstrually (9), and many more asthmatic women, unaware of worsening of their symptoms, demonstrate a menstrual-related decline in pulmonary function (10). The pathophysiology of this cyclical deterioration is unknown; theories include prostaglandin release or direct effects of declining estrogen and progesterone on bronchial smooth muscle.

There are isolated reports of the administration of estrogen or progestogen improving premenstrual asthma, and in severe cases continuous combined oral contraception or intramuscular depot-medroxyprogesterone acetate may be worth considering as supplement to regular asthma preventative and acute treatment medications.

ATOPIC DERMATITIS

Atopic dermatitis is another common condition that has been reported to have significant premenstrual deterioration. About 35% of women of reproductive age with atopic dermatitis report such deterioration. Studies thus far
have been limited by recall bias. There are no randomized controlled data to support hormonal manipulation to alleviate premenstrual deterioration of atopic dermatitis (11).

OTHER EXCEPTIONALLY RARE CONDITIONS

Vicarious Menstruation with Endometriosis/Cyclical Pulmonary Complaints

Recurrent spontaneous catamenial pneumothoraces are a rare but well-documented phenomenon. There are a number of hypotheses about its pathogenesis, which is probably multifactorial, with one, or a combination of, thoracic (pleural) or diaphragmatic endometriosis, congenital diaphragmatic fenestrations (with air entering the abdominal cavity via the genital tract during menstruation), and bronchospasm or vasoconstriction during menstruation (due to high serum prostaglandin F2α) causing rupture of small airways or alveoli (12).

Effective medical control can be attained by long-term suppression of menstruation, usually with continuous combined oral contraception or GnRH analogues. The disadvantages of hormonal manipulation to prevent recurrent catamenial pneumothoraces include both side effects of the medications and the temporary nature of the relief, with a high rate of recurrence once hormone therapy is ceased (3). Long-term hormonal therapy may be appropriate.

Many would advocate surgery, ranging from thoracotomy with excision of any identifiable thoracic endometriosis, closure of diaphragmatic fenestrations, and pleuradesis (13) to successful case reports treated more simply with tubal ligation (12).

Other rare symptoms of thoracic endometriosis include catamenial hemoptysis and catamenial hemothorax, which can also be ameliorated in the short term by hormonal suppression of menstruation.

Autoimmune Progesterone Dermatitis

Autoimmune progesterone dermatitis is a rare cyclical phenomenon with variable manifestations (urticaria, erythema multiforme-like reactions, eczematous eruptions, ulcerative stomatitis, and erosive stomatitis). Exacerbations tend to occur just prior to menses and persist for a few days. By definition, the exacerbations are replicated after a progesterone challenge. The mechanism by which endogenous progesterone becomes antigenic is unknown, with most cases not having symptoms from menarche, but developing them some time later (mainly in the 20s) (14,15).

These conditions are commonly unresponsive to conventional treatments with topical steroids and antihistamines. Therapy is generally centered on suppression of ovulation (and therefore preventing the postovulatory
Table 1  Practical Ways of Suppressing Ovarian Function for Women Suffering from Cyclical Syndromes

<table>
<thead>
<tr>
<th>COCP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Short (28 days), long cycle (break every 3 mo), or continuously without a break</td>
<td>A useful starting combination is the monophasic ethinyl estradiol 30μg, levonorgestrel 150μg</td>
</tr>
<tr>
<td>Other COCPs can be tried later</td>
<td>Migraineurs should try 20μg EE pills first</td>
</tr>
<tr>
<td>Oral progestogens</td>
<td>Norethisterone 5mg twice or three times daily on a continuous basis (can be reduced later to a lower dose (2.5–5mg daily) long-term</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate 10mg twice or three times daily (lowered later)</td>
<td>Depot medroxyprogesterone acetate</td>
</tr>
<tr>
<td>Given intramuscularly as 150mg once every 3 mo</td>
<td></td>
</tr>
<tr>
<td>Subdermal progestogen-only implants</td>
<td>Norplant® (releasing levonorgestrel over a device lifespan of 5yr)</td>
</tr>
<tr>
<td>Implanon® (releasing etonogestrel over a 3-yr device lifespan)</td>
<td>Usually inhibit ovulation during the first 1–2 yr, although ovulation may occur more frequently in later years of device lifespan</td>
</tr>
<tr>
<td>Even when breakthrough ovulation does occur with these devices, the continuous progestogen exposure may minimize the symptoms of “cyclical syndromes”</td>
<td></td>
</tr>
<tr>
<td>Gonadotrophin-releasing hormone analogues</td>
<td>Can be delivered as once-a-month injections or implants, or as daily nasal spray</td>
</tr>
<tr>
<td>Ovulation is usually efficiently inhibited provided that dosage is sufficient</td>
<td>Side effects are often troublesome (especially vasomotor symptoms), and add-back therapy with low-dose estrogen and progestogen is necessary for most women using these long-term</td>
</tr>
<tr>
<td>Long-term therapy is usually expensive</td>
<td></td>
</tr>
<tr>
<td>Danazol</td>
<td>200mg twice daily efficiently inhibits ovulation, and 200mg daily will inhibit ovulation in the majority of women</td>
</tr>
<tr>
<td>Side effects are common</td>
<td>Many women do not like the “androgenic” side effect profile</td>
</tr>
<tr>
<td>Long-term therapy is fairly expensive</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Tamoxifen acts as an antiestrogen in women in the reproductive phase of life</td>
</tr>
<tr>
<td>When taken continuously, ovulation is often inhibited</td>
<td>The antiestrogen effect often ameliorates symptoms for those conditions where estrogen fluctuations contribute to symptomatology</td>
</tr>
</tbody>
</table>

Note: This table lists a range of ways in which the major swings in ovarian estradiol and progesterone during the natural menstrual cycle may be reduced or eliminated, and may thus improve the symptomatology experienced by women suffering from “cyclical syndromes.” These therapies need to be individualized and may need to be tested empirically in an individual woman. Most data are anecdotal.

Abbreviations: COCP, combined oral contraceptive pill; EE, ethinyl estradiol.
surge in progesterone) with the combined oral contraceptive pill or the anti-estrogen tamoxifen.

**Cyclical Thrombocytopenia**

Cyclical thrombocytopenia is a rare disorder in which women become cyclically thrombocytopenic in phase with menstruation. Its pathophysiology remains uncertain (16). It is generally less responsive to corticosteroids and splenectomy than idiopathic thrombocytopenia purpura. Hormonal manipulation with the combined oral contraceptive pill has been described in case reports to ameliorate the condition (17).

**CONCLUSIONS**

Medical disorders that are exacerbated by or occur in phase with the menstrual cycle are extremely varied in nature, severity, and incidence. An understanding of the pathophysiology of each disorder aids in a logical approach to medical manipulation of hormones. Drug treatment of these disorders needs to be individualized both to the disorder and to the patient; however, many of these disorders will respond to one or more of the alternative options for suppressing ovarian function and ovulation (Table 1).

**REFERENCES**

Drugs for Breakthrough Bleeding Due to Hormonal Therapies

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INTRODUCTION

Hormonal therapies are widely used for contraception, menopausal symptoms (such as hot flushes) and for the control of heavy and irregular menstrual bleeding.

Irregular bleeding is relatively uncommon in spontaneous menstrual cycles, but is much more frequent in women taking sex steroids. Hormonal therapies containing estrogen and progestogen may induce regular bleeding, but those containing only progestogen tend to alter bleeding patterns in the great majority of users. This may range from amenorrhea to daily bleeding or spotting.

This review will discuss the significance of this bleeding and the evidence regarding effective drug treatments.

BREAKTHROUGH BLEEDING WITH HORMONAL CONTRACEPTIVES

Contraceptive steroid-induced breakthrough bleeding (BTB) is a major social and clinical problem for women worldwide (1). Changes in vaginal bleeding patterns are particularly common with progestogen-only contraceptives,
which are used by over 20 million women (2). Irregular or “breakthrough” bleeding is also common in users of estrogen and progestogen combined contraceptives (3).

COMBINED ESTROGEN AND PROGESTOGEN CONTRACEPTIVES
Abnormal bleeding has been cited as the primary indication for discontinuation of the combined oral contraceptive pill (COCP) in up to 12% of users (4,5). In the new low-dose (20 μg) estrogen preparations, breakthrough bleeding (BTB) may occur in almost 50% of users at some time (6). Little is known about the mechanisms of irregular bleeding with COCP or how to manage it, although it appears that inadequate suppression of ovarian activity correlates with an increased tendency to BTB in COCP users (7) which may explain why BTB is more common with lower estrogen preparations.

PROGESTOGEN-ONLY CONTRACEPTIVES
Disturbances of vaginal bleeding patterns are almost inevitable in users of progestogen contraceptives, and there are no devices that can guarantee regular bleeding or even amenorrhea. These bleeding disturbances are not known to threaten the health of users of these systems, although they may lead to further investigations to rule out cervical or endometrial pathology. Their major significance is the degree to which bleeding disturbances are disliked by women, leading to rejection or discontinuation of these methods.

There is increasing evidence that fragility of the endometrial microvasculature underlies progestogen-related bleeding (8), but the mechanisms leading to this fragility are still being elucidated.

MENOPAUSAL HORMONE THERAPY
Many women are satisfied with the bleeding patterns that they experience on menopausal hormone therapy (MHT), but a substantial minority suffer from unpredictable, unscheduled vaginal bleeding and spotting. Irregular bleeding occurs in up to 60% of MHT users (9) and leads to discontinuation of therapy in up to one in three users (10). This irregular bleeding is not confined to the initial months of MHT use, and many users of both cyclic and continuous combined preparations continue to experience erratic bleeding (11).

The management of MHT-associated bleeding problems is often unsatisfactory, because there are no established methods of regulating or reducing bleeding. None of the MHT preparations currently available can guarantee either regular bleeding or amenorrhea. Although irregular bleeding in pre-menopausal woman using hormonal therapies is primarily of nuisance value,
erratic bleeding in an older peri- or post-menopausal women may be a pre-
senting symptom of malignancies of the cervix, endometrium, or ovary. Hence current management protocols involve invasive and costly investiga-
tions resulting in anxiety for the woman and her physicians. In a recent study, 
38% of new cyclic MHT users and 41.6% of new continuous combined users
made at least one visit to their gynecologist with irregular bleeding. More than
12% of cyclic users and 20% of continuous combined users were subjected to
one or more endometrial biopsies during the initial two years of use (11).

The mechanisms of MHT-related irregular bleeding are even less well
understood than those with contraceptive hormone therapies. Recent
studies have demonstrated that MHT exposure increases the capacity of
the endometrium to breakdown of the epithelium and local blood vessels
(12) and that vascular structural integrity is reduced (13).

IMPLICATIONS OF VAGINAL BLEEDING PATTERNS

Regular patterns of vaginal bleeding are central to beliefs concerning
fertility, absence of pregnancy, and reproductive health for women from
many cultures. In addition, for some women the presence of irregular or
unpredictable bleeding is a barrier to social, sexual, and cultural activities
and hence represents a major disruption to their life. As irregular bleeding
may also be a feature of infection of the genital tract, and (rarely) of malign-
nancy, this symptom may also prompt additional investigations such as high
vaginal and endocervical bacteriology, cervical cytology, colposcopy, or
even endometrial biopsy.

Many women are keenly aware of the pattern of bleeding, but also the
duration and amount of blood loss, as well as subtle factors such as
the appearance and smell of fluid passed. A certain amount of variation
in this is expected, particularly when exogenous hormones are used, but
major changes in vaginal bleeding are a source of concern for many women.
Amenorrhea may be a convenience for some, but for others deprives them of
the regular reassurance that they are not pregnant and may have other
negative cultural connotations that are currently poorly understood.

The need to wear a pad or tampon at all times is uncomfortable and
becomes expensive when bleeding is prolonged. Hence it is not surprising
that disturbances of menstrual bleeding are consistently the most common
stated reason for patients to discontinue implantable or other progestogen-
only contraceptives. Although irregular bleeding is tolerated by many
women, some are prepared to accept amenorrhea in the context of adequate
support and explanation. A thorough explanation of the likely patterns of
bleeding should be intrinsic to any preinsertion counseling program.

In most cultures, postmenopausal women do not wish to bleed and
would prefer to use hormone therapies that induce amenorrhea (14).
DRUG TREATMENTS FOR BTB DUE TO HORMONAL THERAPIES

The Management of BTB with Progestogen Contraceptives

To date, efforts to prevent or limit BTB in women using sex steroids have been largely unsuccessful. However, these interventions have mostly been empirical, and the improved understanding of the underlying mechanisms of BTB opens the possibility of directed therapies to reduce vascular fragility. Supplemental estrogens have been given to women using progestogen-only contraceptives to try to improve bleeding patterns. However, there is no evidence that estrogens improve bleeding patterns beyond the duration of their use (2). The natural history of BTB is to gradually improve over time and improvements in bleeding pattern observed following alterations in the type and dose of progestogen are likely to reflect this rather than a consistent therapeutic effect.

Potentially Effective Treatment Approaches

Increasing Vascular Stability

In other organ systems, such as the human retina, loss of vascular stability is associated with oxidative stress and the release of free radicals (15). Increased free radical expression has also been seen in association with BTB (16). At a molecular level, this vascular fragility is associated with reduced integrity of endothelial cell tight junctions and vascular basement membrane competence and clinically leads to vascular breakdown and retinal bleeding (17). Flavonoids, part of the vitamin B complex, have been shown in controlled trials to increase peripheral capillary resistance and to improve the systemic symptoms of capillary fragility such as epistaxes, petechiae, and conjunctival hemorrhages (18). Recent pilot data (19) have suggested that oral vitamin E (an antioxidant) given during bleeding episodes may reduce bleeding in users of low-dose progestogens. However, these results were not confirmed in a multicenter study involving 500 users of Norplant® (20).

The prostaglandin synthetase inhibitor mefenamic acid has been used to control irregular bleeding secondary to Norplant use. In a double-blind placebo-controlled study, 34 women who took mefenamic acid were significantly more likely to stop bleeding and had longer bleed-free intervals than the placebo group (21).

Recommended Regimens

Mefenamic acid, 1 g qds, taken during a bleeding episode may shorten the bleeding episode and increase the time until the next bleeding episode.
Reduced Vessel Destabilizers

The introduction of agents specifically targeted to block molecules stimulating breakdown of endometrial vessels and extracellular matrix may help to reduce BTB. MMP activity could be antagonized by selective use of TIMPs.

Recommended Regimens

No MMP inhibitors have yet been clinically trialed in the management of progestogen-associated bleeding.

Improved Epithelial Integrity

Hysteroscopic studies in Norplant users strongly suggest that subepithelial bleeds (seen as petechiae and ecchymoses) are common in these women when vaginal bleeding has not been observed by the patient (8). Norplant use appears to reduce epithelial integrity by interfering with cytokeratin deposition (22). As endometrial bleeding is not problematic unless it manifests as vaginal bleeding, agents which maintain epithelial integrity may also act to contain bleeding. Estrogens induce endometrial epithelial proliferation and may thus effectively terminate prolonged bleeding episodes in progestogen users. Estrogens may also act to maintain endothelial cell junctional integrity, but there is currently little known about the regulation of these tight junctions in the endometrium. Ethinyl estradiol (EE) (50 μg) has been shown in Norplant users to shorten the current bleeding episode, and 67% will stop bleeding within three days of commencing therapy (23). Transdermal estrogen (100 μg patch) is no more effective than placebo (24).

Additional progestogen (as oral levonorgestrel 30 μg bd) will also reduce the duration of the current bleeding episode, but is less effective than 50 μg of ethinyl estradiol (23). Combined estrogen and progestogen is the most effective of these hormonal regimens in terminating the current bleeding episode and increasing the time until the next bleeding episode. However, this beneficial effect has only been demonstrated with high-dose COCP (50 μg of EE and 250 μg of LNG) for 20 days (25) and no benefit was seen with lower dose (30 μg of EE) preparations (26).

As the addition of estrogens to progestogen-only contraception essentially undermines many of the advantages of these preparations, nonestrogenic agents to maintain epithelial integrity are needed. Current selective estrogen receptor modulators (SERMs) aim to avoid endometrial receptor targets. There may be a role for SERMs acting to selectively stimulate the endometrium but not other tissues (27).

Monthly administration of 50 mg of mifepristone has recently been shown to significantly improve bleeding patterns in Norplant users (28) with no evidence in this small study that contraceptive efficacy is compromised. In a larger study, mifepristone 100 mg/day administered to Norplant users for two consecutive days every 30 days reduces the number of prolonged
bleeding episodes and the total number of bleeding days by one-third, compared to placebo patterns in Norplant® implant users (29). One pregnancy occurred in the mifepristone users group in this study, suggesting that mifepristone may potentially undermine the contraceptive effect of Norplant.

It is currently unclear how mifepristone works in these circumstances, but this therapy warrants further investigation, if only to improve bleeding patterns during the early months of progestogen use when bleeding patterns are most troublesome. A recent study demonstrated that a 50 mg dose of mifepristone taken every two weeks decreased the incidence of BTB in new starters of depot medroxyprogesterone acetate (DMPA) without compromising contraceptive efficacy (30).

Recommended Regimens

Medium-dose combined oral contraceptive pill (COCP) (50 μg) for at least three weeks, in those with no contraindications to this short-term dosage of estrogen, or oral mifepristone 50 to 100 mg for two days per month, is recommended. Patients should be advised that mifepristone may compromise the contraceptive efficacy, although this risk is likely to be small.

THE MANAGEMENT OF IRREGULAR BLEEDING WITH MHT

Lack of understanding of the mechanisms underlying MHT-related bleeding has undermined attempts to formulate effective therapies. No combined (estrogen and progestogen) products available are able to guarantee regular bleeding or even amenorrhea. There is no comprehensive evidence that changing women from one product to another, or increasing the relative doses of estrogen or progestogen helps to improve bleeding patterns, although this is a common management strategy in clinical practice. Irregular bleeding tends to settle with time and by six months, 60% of women are amenorrheic and 95% by one year (31). However, these figures are likely to be biased by the women who have discontinued MHT due to bleeding.

The levonorgestrel intrauterine system (Mirena®, Berlex Inc., Schering, AG) is increasingly used for endometrial protection. A new smaller 10 μg device aimed at postmenopausal women is under development (32) and appears to be easier to insert than Mirena and achieved almost 100% amenorrhea at six months in this preliminary study.

There is some evidence that tibolone (Livial™, Organon, U.K.) may induce less bleeding and spotting than combined MHT. Hammar et al. (33) report that by three months only 14% of tibolone users reported bleeding or spotting compared to 27% of those taking oral MHT as 2 mg 17β-estradiol and 1 mg norethisterone acetate (NETA).

RECOMMENDED REGIMENS

No treatment regimens have been shown to be effective in treating prolonged and irregular bleeding with MHT. Patients should consider changing
to tibolone, because this may induce a more favorable bleeding pattern than menopausal hormone therapy (MHT), provided that the woman is truly postmenopausal (34).

CONCLUSION

Hormone therapies are commonly associated with changes in bleeding patterns. In contraceptive users, this has been called “breakthrough bleeding,” although this term is probably not terribly accurate or helpful. Other hormone therapies such as MHT are also commonly associated with irregular bleeding. Evidence from studies of all available preparations suggests that menstrual disturbance is one of the most common reasons for discontinuation of these methods.

Currently, there is no effective long-term management for bleeding disturbances and effective and acceptable treatments are unlikely to be developed without a fuller understanding of the factors underlying this bleeding. Recent information has greatly advanced understanding of the vascular and endometrial changes associated with progestogen and MHT use, but a number of areas require further study before the mechanisms of BTB can be defined. In addition, further information is required from women using these preparations regarding the perception of bleeding disturbances and the relative tolerability of varying bleeding patterns and of amenorrhea.

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Drugs for Breakthrough Bleeding Due to Hormonal Therapies


Drugs for Dysmenorrhea

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INTRODUCTION

Dysmenorrhea is defined as painful menstrual cramps of uterine origin. While variations in the definition of dysmenorrhea make it difficult to precisely determine prevalence, estimates vary from 45% to 95%. Dysmenorrhea appears to be the most frequent gynecological condition among women of many different ages and nationalities (1,2). High rates of absenteeism from work and school are associated with dysmenorrhea, with 13% to 51% ever absent and 5% to 14% frequently absent due to the severity of symptoms (3). This translates not only into a significant impact on personal health, but also into a global economic impact. In the United States alone, it was estimated that the annual loss was 600 million work hours and two billion dollars in the mid-1980s; in today’s dollars, this figure would be much higher (4).

Dysmenorrhea is commonly divided into two categories based on pathophysiology. Primary dysmenorrhea is menstrual pain without organic pathology, and secondary dysmenorrhea is menstrual pain associated with an identifiable pathological condition. Common causes of secondary dysmenorrhea include endometriosis, fibroids (myomas), adenomyosis, endometrial polyps, pelvic inflammatory disease, or the use of an intrauterine contraceptive device.

The etiology of dysmenorrhea has been the source of considerable debate. Until quite recently, many medical and gynecological texts ascribed the source of dysmenorrhea as emotional or psychological problems.
Dysmenorrhea was attributed to a variety of reasons such as anxiety, emotional instability, a faulty outlook on sex and menstruation, or imitation of the mother’s feelings about menstruation (5). However, experimental and clinical research has identified physiological reasons for dysmenorrhea the production of uterine prostaglandins (6). During endometrial sloughing, endometrial cells release prostaglandins: as menstruation begins, prostaglandins stimulate myometrial contractions and ischemia. It has been shown that women who have more severe dysmenorrhea have higher levels of prostaglandins in their menstrual fluid and that these levels are highest during the first two days of menstruation (6). Prostaglandins are also implicated in secondary dysmenorrhea; however, anatomical mechanisms can also be identified, depending on the type of accompanying pelvic pathology (7).

The severity of dysmenorrhea is significantly associated with duration of menstrual flow, younger average menarche, smoking, obesity, and alcohol consumption (8). Studies of the natural history of dysmenorrhea are sparse. A longitudinal study in Scandinavia found that primary dysmenorrhea often improves in the third decade of a woman’s reproductive life, and is also reduced after childbirth (8). A more recent study of nurses in the United States has confirmed this (3). The relationship between the prognosis of secondary dysmenorrhea and the severity of underlying pathology, such as endometriosis, is unclear.

**DIAGNOSIS**

A focused history and physical examination are usually sufficient to diagnose primary dysmenorrhea. The initial onset of primary dysmenorrhea is usually shortly after menarche (6–12 months), with the onset of ovulatory cycles. Lower abdominal or pelvic pain commonly occurs for 8 to 72 hours and is usually associated with the onset of menstrual flow. Associated symptoms such as back and thigh pain, headache, diarrhea, nausea, and vomiting may also be present. With primary dysmenorrhea there are no abnormal findings on examination.

Secondary dysmenorrhea can also occur at any time after menarche, but may arise as a new symptom during a woman’s fourth and fifth decade, after the onset of an underlying causative condition. Women may complain of a change in timing or intensity of pain. Other gynecological symptoms such as dyspareunia, menorrhagia, intermenstrual bleeding, and postcoital bleeding may also be present, depending on the underlying condition. If any of the following conditions are present, secondary dysmenorrhea may be indicated: dysmenorrhea during the first one or two cycles after menarche; dysmenorrhea first begins after 25 years of age; late onset of dysmenorrhea after a history without previous pain with menstruation; pelvic abnormality on physical examination; infertility (consider endometriosis, pelvic inflammatory disease, or other causes of scarring); heavy menstrual flow or irregular cycles (consider adenomyosis, fibroids, and polyps);
Dyspareunia; little or no response to therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, or both (9). In addition, the patient’s family history may be helpful in differentiating secondary dysmenorrhea from primary dysmenorrhea. Endometriosis occurs in up to 7% of first-degree relatives of women with endometriosis compared with a general population incidence of 1% (10,11).

**MANAGEMENT**

Treatment for dysmenorrhea aims to relieve pain or symptoms by either affecting the physiological mechanisms behind menstrual pain, such as prostaglandin production, or by relieving symptoms.

**Simple Analgesics**

Simple analgesics such as aspirin and paracetamol may be useful in treating the painful symptoms associated with mild dysmenorrhea. Aspirin was the first discovered member of the class of drugs known as NSAIDs (see section Non-steroidal Anti-Inflammatory Drugs for more information). Paracetamol, like aspirin and NSAIDs, also works by reducing the activity of the cyclooxygenase (COX) pathways, thus inhibiting prostaglandin production. However, while the other drugs directly block production directly via COX-1 and COX-2, acetaminophen blocks indirectly via COX-3 (12). Evidence shows that NSAIDs are generally more effective than both aspirin and paracetamol; however, simple analgesics may still be worth considering as a treatment starting point, especially in cases where NSAIDs are contraindicated (13).

**Aspirin (Acetylsalicylic Acid)**

**Recommended Doses:**
- 650 mg (two tablets) every four to six hours when required for pain relief
- Maximum of 12 tablets (3.9 g) in 24 hours
- Should be started at the onset of pain or bleeding, whichever happens first

**Brand Names:**
Aspirin, Alka-Seltzer, ASA, Bayer Aspirin, Aspergum, Easpirin, Aspirjen, Halfprin, Ecotrin, Measurin, and Empirin.

**Paracetamol (Acetaminophen)**

**Recommended Doses:**
- 500 mg (one tablet) to 1 g every four to six hours when required for pain relief
- Maximum of eight tablets (4 g) in 24 hours (This dosage may be continued for several days.)
Should be started at the onset of pain or bleeding, whichever happens first

**Brand Names:**
Panadol, Tylenol, Anacin-3, and Datril.

**Nonsteroidal Anti-inflammatory Drugs**

NSAIDs inhibit prostaglandin synthesis by affecting COX pathways. This results in a reduction in uterine contractility. There are different COX enzymes: COX-1 produces prostaglandins that help to maintain gastric mucosal integrity, and COX-2 produces prostaglandins that mediate pain and inflammation. NSAIDs can be classified according to their relative effects on COX-1 and COX-2. Most NSAIDs typically have an inhibitory effect on COX-1 and also a small inhibitory effect on COX-2. More recent NSAIDS (such as nimesulide, meloxicam, and etodolac) are more selective for COX-2 than classical NSAIDs, but still inhibit COX-1. There are data on the relative inhibition for some of these NSAIDs, but for many, their specific levels of inhibition for COX-1 and COX-2 are unclear, so they are difficult to classify. The newest generation of anti-inflammatories are those that are selective COX-2 inhibitors (or COX-2–specific inhibitors), which very clearly inhibit COX-2 and have a very limited or insignificant effect on COX-1. COX-2 inhibitors, called coxibs, include celecoxib, rofecoxib, valdecoxib, parecoxib, and etoricoxib.

COX-2 inhibitors have been successfully marketed based on the presumption that they have less gastrointestinal toxicity; however results remain unclear. There are fewer endoscopically identified ulcers in patients taking coxibs; however, these ulcers do not consistently translate into pain or more serious ulcers, and their absence is not a reliable indicator of benefit (14). There are also still unresolved questions regarding the cardiovascular/cardioprotective safety of coxibs (14).

All NSAIDs and coxibs seem to have similar efficacy for dysmenorrhea, and pain relief is achieved in the majority of women. Evidence shows that between 17% and 95% (mean 67%) of women achieve pain relief with an NSAID (15). Compared to placebo the number needed to treat is 2.1 for at least moderate pain relief over 3 to 5 days.

Gastrointestinal effects (nausea, vomiting, and/or diarrhea) are of particular concern with NSAIDs. Effects are generally tolerable; however, when treating women with risk factors for NSAID-induced ulceration, the potential risks and benefits of using an NSAID should be considered. If an NSAID is offered in this situation, a gastroprotective agent may be useful as a preventative. Women with a previous history of gastroduodenal ulcer, gastrointestinal bleeding, or gastroduodenal perforation should probably seek alternatives.
**Recommended Dose**

Dosage differs depending on the type of NSAID; the most common are as follows: ibuprofen, 400 mg three to four times a day; naproxen, 250 mg three to four times a day; mefenamic acid, 500 mg three times a day.

**Brand Names**

The most common examples of NSAIDs are ibuprofen (brand names include Brufen, Nurofen, Advil, Motrin, and Nuprin), naproxen (such as Naprogesic and Naprosyn), diclofenac (Voltaren), and mefenamic acid (such as Ponstan and Ponstel). Many of these products can be bought over the counter without a prescription. Common examples of COX-2 inhibitors are celecoxib (Celebrex®), rofecoxib (Vioxx®), valdecoxib (Bextra®), parecoxib (Dynastat®, Rayzon®, and Xapit®), and etoricoxib (Arcoxia®).

**Oral Contraceptive Pill**

Dysmenorrhea typically occurs in ovulatory cycles, which helps explain why the initial onset of primary dysmenorrhea occurs shortly after menarche, when ovulatory cycles become established (7). Research as early as 1937 has shown that dysmenorrhea responds favorably to ovulation inhibition (16), and that the synthetic hormones in the combined oral contraceptive pill (OCP) can be used to treat dysmenorrhea. These hormones act by suppressing ovulation and causing a lessening of the endometrial lining of the uterus. Therefore, menstrual fluid volume decreases along with the amount of prostaglandins produced, in turn, effectively reducing dysmenorrhea by decreasing uterine motility and ischemia, and thus uterine cramping.

The use of combined OCPs has been advocated as a treatment for primary dysmenorrhea since their introduction for general contraceptive use in 1960. However, this type of long-term hormonal/endocrine therapy is often viewed as only potentially useful if long-term contraception is also desired. OCP use for secondary dysmenorrhea is also questioned, as although this type of treatment may have some favorable effect on the symptom of dysmenorrhea, ultimately the organic cause of the pain would need to be addressed (17).

One potential drawback of the use of OCPs is the possible perceived adverse effects that can accompany the two hormones used. Estrogen-related side effects may include nausea, vomiting, headaches, breast tenderness, and changes in body weight; progestogenic side effects may include acne, weight gain, increased hair growth, and depression. However placebo-controlled double-blind studies have shown that many of these adverse effects can also occur with similar frequency in placebo-using control groups, and even in the general population (18). Therefore, citing a cause-and-effect relationship between OCPs and these adverse effects may be misleading.
In order to lessen any potential side effects, lower-dose OCPs have been developed. In contrast to older OCPs, which contained 50 to 150 μg of estrogen, modern pills are low dose (<35 μg). The level of progestogen has also decreased along with a move from first-/second-generation progestogens (e.g., norgestrel, levonorgestrel (LNG), and norethisterone) to third-generation progestogens, which are more selective and have fewer effects on metabolic parameters (e.g., desogestrel and gestodene).

There is a lack of good-quality clinical trials of oral contraceptives for dysmenorrhea (19). However, an open clinical trial of a low-dose OCP involving 100,000 women, of those who had dysmenorrhea as a preexisting condition, 65% (23,500 women) of the dysmenorrheic sample felt relief from dysmenorrhea as a result of treatment (20). Therefore, despite the lack of randomized controlled trials, there is some evidence in general populations that combined OCPs can effectively treat dysmenorrhea. One small trial comparing the OCP to a gonadotropin-releasing hormone agonist for pain associated with endometriosis has shown that OCP is also effective for secondary dysmenorrhea (21).

If a woman also wants to avoid pregnancy, then the OCP may well be a worthwhile treatment option for dysmenorrhea. Very rarely, the OCP can cause serious health problems such as venous thrombosis, heart attack, and stroke. Women who are already at higher risk for these conditions are generally advised to avoid the OCP. Smoking, especially in women over 35, increases the chances of these more serious adverse effects. However, there may also be some health benefits, for example, a substantial reduction in the risk of endometrial and ovarian cancer.

OCPs are marketed under a very wide variety of trade names that differ considerably from country to country.

LNG-Releasing IUS
The LNG-releasing intrauterine system (IUS) releases LNG (20 μg/day) into the uterine cavity for at least five years, inhibiting proliferation of the endometrium. In addition to providing contraception, up to 50% of women become amenorrheic after 12 months, and reduction in dysmenorrhea was spontaneously reported by women in early trials (22,23). The LNG-IUS has also been shown to be effective in reducing secondary dysmenorrhea in women with endometriosis (24). It should be noted that nonhormonal intrauterine devices may actually cause dysmenorrhea, and may require removal if adequate pain relief does not occur with NSAIDS. The LNG-IUS is marketed worldwide as Mirena®.

Other Drug Treatments
Simple analgesics, NSAIDs, oral contraceptives, and the LNG-releasing IUS are very effective for the treatment of dysmenorrhea. A combination of analgesics and the oral contraceptive or LNG-IUS is also an option in cases that do not respond to a single therapy. For the small percentage of
patients who do not respond to these treatments or to combination treatments, there are other options.

Progestogens and Antiprogestogens

Progestogens may inhibit ovulation and therefore can successfully treat both primary and secondary dysmenorrhea in many women. Both continuous progestogens and antiprogestogens appear to be effective therapies for the painful symptoms associated with endometriosis, and side effects are tolerable (25,26). Depot medroxyprogesterone acetate (150 mg every three months) has also been shown to significantly reduce dysmenorrhea, and other painful symptoms, in women with endometriosis (27).

GnRHas and Danazol

Menstrual cycle suppressants such as danazol and gonadotrophin-releasing hormone analogues (GnRHas) can be used for resistant dysmenorrhea associated with endometriosis. GnRHas are currently considered the standard reference treatment for endometriosis, but are associated with a number of adverse effects (28). Danazol is another menstrual suppressant that can be used to treat dysmenorrhea associated with endometriosis. Its use is also limited by the occurrence of androgenic side effects. Overall no difference has been shown between GnRHas and danazol with respect to effectiveness of pain relief (29). The side effect profiles of the different treatments are different, with danazol having more androgenic side effects, while GnRHas tend to produce more hypoestrogenic symptoms. Further studies are also required to establish the optimal addback regime for limiting adverse effects (28). GnRH agonists are marketed under a number of different trade names such as Zoladex® (goserelin), Synarel® (nafarelin), and Lupron® (leuprolide).

Vasopressin Antagonists

Another factor contributing to dysmenorrhea is the overproduction of vasopressin, a hormone that stimulates the contraction of smooth-muscle tissue. Vasopressin antagonists, which suppress these hormone levels, show some therapeutic value in relieving primary dysmenorrhea (30,31). In a recent study, an orally active vasopressin antagonist given at a dose of 300 mg per day starting between four hours and three days prior to the onset of pain and/or bleeding significantly reduced pain compared to placebo (31). No serious adverse effects were noted.

Antispasmodics

Anticholinergic antispasmodics relax the uterine smooth muscle by acting on the intramural parasympathetic ganglia. Some antispasmodics such as alverine citrate are licensed for the treatment of dysmenorrhea, but no published evidence on efficacy has been found. There are products that contain
both analgesics and antispasmodics, which are marketed in some countries for the treatment of dysmenorrhea.

Calcium-Channel Blockers

Calcium-channel blockers are reported to be of some benefit in dysmenorrhea, but none are licensed for this indication. Uterine hypercontractility is considered an important factor in primary dysmenorrhea. Calcium antagonists can reduce myometrial activity and relieve dysmenorrhea by controlling the cytoplasmic concentration of free calcium and thereby the contractions of the uterine muscle (32).

Alternative Treatments

For reasons that are not clear, approximately 10% to 20% of women with primary dysmenorrhea do not respond to treatment with NSAIDs or oral contraceptives. In addition, some women have contraindications to these medications. Consequently, researchers have investigated numerous alternatives to drug treatments.

Herbal Products or Medicines and Dietary Supplements

Herbal and dietary therapies number among the more popular complementary medicines. They are especially suitable as treatment for disorders such as dysmenorrhea, as they can be self-administered and are often easily available from health shops, chemists, and supermarkets. This ease of administration, while in some ways beneficial, can in itself create problems with the control of dosage, quality, and drug interactions. Reviews of herbal and dietary supplements have shown the following (1,33). One study has shown that 100 mg of thiamine (vitamin B1) taken daily may be an effective cure for dysmenorrhea (87% of patients cured up to two months after treatment). There is also some evidence that pyridoxine (vitamin B6) supplements, taken alone or with magnesium, can reduce pain, but more research is needed to confirm this. Magnesium may also be an effective treatment. Women in some trials of magnesium experienced a reduction in period pain, and a lowering of prostaglandins in their blood. However, the therapeutic dose is unclear as magnesium supplements were used in a variety of ways (daily or during pain). However, a number of women stopped taking magnesium during the trials, possibly due to lack of benefit or due to adverse effects such as constipation. The use of fish oil capsules (omega-3 fatty acids) may also reduce pain, although more research is needed. Adverse effects associated with fish oil treatment were mild and included nausea and worsening of acne.

Dietary Changes

A low-fat vegetarian diet may significantly decrease symptoms by influencing prostaglandin metabolism. One study has shown a positive effect, but the trial was too small (33 women) to give conclusive results (34).
**Exercise**

Physical exercise, such as aerobic activity, may also reduce dysmenorrhea. However, current studies have too many methodological flaws to be able to confirm results (35). It is hypothesized that exercise works by improving blood flow at the pelvic level as well as stimulating the release of beta-endorphins, which act as nonspecific analgesics.

**Transcutaneous Electrical Nerve Stimulation**

Transcutaneous electrical nerve stimulation (TENS) involves stimulation of the skin using current at various pulse rates (frequencies) and intensities in order to provide pain relief. There is limited evidence from small trials that high-frequency TENS reduces pain (36). About 42% to 60% of patients had at least moderate relief; and less use of additional analgesics was needed in one study.

**Acupuncture**

Acupuncture excites receptors or nerve fibers, which, through a complicated interaction with serotonin and endorphins, blocks pain impulses.

One study has shown that acupuncture significantly reduces menstrual pain, but more research is needed to confirm this finding (36).

**Nitroglycerin**

Nitric oxide can relax the uterine muscle. Nitroglycerin formulations are currently used to relax the uterus for various pregnancy problems, so it may have implications for dysmenorrhea. One study, in patients with dysmenorrhea, used 0.1 to 0.2 mg of nitroglycerin taken hourly during the first few days of the menstrual cycle and found that pain was reduced in the majority of patients (37). However, 20% of women reported headaches as an adverse effect and more research is needed.

**Heat**

Heat therapy has been a traditional home remedy for dysmenorrhea. One trial has evaluated its use compared to ibuprofen, an NSAIDs (38). The heat patch (39°C) used for 12 hours a day was found to be as effective as ibuprofen (400 mg three times a day) and more effective than placebo in reducing pain. Women using both the heat patch and the ibuprofen experienced the most pain relief.

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Drugs for Spontaneous Heavy, Irregular or Infrequent Menstrual Bleeding

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INTRODUCTION

Disturbances of menstrual bleeding are common and are one of the major reasons for a woman to consult a general practitioner or specialist. In the United Kingdom, it has been estimated that 5% of women aged 30 to 49 consult their general practitioners for complaints of excessive menstrual bleeding every year (1).

The most common menstrual bleeding complaint is usually of heavy or excessive bleeding (“menorrhagia”), although spontaneous, irregular bleeding [“intermenstrual bleeding” (IMB)] or irregular breakthrough bleeding (BTB) with hormonal contraception or hormone replacement therapy (HRT) is also common. Absence of menstrual periods (amenorrhea) or infrequent periods (oligomenorrhea) is not uncommon. Each of these different symptom groups is considered in more detail below. Physicians need to be aware that menstrual terminologies and definitions vary greatly from center to center, and especially from country to country, and may make comparison of data from different clinical trials difficult (2).
It is important to recognize that issues of perception and tolerance of symptoms are important in determining the timing of the complaint, and that retrospective recall of the details of menstrual patterns is unreliable. Prospective recording of bleeding patterns on a daily diary or calendar may be the most reliable means of assessing the complaint, although clinical assessment of the volume of menstrual loss is notoriously difficult.

**MENORRHAGIA**

This is the symptom of excessively heavy menstrual bleeding, although many women with this complaint will, on direct questioning, only be complaining of “heavy” rather than “excessively heavy” bleeding. This symptom may also be combined with a complex of additional symptoms, which may include dysmenorrhea, back pain, depression, loss of libido, headache, lethargy, diarrhea, and hot flushes, all of which may be perimenstrual. Many women with a convincing complaint of heavy bleeding may have menstrual blood loss within the normal range, if this is measured objectively on a research basis. The volume of menstrual flow can be extraordinarily difficult to assess clinically, and is greatly influenced by issues of perception and tolerance. The menstrual flow often occurs in “gushes” as the uterus contracts, leading to a substantial social problem of menstrual containment. A detailed menstrual history with leading questions about the use of “super” pads, two pads at a time, frequency of changing sanitary towels, the occurrence of “accidents,” or “floodings,” especially at night, may assist in clarifying the severity of these symptoms. It should also be kept in mind that the menstrual flow is composed of a mixture of whole blood with an endometrial transudate and other genital tract secretions, of which the whole blood component is usually less than 50% (3).

Menorrhagia is typically chronic with repeatedly heavy periods from month to month, although the severity of the symptom may fluctuate. Acute episodes “out of the blue” are uncommon, but can sometimes be quite devastating with the rapid development of substantial anemia.

**Causes**

A wide range of underlying conditions may lead to the symptom of menorrhagia (4,5). These causes can be conveniently divided into three subgroups.

**Pelvic Pathologies**

The most common pelvic condition, which can sometimes cause menorrhagia, is the uterine leiomyoma, especially when this is submucous or pedunculated into the uterine cavity. These can sometimes be associated with very severe degrees of menorrhagia. Intramural myomas may also sometimes cause menorrhagia, but myomas in the subserous location are unlikely to do so. Bleeding appears to occur predominantly from dilated, thin-walled and
fragile vessels on the myoma surface or in the pseudocapsule. However, many women with leiomyomas are asymptomatic.

Other pelvic conditions, which may sometimes be associated with heavy or excessively heavy menstrual bleeding, include adenomyosis, endometriosis, endometrial polyps and endometrial adenocarcinoma. Relative rarities, which can be occasional causes of menorrhagia, are arteriovenous malformations and myometrial hypertrophy. There is no evidence that uterine duplications or pelvic inflammatory disease cause excessively heavy bleeding, although endometritis may cause irregular IMB.

Systemic Diseases
These are generally thought to be rare or uncommon causes of menorrhagia, although nowadays the systemic coagulopathies are being increasingly diagnosed in women presenting with menorrhagia (6). In particular, the less severe forms of von Willebrand’s disease may be substantially commoner than previously recognized. This condition may require repeated testing for diagnosis, but may be present in 10% to 15% of cases, which were previously diagnosed as ovulatory dysfunctional uterine bleeding (DUB). Disorders of platelet number and function may also cause menorrhagia. Untreated hypothyroidism and systemic lupus erythematosus are rare systemic causes of menorrhagia.

Dysfunctional Uterine Bleeding
This diagnosis is usually one of exclusion of the conditions in the above two categories, but, in fact, is probably a true dysfunction either within the endometrium or within the hypothalamic-pituitary-ovarian axis. A useful clinical definition is “excessive bleeding (excessively heavy, prolonged, or frequent) of uterine origin, which is not due to recognizable complications of pregnancy, pelvic disease, or systemic disease” (7). This is conveniently divided into those women who are predominantly ovulatory, where the dysfunction appears to be a disturbance of the endometrial molecular mechanisms that are responsible for control of the volume of blood, which is lost at the time of menstruation, or anovulatory, where the dysfunction appears to be a disturbance within the hypothalamic-pituitary control of ovarian function. Anovulatory DUB typically occurs in adolescence, the perimenopause, or in women with polycystic ovary syndrome. It may be associated with endometrial hyperplasia (which generally forms the more severe end of the anovulatory spectrum) and uncommonly with endometrial adenocarcinoma.

Management of Menorrhagia
The key to effective management is precision in diagnosis and assessment, using appropriate combinations of those investigations that are available to the treating physician. Ideally, these should include access to good-quality transvaginal ultrasound scanning, perhaps with sonohysterography,
outpatient saline hysteroscopy, and endometrial biopsy or curettage. Investigations should generally also include a full blood count (including platelets) and a serum ferritin screen to assess iron status. A coagulation screen should generally only be carried out if specific symptoms suggest the possibility of a coagulopathy (such as an excessively heavy menarche, very easy bruising, or prolonged bleeding from minor cuts and abrasions).

**DRUG THERAPIES FOR MENORRHAGIA**

The main medical therapies for which there is sound evidence of efficacy are summarized in Table 1. Most of these drugs have been tested in randomized, double-blind and placebo-controlled trials, where menstrual blood loss has been objectively measured. The total number of subjects objectively studied is often quite small. Most of these therapies have been studied specifically in women with a diagnosis of ovulatory DUB or in those women with menorrhagia using a copper-bearing intrauterine contraceptive device, but anecdotally women with various pelvic conditions associated with menorrhagia may gain some therapeutic benefit with most of these drugs.

**Drug Classes**

**Fibrinolytic Inhibitors**

There is only one widely used inhibitor in this class—tranexamic acid—which will reduce measured menstrual blood loss by 50% in most women (8). This drug works by inhibiting the activity of tissue plasminogen activator in endometrium (an enzyme that demonstrates increased activity in the endometrium of women with menorrhagia). This drug needs to be ingested in relatively high dosage (because of low bioactivity) of 1.0 to 1.5 g three to four times daily, starting at the onset of bleeding and continued through the days of heavy bleeding. It needs to be taken during every menstrual period for as long as therapy is required.

Tranexamic acid has excellent efficacy in women with ovulatory DUB and women wearing copper-bearing intrauterine contraceptive devices (IUCD) (9) and has good anecdotal efficacy in some women with systemic coagulopathies. It may also have anecdotal efficacy in some women with uterine myomata, adenomyosis, or anovulatory DUB.

Randomized trials have demonstrated that tranexamic acid has greater efficacy for menorrhagia than prostaglandin (PG) synthetase inhibitors and oral progestogens (10,11). Unfortunately, tranexamic acid does not reduce accompanying symptoms such as dysmenorrhea. Minor side effects are relatively common and are dose related, but are rarely a problem with the short-term treatments required for menorrhagia. Up to one-third of women on high-dose therapy will experience some gastrointestinal symptoms.
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug name</th>
<th>Trade name</th>
<th>Dosage</th>
<th>Mechanism of action</th>
<th>Specific indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinolytic inhibitor</td>
<td>Tranexamic acid</td>
<td>Cyklokapron</td>
<td>1.0–1.5 g three times daily during heavy bleeding; oral</td>
<td>Inhibitor of tissue plasminogen activator and plasmin</td>
<td>Ovulatory DUB; systemic coagulopathies; IUCD menorrhagia</td>
</tr>
<tr>
<td>Prostaglandin Inhibitors</td>
<td>Numerous: mefenamic acid and naproxen are comprehensively studied</td>
<td>Numerous: ponstan, anaprox, and naprosyn</td>
<td>Mefenamic acid 500 mg tds; Naproxen 250 mg tds during bleeding, beginning at onset of bleeding</td>
<td>Cyclooxygenase inhibitors plus variable end-organ inhibition</td>
<td>Ovulatory DUB; IUCD menorrhagia; Associated menstrual symptoms such as dysmenorrhoea, PMS, depression, diarrhea</td>
</tr>
<tr>
<td>Hormonal therapies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COCP</td>
<td></td>
<td>Microgynon 30, Nordette 30, (and generics)</td>
<td>ethinyl estradiol 30 μg daily, levonorgestrel 150 μg daily for 3 out of 4 wk</td>
<td>Inhibition of ovulation and endometrial suppression</td>
<td>Ovulatory and anovulatory DUB; systemic coagulopathies</td>
</tr>
<tr>
<td>Monophasic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral progestogens</td>
<td>Norethisterone; Medroxyprogesterone acetate</td>
<td>Primolut N</td>
<td>5–10 mg daily to 5–10 mg three times daily for 10 – 21 days</td>
<td>Suppression of ovulation (21 days)</td>
<td>Ovulatory DUB and other causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Provera</td>
<td></td>
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<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug name</th>
<th>Trade name</th>
<th>Dosage</th>
<th>Mechanism of action</th>
<th>Specific indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine progestogen</td>
<td>LNG-IUS</td>
<td>Mirena</td>
<td>20 µg LNG daily on a continuous basis over 5 yr</td>
<td>Endometrial suppression</td>
<td>Multiple indications</td>
</tr>
<tr>
<td>Impended androgens</td>
<td>Danazol</td>
<td>Danocrine and generics</td>
<td>100–200 mg twice daily for up to 6 mo</td>
<td>Inhibition of ovulation and endometrial suppression</td>
<td>Short-term therapy if other therapies do not work</td>
</tr>
<tr>
<td>GnRH analogues</td>
<td>Goserelin</td>
<td>Zoladex implants; Synarel spray</td>
<td>3.6 mg monthly for 6 mo, 200 µg twice daily intranasal</td>
<td>Suppression of ovarian function</td>
<td>Short-term therapy if other therapies do not work</td>
</tr>
</tbody>
</table>

*Specifically for ovulatory dysfunctional uterine bleeding, systemic coagulopathies, but may have roles for menorrhagia due to other causes—see text.

**Abbreviations:** COCP, combined oral contraceptive pill; LNG, levonorgestrel; EE, ethinyl estradiol; IUS, intrauterine system; IUCD, intrauterine contraceptive device; DUB, dysfunctional uterine bleeding; PMS, premenstrual syndrome; GnRH, gonadotrophin-releasing hormones.
The theoretical concern about a possible risk of deep venous thrombosis has not been supported by clinical experience.

Prostaglandin Synthetase Inhibitors

Many different PG inhibitors have been studied for the menorrhagia indication (12). All these agents work by inhibiting the cyclooxygenase enzyme complex, but the fenamates also inhibit the binding of some PGs (especially PGE2) to their receptors. The most potent are meclofenamic acid and mefenamic acid, which may be marginally more effective than PG synthetase inhibitors of other chemical classes. Mefenamic acid has been particularly well studied with an average menstrual blood loss reduction of around 30%, being more effective in women with heavier losses (13,14). The clinical benefit is maintained over the long term provided that women continue to use it meticulously every period. Treatment needs to be started at the first sign of menstrual bleeding and continued until the period is tailing off. Women should carry a few tablets or capsules with them at all times. Reduction in blood loss is dose related, and an optimal dose of mefenamic acid is 500 mg three to four times daily. Naproxen and naproxen sodium have also been well studied, as have ibuprofen, flurbiprofen, and sodium diclofenac with varying percentage blood loss reductions recorded between 12% and 47% (15).

Most PG inhibitor efficacy data relate to ovulatory DUB and inert or copper-bearing IUCDs (16), and they appear anecdotally to be ineffective in women with leiomyomas or anovulatory DUB. However, they have good efficacy for dysmenorrhea and other menstrually related symptoms such as depression and diarrhea (13).

Side effects are generally mild, and the most common are nausea, dyspepsia, diarrhea, headaches, and dizziness. These are not usually a problem because of the short duration of each treatment, and can be minimized by taking the dosage with a small amount of food. The occasional patient may develop an acute gastric erosion.

Hormonal Therapies

Combined Oral Contraceptive Pill: Oral contraceptives are widely used for the treatment of menorrhagia, although the evidence to support their use is surprisingly limited (8,4,17). These drugs reduce measured menstrual blood loss by between 40% and 50%, and may also effectively reduce associated symptoms such as dysmenorrhea. They have a dual mechanism of action, in that they firstly suppress ovulation and reduce spontaneous ovarian follicular activity and cyclical estradiol production. Secondly, the exogenous estrogen and progestogen have a direct effect on endometrial development, resulting in a histologically and biochemically “suppressed” endometrium, which bleeds much less during the shedding process. It is unclear exactly how the expression of various molecular mechanisms in endometrium is modified by this process.
There is anecdotal evidence that monophasic pills are more effective than triphasic, and that higher-dose preparations are better than the lowest dosages. There is also a clinical impression that those with a mildly androgenic progestogen, e.g., levonorgestrel (LNG), are more effective than those with nonandrogenic progestogens.

Most of the evidence to support the use of the combined oral contraceptive pill (COC) in menorrhagia has come from studies of women with ovulatory DUB, but clinical impression suggests that many women with menorrhagia associated with myomata, adenomyosis, endometriosis, coagulopathies, and anovulatory DUB may also benefit. However, a significant minority will be treatment failures, because of persistent menorrhagia or BTB.

Side effects and contraindications are the same as for women using these drugs for contraception.

**Oral Progestogens:** Oral norethisterone (NET) and medroxyprogesterone acetate (MPA) have been used extensively on a cyclical basis for the management of menorrhagia due to anovulatory DUB, but objective evidence for efficacy is limited (18,19). The theoretical basis for this therapy is sound, because exogenous replacement of endogenous progesterone should be expected to produce rapid and effective secretory transformation of anovulatory endometrium unless complex endometrial hyperplasia is present (when longer-term therapy may be valuable). Regimens that are usually utilized are NET 5 mg three times daily for 14 to 21 days or MPA 10 mg three times daily for 14 to 21 days. These treatments may need to be continued on a long-term cyclical basis for many years, often until menopause, because anovulatory DUB does not usually revert to normal menstrual patterns.

These oral regimens should reduce objectively measured menstrual blood loss by around 50% after two or more cycles of therapy in women with anovulatory DUB (18). By contrast, 14-day courses of “luteal phase supplementation” in ovulatory DUB have little effect on measured blood loss (20), and courses of oral progestogens need to be extended to 21 days out of 28 to be effective in ovulatory DUB (10).

Side effects with these regimens are not usually a problem, although nuisance-value BTB may occur. With prolonged cyclical use, some women may complain of weight gain, mood changes, headaches, or other symptoms, which may be difficult to define. Dosage may need to be modified or the progestogen changed.

**Intrauterine Progestogens:** In practice, this means the use of the LNG-intrauterine system (LNG-IUS; Mirena, Schering), which was originally developed as a contraceptive, but has also been found to be highly effective at treating menorrhagia in a variety of different circumstances.
Extensive and increasing evidence has demonstrated that the LNG-IUS will reduce measured menstrual blood loss by up to 95% in women with ovulatory DUB (21–24). There is increasing evidence to support its use in menorrhagia with anovulatory DUB, endometrial hyperplasia (25), uterine leiomyomata (26), adenomyosis (27), coagulopathies (28), and, perhaps, other indications.

This is a device with tremendous potential for treating and also preventing a range of gynecological conditions that may be associated with menorrhagia. It has been suggested that this is an ideal contraceptive for women entering the perimenopause when unpredictable and heavy, anovulatory menstrual bleeding can be a major problem. Recent evidence has also supported its use in younger and nulliparous women (29).

This device is designed to release approximately 20 μg daily of LNG at a relatively constant rate over a lifespan of five years. Insertion of the device is relatively straightforward in parous women, although it may require a paracervical block or even a brief general anesthetic in nulliparous women. The major side effect is nuisance-value menstrual spotting or staining, which gradually settles over the next few months in most women (30). Uterine perforation during insertion is rare, and postinsertion infection is very uncommon. Pelvic inflammatory disease (PID) is much less common than during the use of copper IUCDs, which suggests a measure of protection against PID in LNG-IUS users (31).

**Impeded Androgenic Steroids:** Danazol and gestrinone are unique steroids with mild, impeded androgenic actions that produce a high incidence of amenorrhea in users. This may sometimes be of benefit in providing “thinking time” and the opportunity to recover from menorrhagic anemia in a minority of women (32,33). However, a minority of women experience troublesome androgenic side effects, including acne, weight gain, hirsutism, and even voice change.

Dosages recommended are 100 to 200 mg twice daily for a maximum of six months with danazol and 2.5 mg twice weekly for gestrinone (34) for no more than six months. Abnormal liver function tests become common after this time, and the risk of hepatic adenoma increases.

**Gonadotrophin-Releasing Hormone Analogs:** These expensive hormonal preparations are effective at producing amenorrhea in women with menorrhagia (35), and may therefore be an option for temporary management of severe menorrhagia in women who need “thinking time” to decide about long-term alternative options. However, their use is accompanied by a very high incidence of vasomotor symptoms in the short term, and the possibility of headaches and bone loss in the longer term. Usage over six months needs to be accompanied by low-dose “add-back” therapy with oral progestogens or HRT (36).
Conservative, Observational Management

Because many women presenting with a history of “menorrhagia” actually have measured menstrual blood loss within the normal range, management of their problem may involve careful assessment of the history, exclusion of serious pathology, and reassurance that no serious abnormality exists. This also requires good counseling, but may avoid long-term active medical or surgical therapy (36).

Surgical Therapy

It should not be overlooked that many women will find long-term medical therapy ineffective or unacceptable, and that endometrial ablation or hysterectomy may be important options for effective management of troublesome and persistent menorrhagia (37). It needs to be appreciated that the so-called “therapeutic” curettage is ineffective for medium- to long-term management of objectively confirmed menorrhagia (8).

INTERMENSTRUAL BLEEDING

This is generally defined as episodes of abnormal bleeding occurring in between otherwise fairly normal menstrual periods. The pattern of this type of abnormal bleeding varies greatly. It is frequently light in volume, varies unpredictably from day to day and in duration of each episode, and these episodes may stop and start erratically. It is typically also associated with postcoital bleeding. Both of these symptoms may be caused by surface lesions of the genital tract (for example, cervical polyps, cervical ectropion, cervicitis, cervical carcinoma, endometrial polyps, endometritis, endometrial adenocarcinoma, etc.) Cigarette smoking may also be associated with IMB, and this appears to be worse with heavier smoking.

IMB should be distinguished from “BTB,” which is usually defined as unscheduled bleeding occurring during exogenous estrogen, progestogen, or combined estrogen–progestogen therapy (typically when these are used for contraception or HRT, but may also occur when these hormones are used for therapy of gynecological disorders such as endometriosis). Management of progestogen-related BTB is considered in a separate chapter (see Hickey Chapter 3).

Management of intermenstrual and postcoital bleeding requires a precise diagnosis of the underlying pathology, using an appropriate combination of transvaginal ultrasound scanning, sonohysterography, colposcopy, outpatient hysteroscopy, and biopsy of any lesions (38). The type of diagnostic approach will be dependent on the availability of different technologies, and will also depend on the exact nature of the associated symptoms.

Treatment usually involves appropriate surgery to remove the causative lesion, but drug therapy may be required for active treatment of infections such as cervicitis or endometritis.
AMENORRHEA AND OLIGOMENORRHEA

Secondary amenorrhea is complete absence of menstruation (usually for a period of greater than six months), in a woman who has been previously menstruating. Primary amenorrhea is the failure of a young woman to have initiated spontaneous menstruation by the time she reaches the age of 16 years, and oligomenorrhea is infrequent bleeding, usually at intervals varying between six weeks and six months. In women with oligomenorrhea, most of the periods tend to be light, if not scanty, but of variable duration. Occasionally, these infrequent periods are excessively heavy and constitute anovulatory DUB.

Causes

The great majority of cases of oligomenorrhea (greater than 75%) are associated with polycystic ovary syndrome. This common reproductive endocrinopathy may affect 5% of most populations.

Secondary amenorrhea may have a variety of causes:

- Hypothalamic (common), often associated with weight loss or excessive exercise
- Hyperprolactinemia (less common), sometimes associated with a pituitary microadenoma
- Polycystic ovary syndrome (common)
- Premature ovarian failure (uncommon)—various causes
- Asherman’s syndrome (uncommon to rare) (typically, these intrauterine synechiae follow a curettage for removal of adherent placental remnants in a woman with secondary postpartum hemorrhage)
- Rarities

There are greatly varying incidences of these different types of secondary amenorrhea in different specialist clinics, presumably influenced by referral patterns.

Management

Effective management of amenorrhea and oligomenorrhea is dependent on the precision of diagnosis of the underlying endocrine or pathological condition.

Drug Therapies for Amenorrhea or Oligomenorrhea

1. HRT if serum estradiol levels are very low (less than 150 pmol/L), and the patient is not trying to conceive. Regimens for younger women with very low estrogen levels can be the same as for women using perimenopausal HRT, although sometimes higher doses are needed. This especially relates to a need for additional local estrogen to maintain healthy vaginal epithelium and secretions for
normal sexual function in these younger women. (Readers are referred to the Chapter 7 on HRT for a full discussion of these regimens.)

2. If pregnancy is desired, then induction of ovulation will be required. This may be carried out with clomiphene, tamoxifen, gonadotrophin injections, or dopamine receptor–agonist therapy with cabergoline or bromocriptine. Induction of ovulation may sometimes be combined with in vitro fertilization or other assisted reproductive technologies.

3. Drugs for the management of polycystic ovary syndrome (PCOS) (please see Chapters 13 and 14 PCOS for a full discussion of these issues).

- Metformin, when insulin resistance is demonstrated, with or without other symptoms
- Antiandrogens with or without simultaneous use of the COCP, when androgenic symptoms are present
- Cyclical oral or continuous intrauterine progestogens, when anovulation and/or menorrhagia occur in women not desiring immediate pregnancy
- Induction of ovulation, in anovulatory PCOS, in women with a desire to conceive

CONCLUSIONS

There are steadily increasing choices for the medical management of different causes of menorrhagia, and with care and persistence—and with good counseling—many women with troublesome menorrhagia may control their symptoms effectively without surgery. However, a minority of women will still require endometrial ablation or hysterectomy. This proportion is steadily decreasing as improved medical therapies become available.

REFERENCES


Drugs for the Management of Premenstrual Syndrome and Related Syndromes

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INTRODUCTION

Controversy and debate have accompanied the diagnosis of premenstrual syndrome (PMS) ever since the first clear description of the syndrome by Frank (1). However, recent research and agreement on diagnostic criteria has led to greater understanding and unanimity of approach. Much of the controversy among women and clinicians has been about whether PMS should be considered as a disease or as a normal phenomenon not usually needing treatment. This has been largely due to the failure to appreciate that severity of the presentation varies tremendously. Although most women experience mild mood and somatic symptoms premenstrually, a small but significant number are severely disabled by the disorder. Furthermore, scientists in the field of PMS have not agreed on which terminology to use. With the diagnostic criteria published by the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), a severe form of PMS with mood symptoms has been defined as premenstrual dysphoric disorder (PMDD).

The effects of ovarian hormones and their metabolites on mood and on related disorders of the central nervous system (CNS) have become an
issue of great interest today, because it was discovered that some of these metabolites are potent modulators of neurotransmitter systems in the brain. PMS is a model condition of menstrual cycle–linked, CNS-related condition, where ovarian hormones have a complex and subtle etiological role (2,3).

ETIOLOGY
Despite numerous efforts, no consistent endocrine disturbance has been found in PMS patients. The standing hypothesis is, however, that differential sensitivity to circulating progesterone metabolites rather than abnormal hormone production is the cause of symptoms. The relationship between symptom development and progesterone–allopregnanolone (a CNS-active metabolite of progesterone) production in the luteal phase is striking, and the most important recognized correlation is the necessity of an ovulation and a corpus luteum formation for premenstrual symptom development. During anovulatory cycles, spontaneous or induced, when a corpus luteum is not formed, the cyclicity in symptoms disappears. There is evidence that it is the steroids from the corpus luteum that are the provoking factor. However, there must exist a response system within the brain where the action is taking place.

Two neurotransmitter systems are suspected of playing major response roles, namely the serotonin and gamma-amino butyric acid (GABA)-A systems. The serotonin system is considered particularly because the selective serotonin reuptake inhibitors (SSRI) are effective treatments of PMS and PMDD. The direct mechanism by which this takes place is still not clear. The GABA-A system is suspected because allopregnanolone is a potent GABA-A receptor agonist, similar to benzodiazepines, barbiturates, and alcohol. It is known from animal and human studies that low dosages of allopregnanolone, benzodiazepines, barbiturates, and ethanol induce loss of impulse control, negative mood, and aggression/irritability in certain sensitive individuals. This phenomenon induces severe negative mood symptoms in 2% to 6% of individuals and moderate symptoms in up to 20%. The frequency is similar to individuals in the general population having PMDD (2–6%) and the milder form, PMS (15–25%). In addition, a changed sensitivity occurs during the luteal phase to benzodiazepines, alcohol, and pregnanolone in women with PMS.

DIAGNOSTIC PROCEDURES AND CRITERIA
The correct diagnosis of PMS hinges on establishing the cyclicity of symptoms by using daily prospective self-ratings. If the patient presents at least five severe PMS symptoms during the premenstrual week, of which one or more is mood related, and is symptom-free in the follicular phase, severe PMS (or PMDD) can be confirmed. Because none of the symptoms of
PMDD/PMS is unique to the syndrome, patients need to keep a daily diary of symptoms for at least two months to establish the temporal relationship between onset of symptoms and the premenstrual period. Furthermore, ovulation should be diagnosed, preferably by measuring luteal progesterone.

**TREATMENT OF PMS**

Generally, PMS will last until the menopause, and can be managed rather than cured. Therefore, when choosing treatment strategy, the consideration should be that the intervention is effective, safe for long-term use, and relatively undisruptive in terms of side effects. For many women, conservative therapies such as lifestyle changes, cognitive behavioral therapy, exercise, or dietary regulation may be enough (4). For some, however, the severity of symptoms is so disruptive that they require pharmacological intervention. Nevertheless, medical therapy for PMS/PMDD should always include a thorough evaluation and advice about lifestyle, exercise, diet, recreation, and other drugs, as well as regular follow-up and support.

There are two main principles for the medical treatment of PMS. One treatment strategy focuses on hormonal treatments of different types mainly by inducing an anovulatory state (3–5). The other treatment strategy relates to effects within the CNS to ameliorate or block the effects of the provoking factor by modulating serotonergic neurotransmission. The treatments that in several randomized controlled studies have shown benefit over placebo treatments are the usage of SSRI (6), and treatments suppressing ovulation such as gonadotrophin-releasing hormone (GnRH) agonists, high dosage of estrogen, low dosage of danocrine, or even surgical oophorectomy. Spironolactone, an aldosterone, androgen, and progesterone antagonist, also has some beneficial effect.

**Selective Serotonin Reuptake Inhibitors**

Despite the uncertainty of the exact mechanism, numerous clinical trials have now confirmed the effectiveness of tricyclic antidepressants with a serotonergic profile, and of SSRIs (6). Although several types of antidepressants have been successful in treating PMS, patients are often reluctant to take them because of side effects, and we will therefore concentrate on SSRIs. There is now very good evidence to support the use of SSRIs in the management of PMS/PMDD.

Although serotonin-deficient affective disorder symptoms such as depression, anxiety, aggression, appetite disturbance, and irritability are similar to PMS and PMDD, several factors indicate that the mechanism of action of SSRIs is different when treating premenstrual symptomatology, compared to affective disorders. Onset of action is much more rapid, usually within a very few days. Furthermore the dose required is lower than
for affective disorders, usually at the lowest dosage used for antidepressive treatment.

Although continuous treatment is usually recommended, most patients will benefit from cyclical treatment taken only during the luteal phase. This may lower the impact in terms of prescription cost as well as side effects. The treatment can start two days before expected onset of symptoms and end when full flow menstrual bleeding has commenced. Some women respond less well to SSRIs, but this does not appear to be a function of dosage and increasing the dosage does not help.

SSRIs do not appear to have any effect on ovarian steroid production or ovulation, but side effects such as insomnia, gastrointestinal disturbances, reduction of sexual desire, and fatigue are sometimes reported.

There is a range of SSRIs licensed in many countries for affective disorders, of which fluoxetine is the most comprehensively investigated.

Vaginal or Oral Progesterone

Natural progesterone has been advocated for many years as a treatment for PMS. However, controlled double blind studies have not been able to show any beneficial effect (3,7). Rather, there are now data indicating that these progesterone metabolites could even be a provoking factor (see above). These compounds have not been used in clinical trials, but oral micronized progesterone treatment, resulting in supraphysiological levels of allopregnanolone and pregnanolone, has been tried in placebo-controlled studies. This progesterone treatment has given divergent results and has not always alleviated the overall premenstrual distress. In vaginally administered treatments, progesterone itself is the dominating steroid in blood, and very low amounts of metabolites are formed. With the oral route, large amounts of 3-alpha-hydroxy, -5-alpha/beta metabolites are formed. These metabolites have benzodiazepine-like effects, and may therefore have some anxiolytic action, but a meta-analysis does not support this statement, and this treatment cannot be recommended.

Hormonal and Antihormonal Treatments

Suppression of Ovulation

By suppressing ovulation, premenstrual symptom cyclicity disappears. This can be accomplished with the use of GnRH analogs, but other ways are also successful. Estradiol implants in doses high enough cause anovulation, danazol, or medroxyprogesterone acetate in medium-to-high dosages are also able to suppress ovulation and consequently have an effect on the cyclicity of symptoms. Oophorectomy, the first treatment ever described for PMS, has a marked beneficial effect on PMS symptoms. However, hysterectomy with ovaries left intact does not relieve PMS. With regard
to negative side effects, surgical oophorectomy can rarely be justified for this condition.

Oral Contraceptive PMS Treatment Studies

Women with PMS are more sensitive to some types of hormonal provocation than women without. A few studies suggest a similarity of the symptoms reported as side effects of combined oral contraceptive (COC) and those experienced in PMS. Women on COC often continue to show cyclical mood changes, but have a different pattern during the treatment cycle compared to the natural cycle. Clinical trials with oral contraceptives (OCs) as possible therapeutics for PMS have yielded mostly negative findings (3, 4). The rationale for using COC as treatment for PMS is that they suppress ovulation. The results have been disappointing, because most studies have only shown placebo effects. In one study, only appetite, acne, and food cravings reached statistically significant improvement. With the above-mentioned information, it seems, as though, COCs do not have a place in the treatment of PMS at least for the mental symptoms. Remaining questions include whether there are certain COCs that are less provoking of symptoms than others, and whether there are some individual women who do gain significant sustained benefit from these therapies.

GnRH Agonists

Anovulation and amenorrhea can be achieved either by depot injection or nasal spray in similar dosages as are used for endometriosis treatment. The use of GnRH agonists depends on their ability to cause pituitary desensitization to GnRH through downregulation of the GnRH receptor. During downregulation, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion by the pituitary are substantially reduced. As a consequence, the ovarian sex steroid production is interrupted, and anovulation and amenorrhea are obtained. Symptom relief occurs in psychoemotional as well as physical symptoms.

Side effects: The main drawback to GnRH agonist treatment in this dosage is the hypoestrogenism and its consequences for bone mineral density, and postmenopausal symptoms (8). Due to the side effects, GnRH agonist treatment cannot be used in clinical practice without adding back estradiol and progestogen in a hormone replacement therapy (HRT). Some of the PMS symptoms may return during add-back therapy as progestogenic side effects, but the usage of estradiol/progesterone patches as add-back works better for some women than tablets. It is likely that add-back HRT may need to be tailored to individual indications. The add-back dosage should be as low as possible and usually it is enough with 10–25 µg transdermal estradiol/24 hr combined with 125–300 µg/24 hr of norethisterone (NET) acetate. With this low dosage, the climacteric symptoms are
usually acceptable, bone density does not change, and PMS symptoms do not usually return. A follow-up of bone density and endometrial thickness is advised. Costs may be prohibitive with long-term therapy in some countries.

GnRH Analog Treatment in Lower Dosage

If the GnRH agonist is used in a lower dosage (e.g., buserelin 200–400 mg/day nasal spray), the downregulation of the FSH and LH production from the pituitary will not be complete. In such a situation, ovulation will usually be inhibited, but some estradiol production will continue. With this treatment, climacteric symptoms are much less obvious. Instead women will have irregular or rather regular bleedings, but with some unpredictability of the intervals. With this dosage, an endometrial hyperplasia often develops in a long-term treatment. If the treatment should continue for a long time, progestogens have to be given at regular intervals to provide proper protection of the endometrium. Negative progestogenic side effects may occur, perhaps giving less benefit from the treatment. GnRH agonist treatment with ultralow dosage (100 μg nasal spray and buserelin) has also been tried. The women ovulated, but the steroid production from the corpus luteum was decreased. The results showed significant beneficial effects compared to placebo, but further studies are needed before this type of treatment can be generally applied.

Suppression of Ovulation by Means Other Than GnRH Agonists

A high dosage of estradiol in subcutaneous pellets or transdermal estradiol patches (2 × 100 μg) has been given to suppress ovulation in controlled studies. Both routes of administering estradiol are effective management for both mental and physical symptoms of PMS (9). To prevent the endometrial hyperplasia of unopposed estrogen, cyclical progestogens need to be given to ensure a regular withdrawal bleed. Progestogenic side effects may occur but the net improvement is usually larger than with placebo. A significant incidence of side effects and dropout rate is attributed to estrogen in higher dosages.

High dosages of progestogens alone given orally or by injection have also been used to suppress ovulation. Depot medroxyprogesterone acetate (DMPA, Depo-Provera) 150 mg every three months or an oral dose of 10–20 mg daily of MPA or NET 5–10 mg daily will effectively suppress ovulation. MPA significantly improves individual psychological symptom scores by the second active treatment cycle and pooled psychological symptom scores in first and subsequent active cycles; NET was no more effective than placebo. Breakthrough bleeding is the main side effect. Progestogens including MPA are known to increase appetite and weight in a minority of women.
Danocrine (danazol), a unique steroid with some weak androgenic properties, has also been used effectively in PMS treatment, but with dosages lower than those used for endometriosis (200 mg/day). With this dosage, ovulation suppression occurs in the majority of cases. Barrier contraception is usually advised during this treatment. Danazol is known to be capable of causing androgenic side effects on lipids, acne, hirsutism, change in voice, and negative mood in the higher dosages used for endometriosis, and is probably inappropriate for long-term PMS/PMDD management.

Treatment with Spironolactone

Spironolactone is an aldosterone receptor antagonist used as a mild diuretic and antihypertensive. What is perhaps not so well known is that spirinolactone can antagonize steroid- and pentobarbital-induced anesthetic effects. This effect is not related to its antimineralocorticoid activity and is independent of the other known pharmacological actions of spironolactone. The exact mechanism is unclear. Different categories of PMS patients seem to react differently to this medication and women with a “pure PMS” conforming to the DSM-IV criteria for PMDD have been found to react better to spironolactone than women with premenstrual aggravation of more persistent symptoms. In a dosage of 100 mg/day, substantial improvement was seen on both mental and especially somatic symptoms compared to placebo. Some controversy still exists concerning spironolactone as a treatment of PMS, but the evidence from controlled studies suggests that it may be valuable for many women.

Other Treatments

A number of treatments have been suggested in open studies, but in blinded and controlled studies, these treatments have only shown placebo effects. It is essential to recognize that there is a large placebo effect on PMS symptoms, and if treatment trials are not blinded and controlled with placebo, the interpretation of results should be made with caution. There is also a relationship among affective disorders, stress-induced disorders, and PMS/PMDD. Treatment specifically focused against these disorders may be more appropriate than against PMS. Because PMS and PMDD become more clearly defined as entities, distinct from affective disorders, no doubt more precise treatments will be developed in future.

CONCLUSION

A significant number of women in fertile life are severely handicapped by menstrual cycle–linked symptom changes, but the severity varies tremendously. Ovulation is needed for the symptoms to develop. Progestagens are suspected to be symptom-provoking factors in PMS. Relevant
neurotransmitter response systems within the brain include the serotonin and GABA-A systems. Pretreatment assessment is essential before initiating medical therapy. A number of well-controlled clinical trials show high efficacy for several SSRI preparations. Suppression of ovulation, for example, with GnRH agonists combined with low-dosage HRT add-back has also proven effective in controlled clinical trials. Medroxyprogesterone acetate and spironolactone may have specific benefits. Progesterone and combined OCs generally have no improved treatment effect over placebo for the majority of women, although some individuals report sustained benefit. A summary of some recommended therapies is listed in Table 1.

**REFERENCES**

INTRODUCTION

Menopausal hormone therapy (MHT) has its origin in the effort to alleviate specific symptoms associated with the decline of estrogen production at menopause. In the Study of Woman’s Health Across the Nation, researchers found that vasomotor symptoms consistently loaded on a separate factor from other symptoms across all racial/ethnic groups. All symptoms increase in prevalence from premenopause to early perimenopause, while the percentage reporting hot flushes and night sweats declines noticeably from late perimenopause to postmenopause. This is in contrast to a much smaller decline in symptoms of psychological distress. In the last decade, however, the focus of MHT changed from short-term treatment of symptoms to the preventive health care benefits associated with long-term treatment. In particular, these are the disabilities of osteoporosis and the impact on cognition. However, long-term use was challenged by the clinical trial data of older-age women indicating that hormone therapy (HT) does not protect against cardiovascular disease and that the risk of breast cancer was increased.

In deriving guidance on the use of MHT, one should remember the most common reason for women taking hormones has not changed and still is menopausal symptom relief. The large proportion of hormone replacement therapy (HRT) use in European women is from the late 1940s until
the late 1950s, i.e., during the years of menopausal transition. Use above 60 years of age is relatively uncommon.

INTERNATIONALLY AVAILABLE HORMONE PREPARATIONS

The International Menopause Society refers to HRT as HRT in symptomatic women from peri- to five years postmenopause. HT is the preferred term for hormone therapy in asymptomatic more than five years postmenopausal women. MHT as MHT will serve as the global term for both HRT and HT.

Estrogens

Formulations

Up until today, conjugated estrogens (Premarin®) are the most widely used estrogens in clinical therapy. There are a large number of steroids in Premarin, even androgens and progestins, but only the 10 estrogens are present in sufficient quantity to produce clinical effects (Table 1).

Dissociation constants for binding of estradiol to the estrogen receptor (ER) isolated from different organs in different species have been calculated. If one takes insect cells infected with ER-x-encoding baculovirus vectors, one could determine relative binding affinities of estrogens to the human ER x (Table 2).

Worldwide commercially available estrogens and their relative potencies with respect to follicle-stimulating hormone levels, liver proteins, and bone density are listed in Table 3.

Of the two types of estrogens available, synthetic and natural, the synthetic estrogens such as ethinyl estradiol and mestranol are less suitable for HRT because of their greater metabolic impact. The endogenous estrogens estradiol, estrone, and estriol are prepared by chemical synthesis or extraction from a plant (soya bean or yam) or animal source. Oral preparations contain micronized 17β-estradiol, estradiol valerate, or conjugated equine estrogens (CEEs). Patches, systematically active gels and nasal sprays, and

<table>
<thead>
<tr>
<th>Table 1 Composition of Conjugated Estrogens</th>
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<tbody>
<tr>
<td>Sodium estrone sulfate</td>
</tr>
<tr>
<td>Sodium equilin sulfate</td>
</tr>
<tr>
<td>Sodium 17α-dihydroequilin sulfate</td>
</tr>
<tr>
<td>Sodium 17α-estradiol sulfate</td>
</tr>
<tr>
<td>Sodium Δ8,9-dehydrosterone sulfate</td>
</tr>
<tr>
<td>Sodium equilenin sulfate</td>
</tr>
<tr>
<td>Sodium 17β-dihydroequilin sulfate</td>
</tr>
<tr>
<td>Sodium 17α-dihydroequilenin sulfate</td>
</tr>
<tr>
<td>Sodium 17β-estradiol sulfate</td>
</tr>
<tr>
<td>Sodium 17β-dihydroequilenin sulfate</td>
</tr>
</tbody>
</table>
vaginal rings deliver 17β-estradiol. In Europe, no estrone preparations are available. Local preparations mostly contain estriol or estradiol.

Therapeutic doses of estrogen are organ- and individual-specific. As an example, the widely accepted minimum bone-sparing doses of estrogen are listed in Table 4; the estrogens may be effective even in lower doses. Reduced estrogen doses also improve vasomotor symptoms and decrease side effects. Young women who experience a surgical menopause may require higher doses of estrogen initially to alleviate menopausal symptoms.

In elderly women, preparations containing an estrogen dosage at the lower end of the range of the minimum bone-sparing dose are advised. Long-term low-dose treatment is effective after the age of 60. Acceptance, by avoiding side effects such as mastalgia, is enhanced.

Routes of Administration

Parenteral estrogen administration avoids the gut and first-pass effects on the liver. Following oral administration, the dominant circulating estrogen

Table 3 Relative Estrogen Potencies

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Follicle-stimulating hormone levels</th>
<th>Liver proteins</th>
<th>Bone density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated estrogens</td>
<td>1.0 mg</td>
<td>0.625 mg</td>
<td>0.625 mg</td>
</tr>
<tr>
<td>Micronized estradiol</td>
<td>1.0 mg</td>
<td>1.0 mg</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Estropipate (piperazine estrogen sulfate)</td>
<td>1.0 mg</td>
<td>1.25 mg</td>
<td>1.25 mg</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>5.0 μg</td>
<td>2–10 μg</td>
<td>5.0 μg</td>
</tr>
<tr>
<td>Estradiol valerate</td>
<td>–</td>
<td>–</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Esterified estrogens</td>
<td>–</td>
<td>–</td>
<td>0.625 mg</td>
</tr>
<tr>
<td>Transdermal estradiol</td>
<td>–</td>
<td>–</td>
<td>50 μg</td>
</tr>
</tbody>
</table>

Source: From Ref. 2.
is estrone, while, after parenteral administration, it is estradiol. Thus, after oral estrogen replacement therapy (ERT), the estrone/estradiol ratio corresponds to the hormonal milieu after menopause, whereas the ratio after parenteral administration corresponds to the dominant premenopausal estradiol/estrone relationship.

Oral estrogens, in particular CEEs, increase the production of renin substrate. The type in use is not normally associated with hypertension, and the clinical significance is not clear, because blood pressure does not tend to increase on this form of HRT; even moderate decreases of diastolic blood pressure are observed. Oral estrogen also induces hepatic production and release of sex hormone–binding globulin, thereby reducing the amount of free (and therefore biologically active) estrogens as well as testosterone. A reduction of biologically active androgen and estrogen may reduce libido as an important aspect of quality of life; but it may also reduce favorable estrogen effects in women presenting with relative postmenopausal androgen dominance as manifested by hirsutism and oily skin. The synthesis of certain coagulation factors and lipids is also influenced by the route of administration. As a consequence, parenteral estrogen administration is recommended in women with high levels of triglycerides and in patients with a history of thromboembolism or a suspicion of thrombophilia.

There is no clear advantage of the transdermal or the oral route of estrogen therapy in healthy menopausal women. All estrogens—regardless of the route of administration—eventually pass through the liver and are recycled by the enterohepatic circulation. In routine clinical practice, the practitioner should therefore respect the preference of each woman, but certain clinical conditions may merit preference for a particular regimen.

Transdermal estradiol and progestogens can diffuse through the skin. Two transdermal systems are now available: patch and gel. The patch technologies are (i) alcohol-based reservoir patches with an adhesive outer ring and (ii) matrix patches where the hormone is evenly distributed throughout the adhesive. Skin reactions are less common with matrix than with reservoir patches. The estrogen gels are applied to the abdomen, thighs, upper arms, and shoulders. Both estrogen patches and gels have been shown to effectively reduce hot flushes and prevent bone loss.

Estradiol can also be delivered by nasal spray. Following intranasal application, estradiol is rapidly absorbed with plasma concentrations

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**Table 4**  Minimum Bone-Sparing Doses of Estrogens

<table>
<thead>
<tr>
<th>Estrogen Type</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol oral</td>
<td>0.025–1 mg</td>
</tr>
<tr>
<td>Estradiol patch</td>
<td>14–50 µg</td>
</tr>
<tr>
<td>Estradiol gel</td>
<td>1–5 g, depending on preparation</td>
</tr>
<tr>
<td>Estradiol implant</td>
<td>25 mg, 50 mg, 6-monthly</td>
</tr>
<tr>
<td>Conjugated equine estrogens</td>
<td>0.3–0.625 mg daily</td>
</tr>
</tbody>
</table>
reaching maximal levels after 10 to 30 minutes and returning within 12 hours to the levels of untreated postmenopausal women. This pattern has been referred to as “pulsed administration” of estradiol and contrasts with the prolonged estrogen release of transdermal patches and implants.

Intranasal administration of 300 µg per day estradiol appears to be as effective as oral administration of 2 mg per day estradiol in alleviating postmenopausal symptoms and in preventing bone loss. Some of the estrogen side effects such as abdominal bloating are less common with nasal administration than with tablets or patches.

Estradiol implants are quite common in the United Kingdom and some other European countries. These are crystalline pellets of estradiol, which can be inserted subcutaneously under local anesthesia. These implants will release estradiol over many months. Tachyphylaxis has been reported in some women, because recurrence of menopausal symptoms was observed while the implant was still releasing adequate amounts of estradiol. A check on plasma estradiol should be considered in order to ensure appropriate estradiol levels.

Systemic delivery of estradiol has also been achieved with vaginal rings, which are available in some countries. The low-dose estradiol vaginal ring is used for local treatment only.

Progestins

As part of MHT, progesterone and progestins are only required for the protection of the endometrium. However, additional roles of available progestins are continuously emerging. The basic structure of the 21-carbon progestins is the pregnane nucleus. The 19-carbon series includes all the androgens and is based on the androstane nucleus. The synthetic progestins used in clinical practice are derived either from testosterone (19-nortestosterone derivatives) or from progesterone (17-OH-progesterone derivatives). In addition, there are more recently synthesized nonpregnanes constituting 19-nor-progesterone derivatives: Nestorone, nomegestrol acetate, promegestone, and trimegestone. The “progestogen tree” identifies and categorizes steroid hormones derived from progesterone, the pure agonist and mother compound, which are represented by the trunk of the tree (Fig. 1). A great variety of nonprogesterone partial effects of progestins are apparent. Among these, levonorgestrel (LNG) is known for its antiestrogenicity, while norethisterone acetate (NETA) exerts estrogenic partial effects. Medroxyprogesterone acetate (MPA) and megestrol acetate have partial glucocortical effects, while drospirenone (DRSP) is antimineralocorticoid. LNG, desogestrel, and gestodene are known for androgenic partial effects. On the other hand, cyproterone acetate (CPA), chlormadinone acetate, dienogest (DNG), and DRSP have documented antiandrogenicity. The latter may be of particular interest in hormone treatment of postmenopausal women.
The androgen-dominant hormonal status of the climacteric is associated with adverse metabolic effects as well as clinical signs of androgenization such as seborrhea, acne, and hirsutism.

**Preparations Available**

Post-MHT initially consisted only of sequential regimens that were logical reflections of the cyclic estrogen and progesterone patterns in a premenopausal woman. Withdrawal bleeding occurs in 80% to 90% of women on a sequential regimen. A continuous combined method of treatment evolved to improve patient continuance, which was adversely affected by bleeding and other symptoms triggered by the cyclic hormonal changes. The addition of a daily dose of a progestin to the daily administration of estrogen allowed the progestin dose to be smaller, provided effective protection against endometrial hyperplasia, and resulted in amenorrhea within one year of treatment in 80% to 90% of patients.

There has been a progressive reduction in hormonal doses used for postmenopausal therapy. For many years, the standard dose of estrogen was 0.625 mg conjugated estrogens, 1 to 2 mg micronized estradiol, and 1 to 2 mg estradiol valerate. However, lower doses have been proven on the average to be as effective as these “standard doses.” These alternate options include conjugated estrogens in a dose of 0.3 or 0.45 mg, which effectively produced a gain in bone density when combined with 1.5 mg MPA, and a dose of 0.5 mg micronized estradiol producing similar effects. The 0.45/1.5 mg and 0.3/1.5 mg conjugated estrogens/MPA combinations

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**Figure 1** The progestogen tree. *Abbreviations:* LNG, levonorgestrel; NETA, nor-ethisterone acetate; MPA, medroxyprogesterone acetate; MGA, megestrol acetate; CPA, cyproterone acetate; CMA, chlormadinone acetate; DNG, dienogest; DRSP, drospernone; DSG, desogestrel; GST, gestodene. *Source:* From Ref. 3.
improved vaginal atrophy and reduced hot flushes quantitatively and qualitatively similar to the 0.625/2.5 mg combinations with less mastalgia. These lower-dose combinations are associated with less breakthrough bleeding and a higher rate of cumulative amenorrhea as compared to older standard doses and retained the favorable changes in the lipid profile. At such lower doses of conjugated estrogens, the combination with the progestin produces an additive effect; on the other hand, these lower doses will, in the absence of a progestin, not be as effective for example on hot flushes.

Many women, upon treatment with progestational hormones, produce side effects like breast tenderness, bloating, and depression. These reactions are detrimental to the continuation of therapy. As most placebo-controlled studies failed to document adverse physical or psychological effects with short-term use of progestins—except for breast discomfort—a relation of these progestin side effects to duration of treatment was suggested.

In order to be able to minimize progestin side effects, the question was raised as to whether the progestational agent can be administered less frequently. The administration of MPA every three months was associated in one study with longer, heavier menses and unscheduled bleeding and a 1.5% incidence of hyperplasia at one year; another study produced less overall bleeding, but an incidence of hyperplasia approximating 4%. The Scandinavian Long Cycle Study, a clinical trial scheduled to last five years, was cancelled after three years because of a 12.5% incidence of endometrial pathology and one case of endometrial cancer. Therefore, whenever a patient chooses an extended cycle regimen, endometrial monitoring is required.

The worldwide available progestins are listed in Table 5.

Route of Administration

The progestogens used in HRT are mainly applied in tablet form, although norethisterone and LNG are available in transdermal patches combined with estradiol, and LNG can be delivered directly to the uterus via a medicated intrauterine device. The native molecule progesterone is formulated as a 4% vaginal gel and is licensed for use in HRT in some European countries. A progesterone pessary to be used vaginally or rectally is available, but currently is not licensed for HRT.

TREATMENT OPTIONS

HRT is the first line of treatment for a woman experiencing symptoms. It has been shown to have a direct effect on reducing the frequency and the intensity of hot flushes and relieves urogenital symptoms. There is less consistent support for its role in improving sexual, psychological, and cognitive dysfunction, although clinically positive responses are noted. Other chronic
disorders associated with menopause such as osteoporosis, cardiovascular
disease, and obesity have been subject of intense basic and epidemiological
investigation.

Climacteric Symptoms

Symptoms of ovarian failure such as hot flushes, mood changes, and vaginal
dryness may start several months or years before menopause. Amenorrhea
is not a necessary condition for starting HRT. Vasomotor and vaginal

<table>
<thead>
<tr>
<th>Table 5 Progestins Available Worldwide</th>
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</thead>
<tbody>
<tr>
<td>Estimated comparable doses</td>
</tr>
<tr>
<td>21-carbon derivatives</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate 5.0 mg</td>
</tr>
<tr>
<td>Megestrol acetate 5.0 mg</td>
</tr>
<tr>
<td>Cyproterone acetate 1.0 mg</td>
</tr>
<tr>
<td>Dydrogesterone 10.0 mg</td>
</tr>
<tr>
<td>Chlormadinone acetate 5–10.0 mg</td>
</tr>
<tr>
<td>Medrogestone 10.0 mg</td>
</tr>
<tr>
<td>19-nor pregnanes</td>
</tr>
<tr>
<td>Trimegestone 0.0625–0.50 mg</td>
</tr>
<tr>
<td>Promegestone 0.5 mg</td>
</tr>
<tr>
<td>Nomegestrol 5.0 mg</td>
</tr>
<tr>
<td>Nomegestrol acetate 3.75–5.0 mg</td>
</tr>
<tr>
<td>Demegestone 0.05–0.1 mg</td>
</tr>
<tr>
<td>Nestorone (nonoral) 0.05–0.1 mg</td>
</tr>
<tr>
<td>19-nortestosterone family</td>
</tr>
<tr>
<td>Ethinylated</td>
</tr>
<tr>
<td>Norethindrone 0.7–1.0 mg</td>
</tr>
<tr>
<td>Norethindrone acetate 1.0 mg</td>
</tr>
<tr>
<td>Levonorgestrel 0.075 mg</td>
</tr>
<tr>
<td>Desogestrel 0.15 mg</td>
</tr>
<tr>
<td>Norgestimate 0.09 mg</td>
</tr>
<tr>
<td>Gestodene 0.02 mg</td>
</tr>
<tr>
<td>Norethynodrel</td>
</tr>
<tr>
<td>Lynestrenol</td>
</tr>
<tr>
<td>Ethynodiol diacetate</td>
</tr>
<tr>
<td>Nonethinylated:</td>
</tr>
<tr>
<td>Dienogest 2.0 mg</td>
</tr>
<tr>
<td>Derived from spironolactone and nonethinylated</td>
</tr>
<tr>
<td>Drospirenone 2.0 mg</td>
</tr>
</tbody>
</table>

Source: From Ref. 2.
symptoms typically attributed to menopause occur in approximately 70% of Western women and may be severe in up to 20%.

The alteration in the central nervous system thermoregulatory set point might be mediated by decreased estrogen or increased gonadotropin concentrations, thus affecting main neurotransmitters. Estrogen might exert sensual function, not only by interacting with its receptor and direct transcriptional effects on estrogen response-element containing genes, but also through indirect downstream interactions with other mechanistic pathways that regulate sleep, mood, and cognition. Such interaction may result in nonadrenergic hyperactivity, and a decrease in brain amine such as serotonin.

The treatment of hot flushes, in the first place, may neglect strategies such as tolerance, fans, air conditioners, or cold water to ameliorate the symptoms. Other nonmedical treatments commonly used include exercise, diet, acupuncture, behavioral therapies, and lifestyle modification. Estrogens have been the mainstay of treatment because there is a causal association of hot flushes and estrogen depletion and HRT (Fig. 2). In large randomized, clinical trials, HRT decreases hot flushes by 50% to 100% in postmenopausal women. Similarly, transdermal estrogen seems to be a promising treatment. Placebo-controlled investigation suggests that HRT is two to five times more effective than placebo. When HRT is discontinued, most women will note the return of the hot flushes. The estrogen component should therefore be discontinued gradually over weeks.

Transdermal progesterone cream was associated with an 85% reduction in hot flushes compared to 19% in a placebo group. MPA showed much the same reduction in hot flushes. HRT with either estradiol or progestational agents seems to be the treatment of choice for most women with hot flushes and their associated symptoms.

Pharmacologic alternatives to estrogens and progestogens may be indicated. Clonidine is a new $\alpha_2$-adrenergic receptor agonist given orally or

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**Figure 2** Pharmacologic management of vasomotor symptoms. **Abbreviations:** SSRI, selective serotonin reuptake inhibitor; SNRI, selective norepinephrine uptake inhibitors; HT, hydroxy tryptamine. **Source:** From Ref. 4.
transdermally. Although it seems to be moderately more efficacious than placebo, side effects such as dry mouth, constipation, drowsiness, and orthostatic hypotension have been observed in 10% to 50% of patients. Recently, the gamma amino butyric acid (GABA) analog gabapentin has also been reported to reduce hot flushes.

Selective serotonin reuptake inhibitors (SSRIs) represent a class of compounds with a worldwide application in the treatment of depression. Results from trials of venlafaxine and paroxetine suggested a reduction greater than 50% in hot flush frequency. Thus, SSRIs can be offered to women who do not want or should not be treated with estrogens. A summary of pharmacotherapeutical alternatives in common dosages is presented in Table 6.

### Chronic Disorders Associated with Menopause

The menopause offers the health care provider an opportunity to assess a woman’s health, her concerns, and the need for health promotion and disease prevention measures. Each phase of a woman’s life is associated with specific issues related to reproductive and general health. Recommendations should be specific to each woman and her background. There are country-specific and cultural variations in menopause symptoms, the frequency of different postmenopausal diseases, clinical practice, health care resources, and affordable interventions. Country- and culture-specific practices will therefore vary.

### Osteoporosis

Estrogens and androgens affect both osteoclast and osteoblast functions and reduce bone resorption. Sex steroids affect bone cell function and bone turnover through both direct and indirect mechanisms. While sex steroids have direct inhibitory effects on osteoclast function and osteoclastogenesis,
they also affect the osteoblast lineage. Estrogens provide an inhibitory effect on proliferation and activity of early osteoblast precursors, which in turn control osteoclastogenesis. An increased number of osteoclast-supporting cells, the consequence of a release from an inhibitory action of estrogen, are the pathogenetic mechanism of estrogen-dependent increased bone turnover and bone loss.

HRT has been consistently shown to reduce postmenopausal bone loss and reduce fracture incidence. Lower doses than previously thought necessary (Table 4) are now proving effective. The Women’s Health Initiative (WHI) trials have confirmed the fracture reduction efficacy of HRT, including hip and spine fractures. These studies were done in women aged between 50 and 80, who did not have increased fracture risk, and who were supposed to be in general good health. Considering primary prevention of osteoporosis in women with increased fracture risk, the benefit-risk balance of HRT has not been studied in larger randomized, clinical trials. It has been shown that doses of 0.3 mg per day CEE, of 0.25 to 0.5 mg oral micronized 17β-estradiol, of 14 to 25 μg transdermal 17β-estradiol, or of 150 μg per day intranasal 17β-estradiol maintain bone in most women when taken with adequate calcium (Table 7). When medication is indicated, based on a combination of clinical risk factors and low bone mineral density, the choice varies with the age of the patient and the severity of osteoporosis. Timing of HRT and maintenance of the microarchitectural integrity of the bone are important. Estrogen must be used continuously to preserve bone. Observational data suggest that bone density in older women who have never received estrogen is similar to women who were on estrogen for 10 years and then discontinued it for another 10 years.

Of the alternatives to HRT for the secondary prevention of osteoporosis, currently licensed therapies include bisphosphonates, raloxifene, teriparatide, strontium ranelate, calcium, and anabolic steroids. Calcium supplements are licensed as an adjunct to therapy. Of these, only alendronate and risedronate have been shown to reduce hip fracture incidence, yet hip fracture is the most important osteoporotic fracture to prevent. However, bisphosphonates like alendronate and risedronate have only been shown to prevent hip fracture in elderly women with a mean age above 65, who had developed osteoporosis already, and in most

| Table 7 Osteopenia or Osteoporosis: Choose and Adjust the Dose of Estrogen |
|---------------------------------|--------|---------|--------|
| Estrogen                        | Low    | Intermediate | High   |
| 17β-estradiol                   | 0.25-0.5 mg | 1 mg      | 2 mg   |
| Conjugated equine estrogens    | 0.3 mg | 0.625 mg | 0.9 mg |
| Estradiol patch                | 14-25 μg | 50 μg    | 100 μg |
instances sustained a fracture. This effect has not been verified in younger women with increased risk rather than established disease. As hip fractures most commonly occur in elderly women, bisphosphonate use is often more appropriate than current HRT regimens.

There is no doubt as to the efficacy of HRT for primary prevention of osteoporosis in postmenopausal women; but its current role in prevention of fractures seems best suited to those younger postmenopausal women at increased risk.

Cardiovascular Disease

Extensive data from animal investigations and observational studies have shown that HRT has many beneficial effects on coronary heart disease risk factors, including favorable alterations in the lipid profile, vasodilatatory effects, and the promotion of angiogenesis. However, the use of HRT for preventing the progression of established disease remains controversial, as noted by the results of studies such as Heart and Estrogen/Progestin Replacement Study (HERS).

1. ERT does modulate and improve estrogen deficiency-related changes in the lipid profile, but has only a secondary role for the treatment of dyslipidemia.
2. Timing of ERT is important: Early ERT (within first five years of menopause) will retard or prevent progression of atherosclerotic disease.
3. ERT in older women (>60 years) with established disease may result in early adverse events, albeit in a minority of instances.
4. Women with diseases involving cardiovascular risk—hypertension, diabetes, and dyslipidemia—need to be treated with disease-specific therapies.

Even in the absence of clinical trial data, lifestyle and diet recommendations can be made to all women. Tables 8 and 9 summarize the recommendations of the International Menopause Society as to adequate nutrition and exercise. The gold standard for pharmacological primary prevention is given to well-established alternatives such as statins.

Secondary prevention of cardiovascular disease (CVD) should be performed by other, nonhormonal substances. The prescription of HRT solely for secondary cardiovascular prevention is contraindicated. However, pre-existing HRT can be continued if there is an indication.

Dementia

Estrogen stimulates neuronal function in vitro, increases the number of developed glia sites, suppresses amyloid deposition, improves cholinergic transmission, and protects the brain from the oxidative stress induced by
amyloid deposition. There is also experimental data support for the concept of estrogens favorably affecting cognitive function. Recent epidemiology also suggests that ERT is associated with a decreased prevalence of Alzheimer’s disease. As with CVD protection, the key issue probably is early timing of estrogen replacement.

The evidence of ERT/HRT for primary prevention of dementia still is contradictory. The WHI showed an increase in dementia in women after the age of 75, other trials such as the Cash County Study suggest that estrogens may delay the onset of Alzheimer’s disease if their administration is started early after menopause. Several other epidemiological investigations have confirmed that estrogen use may delay or prevent the onset of Alzheimer’s disease, depending on both dose and duration of use. However, once Alzheimer’s disease has become clinically evident, its symptomatic progression does not appear to slow or to improve with HRT.

As far as cognitive function in nondemented women is concerned, prospective studies suggest that estrogens exert a favorable effect on cognition.

Table 8 Nutrition

Encourage a well-balanced and diversified eating pattern that is low in saturated fat and high in fresh fruits and vegetables and fiber. Prefer fats with higher monounsaturated content (e.g., olive oil, and canola oil). Prefer seafood and skinless chicken to red meat. Prefer soft unsaturated margarine to hard margarine or butter. Use skim milk and skim milk products or at most 1% milk instead of products with a higher fat content. Limit the intake of high-cholesterol foods, and avoid fast-food meals. Consume more than five servings of fruits and vegetables daily. Total dietary fiber intake from food should be 25–30 g/day.

A clinical trial showed that eating fish 2–3/wk reduced the risk of cardiovascular disease.

Encourage increased dietary consumption of omega-3 fatty acids, e.g., certain types of fish (mackerel).

A clinical trial showed that a Mediterranean diet supplemented with ω-linoleic acid significantly reduced the risk of recurrent coronary events in patients with heart disease.

Diets rich in antioxidant vitamins (i.e., nuts, fruits and vegetables) are preferred over vitamin supplements.

Limit salt intake to 6 g/day. A reduced salt/reduced saturated fat diet has been shown to reduce blood pressure in clinical trials.

Prefer spices to salt in food preparation. Reduce intake of canned and commercial bakery goods, which are usually high in salt.

Limit alcohol to less than one to two glasses per day: one glass = 0.254 oz wine (approximately 120 ml), 12 oz beer (approximately 360 ml), or 1.5 oz 80-proof spirits (approximately 45 ml).

Source: From Ref. 5.
Improvement in visual memory (short-term memory) and in vigilance (adaptive behavior) has been documented.

Diabetes Mellitus

Controversial statements of American and European medical authorities resulted in diabetic women being up to 50% less likely prescribed HRT than nondiabetic. The North American Menopause Society recommended that the greatest benefits may be obtained from the use of transdermal estrogen preparations, or oral estrogens in low doses. While estrogens apparently increase insulin sensitivity, the choice of progestogens is less clear. Micronized progesterone or dydrogesterone would appear to have the least adverse effect on insulin sensitivity and HDL-cholesterol concentrations. Studies in diabetic women have, however, been criticized, as they tend to be small and short-term. Long-term interventional research is required.

Obesity

Adipocytes of female subcutaneous fat are regulated depending on its regional distribution to the abdomen or gluteofemoral area. Fat tissue of the abdominal region is mobilized by androgens, whereas cortisol induces

Table 9  Exercise

<table>
<thead>
<tr>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brisk walking and vigorous exercise are associated with substantial reductions in coronary events and stroke</td>
</tr>
<tr>
<td>Physical activity lowers blood pressure, improves the lipid profile, reduces insulin resistance and enhances fibrinolysis</td>
</tr>
<tr>
<td>Exercise reduces central body fat mass while preserving muscle when combined with appropriate nutrition and diet</td>
</tr>
<tr>
<td>Any form of aerobic exercise is beneficial—brisk walking, jogging, swimming and cycling—and should be tailored to the individual’s preference, age and medical condition</td>
</tr>
<tr>
<td>Cardiorespiratory and muscular fitness depend on the frequency, duration and intensity of exercise. Optimum results will be obtained with a 5 days/wk regimen, with 30–40 minutes of aerobic exercise at 70% of the maximum heart rate (MHR)</td>
</tr>
<tr>
<td>The formula used to estimate the MHR (220-age) underestimates the true value, especially in aging women. A modified exercise stress test will allow for a more accurate assessment of the MHR and, by quantifying the total exercise test, the individual’s muscle endurance—an important prerequisite for optimal aerobic exercise</td>
</tr>
<tr>
<td>Medically supervised and individualized programs are recommended for women who have had a recent MI or revascularization procedure</td>
</tr>
</tbody>
</table>

*Abbreviations: MHR, maximum heart rate; MI, myocardial infarction.

Source: From Ref. 5.
accumulation of fatty acids in abdominal fat cells. The gluteofemoral region is dependent on estradiol and progesterone, leading to body fat accumulation in this area. Details of these hormone-related signals to body fat distribution are illustrated in Figure 3.

Fasting results in a fat cell loss. The resultant decrease in leptin concentration will induce release of neuropeptide Y. The individual will feel hungry. Following satiety with growing adipocytes, incremental leptin will affect melanocyte-stimulating hormone (MSH) secretion with resultant loss of hunger and elevated sympathetic tone (Fig. 4).

It is accepted that women who enter the transitional age will gain some 10% to 15% of their body weight, and yet, changes in body weight are one of the predominant reasons why women do not accept HT. HRT can counteract, at least in part, the postmenopausal increase in body weight and body fat, preventing central body fat distribution after the menopause.

Skin Aging

The aging process of the skin would result in dryness, variable hair loss, and losses in collagen fibers, skin thickness, glucosaminoglycans, elasticity, and vascularity. HRT with CEEs or transdermal estradiol in either cyclical or continuous fashion, after 12 months of therapy, has been shown to significantly increase skin collagen content over controls. Thus, skin wrinkles tend to disappear and women look younger.

The new progestins with antiandrogenic properties may benefit postmenopausal women who require HRT and suffer from preexisting androgen-related conditions such as acne and hirsutism. In the order of antiandrogenic importance, the progestins in clinical use are CPA, DNG, DRSP, trimegestone, nomegestrol acetate, and chlormadinone acetate. In combination with an estrogen, certain antiandrogenic progestins do not
appear to inhibit the beneficial effects of estrogen on surrogate markers of cardiovascular function and do not have a negative effect on libido or mood.

ADVERSE EFFECTS OF MENOPAUSAL HORMONE THERAPY

There are some medical conditions where more careful assessment is required and where modifications of treatment may be indicated. In general, estrogen administration may have negative effects such as vaginal bleeding, breast tenderness, fluid retention, nausea, and bloating. Within a few months, these adverse effects usually diminish; if not, lowering the estrogen dosage is an effective strategy.

Endometrial Disease

Unopposed estrogen use is associated with an increased risk of endometrial abnormalities such as hyperplasia and carcinoma. The risk increases with dosage and duration of estrogen treatment. After 10 years of unopposed estrogen use, the relative risk of endometrial cancer approaches 10. On the other hand, low estrogen dosages and relatively weak estrogens such as estriol succinate may also increase the risk. It is standard clinical practice to oppose the risk by combining an estrogen with adequately dosed and timed progestins. The recommended duration for sequential combination with the progestin is at least 12 days, preferably 14 per month. The reason
is the observed increased endometrial cancer risk following short-term progestin (<12–14 days). Combining estrogen and progestins on a daily basis has been reported to reduce the risk of endometrial cancer by about 40% to 60%. On the other hand, there is some debate as to whether the addition of a progestogen to low estrogen is indicated in the elderly, because absolute risks for unopposed estrogen are rather low and progestogens may induce several adverse effects.

**Thromboembolism**

The risk of thromboembolic disease will increase about two to four times with any type of MHT. This increased risk is predominant in the first two years after starting MHT. From limited data available, it was argued that this increased risk appears to be related to the oral route of hormone use, while transdermal administration was preferably associated with a smaller increase in risk.

**Breast Cancer**

In the general population, 10% of women will be diagnosed as having breast cancer, while 3% to 4% will die from it. One of the most important risk factors is obesity, which exceeds the effect of HRT by far. In overweight postmenopausal women, the elevated risk of breast cancer is not further increased by HRT. The data from the WHI suggest that combined HT would increase the risk of breast cancer by 24%, whereas the estrogen-alone treatment would result in a 23% decrease of risk. This result was unexpected. One way of explaining the HRT and ERT difference in the WHI study would be the hormonal impact on the metabolic syndrome including insulin resistance and hyperinsulinemia (54). HRT with relatively low doses of estrogen may improve insulin resistance and, hence, reduce the elevated breast cancer risk in obese patients, whereas this beneficial estrogen effect may be antagonized by progestins. A principal option for the reduction of breast cancer would therefore be treatment of insulin resistance, the use of low doses of estrogens, and the reduction of exposure to progestins.

In order to adequately interpret current epidemiological knowledge on HRT and breast cancer, most authors give reference to the Oxford collaborative reanalysis of 1997. Absolute additional risks in older postmenopausal women are estimated to be in the order of 2 per 1000 women after five years and 6 per 1000 women after 10 years of MHT. These additional risks disappear within five years of treatment discontinuation.

**Ovarian Cancer**

Mortality from ovarian cancer is more than doubled in women who were on estrogen therapy for 10 years or more compared to women who never used estrogens. An updated, collaborative reanalysis of European case-control
studies documented an increased risk of ovarian cancer of 1.28 for current or past use of MHT versus never-use (95% confidence interval: 1.05–1.56).

**Cardiovascular Disease**

Early after starting MHT, the risk of coronary heart disease increases both in healthy women and in those with established coronary disease. The WHI trial was challenged as to not being representative for primary prevention, because it was performed in a rather old and prediseased population. Timing of HRT is of utmost importance. The potential for access CVD, however, must be considered especially when starting HT in older women. This is no option except adequate medical cardiovascular treatment has already been established.

**Gallbladder Disease**

There are limited data on the effect of HRT on cholelithiasis. In a recent randomized, controlled trial of oral HRT in elderly women on the secondary prevention of cardiovascular disease (HERS), an increased incidence of gallbladder disease was found. The relative risk of biliary tract surgery is increased by 83% in women receiving MHT. The reason may be the estrogen-induced increases in biliary cholesterol saturation. In women with preexisting disease, the nonoral route is recommended.

**INDIVIDUALIZED TREATMENT**

The need to reduce the dose of estrogen or estrogen and progestin for postmenopausal therapeutic intervention is apparent. Lower doses of estrogen, in particular CEE 0.45 and 0.3 mg with MPA 2.5 or 1.5 mg, have been shown to produce comparable effects in terms of lipids, menopausal symptoms, superficial vaginal cell counts, and endometrial hyperplasia, when compared with the higher dose of CEE 0.625 mg with MPA 2.5 mg. Clinical trials with direct comparison of lower doses of estradiol 1.0 mg with NETA 0.5 mg versus the estradiol 2.0 mg and NETA 1.0 mg have not been reported. However, the lower dose E₂ (estradiol) 1.0/NETA 0.5 has definitely been shown to produce less frequent adverse clinical effects. Lower doses of ethinyl estradiol had differential effects on bone and bleeding outcomes in the EE (ethinylestradiol) + NETA trial and therefore the best regimen was selected as using EE 5 μg and NETA 1.0 mg.

One should always be aware that postmenopausal women, even when achieving similar peripheral levels of estradiol, may respond differently with symptoms and subjective comfort. To start HRT with individual adaptation of the required dose of estrogen is therefore recommended.

Individual adaptation and optimal reduction in the doses of estrogen and progestin appears to reduce the incidence of unwanted uterine
bleeding and the adverse clinical side effects. Breast tenderness would also respond to lower doses, which otherwise maintain efficacy in terms of menopausal symptom relief, improvement of vulvovaginal atrophic changes, and prevention of bone loss.

CONCLUSIONS
The leading symptoms that distinguish premenopausal from postmenopausal women are vasomotor flushes and vaginal atrophy. Observational studies in the 1960s and 1970s in hospital and clinical settings documented that estrogens were powerful medications to relieve women of these symptoms. In the 1980s, there was a shift to find other positive benefits of estrogens, including prevention of osteoporosis and prevention of heart disease as well as other chronic medical conditions such as dementia of Alzheimer type. Following longer-term epidemiological investigation, we learned of the complications of estrogens, which included the potential for breast cancer. Another decade later, randomized, controlled trials were in variance from observational trials in that the benefit of heart disease prevention evaporated. Both health care providers and our patients were increasingly reluctant to utilize estrogens. A search for alternatives was started. This included soy products as well as complementary medicines. Unfortunately, these agents are not as effective as estrogen for the relief of severe symptoms. Today, the pendulum is swinging back toward utilization of estrogens as long as the patient understands the benefits and risks of therapy. We are currently applying much lower doses and prefer different routes of administration, which may be safer, for shorter periods of time. We have also recognized the importance of timing in the onset of MHT. Early treatment during the perimenopausal transition may provide longer-term preventive benefits.

FURTHER READING
Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51


REFERENCES

INTRODUCTION

Many women have turned to complementary and alternative medicine (CAM) for relief from their menopausal symptoms. A wide scope of CAM is used by women. Not only supplements and herbal medicine but also such therapies as acupuncture, relaxation, and reflexology. In a survey of 100 perimenopausal women carried out in the United States, 29% were taking hormone replacement therapy (HRT), 16% used HRT plus dietary supplements, 32% used dietary supplements alone, and 13% were on no medication.

HERBAL MEDICINE

Black Cohosh (Actaea/Cimicifuga racemosa)

Black cohosh is a perennial plant of the buttercup (Ranunculaceae) family and native to eastern United States and Canada. There is no consensus on how it might work to relieve hot flushes, although central activity is suggested.

There are four randomized controlled trials (RCTs) of black cohosh for the treatment of menopausal symptoms in healthy women. Two of these trials are of poor methodological quality and therefore extrapolation of the results is difficult. The results from the two trials with better methodological quality are promising. In a study of 80 postmenopausal women who...
received treatment with Remifemin® (80 mg daily), estrogen (0.625 mg daily), or identical placebo for 12 weeks, improvements were seen in the Kupperman Index and the Hamilton Anxiety Scale in all groups, with the greatest improvement seen in the black cohosh group, although there were no significant differences between the groups. In a trial by Wuttke et al., 62 postmenopausal women were treated with the black cohosh preparation CR BNO1055 (40 mg daily), conjugated estrogens (0.6 mg daily), or matching placebo for 12 weeks. Reduction of menopausal symptoms with black cohosh and conjugated estrogens was similar but with no significant difference over placebo.

**Dong Quai (Angelica sinensis)**

In the Chinese Materia Medica, dong quai is indicated for disorders of menstruation including menopausal symptoms. Whether dong quai contains phytoestrogens is unclear. Hirata et al. randomized 71 postmenopausal women to receive either dong quai powder or placebo (maltodextrin) for 24 weeks. Although there were improvements in symptoms (Kupperman index and daily flush diary) in both groups compared with baseline, there was no evidence that dong quai was superior to placebo in relieving symptoms.

**Evening Primrose (Oenothera biennis)**

Evening primrose belongs to the fuchsia (Onagraceae) family. Evening primrose oil (EPO) contains approximately 9% cis-gamma linolenic acid, a precursor of prostaglandin E1, and yet there is no good scientific rationale yet for the use of EPO and hot flushes; despite this, there is a view amongst the public that it is effective in the control of menopausal vasomotor symptoms. There is one RCT in which 56 menopausal women were randomized to receive either EPO (4000 mg/day) or placebo (liquid paraffin) for 24 weeks. Unfortunately only 35 women completed the trial (18 EPO, 17 placebo), in all cases the reason given was a poor response to treatment.

**Ginseng (Panax ginseng)**

*P. ginseng*, a perennial herb native to Korea and China, has been used as an herbal medicine in eastern Asia for thousands of years. Wiklund and co-workers investigated the effects of a standardized ginseng extract, Ginsana®, on 384 postmenopausal women in a placebo-controlled 16-week study. The outcome measures included three quality of life questionnaires as well as physiological parameters including hot flushes. Only the Psychological General Well-Being Index (*p* < 0.01) and its subscales for depression, well-being, and health (*p* < 0.05) showed a statistically significant improvement with ginseng compared to placebo. No other significant differences between
treatment groups were observed, although a considerable decrease in symptoms was seen in both groups.

Kava Kava (*Piper methysticum*)

In the South Pacific, extracts from the rhizome of kava kava have been used for recreational and medicinal purposes for thousands of years. A Cochrane review concluded that kava kava extract may be an effective symptomatic treatment for anxiety with four of the included trials relating specifically to menopausal women. However, concern regarding the number of cases of liver damage associated with the ingestion of kava kava had led regulatory authorities in the United States, Canada, Australia, and the United Kingdom to suspend or withdraw kava kava products from the market, pending further evidence of their safety.

Herbal Combinations

There have been several RCTs of herbal combinations for menopausal symptoms. Results of these are difficult to extrapolate because they refer to single trials with defined herbal mixtures. Positive results were seen in a trial of the combination of Actaea racemosa and Hypericum perforatum, although improvements were not thought to be clinically relevant. In placebo-controlled trials of herbal mixtures of *Arctium lappa, Glycyrrhiza glabra, Leonurus cardiaca, A. sinensis* and Dioscorea barbasco, *Rehmannia glutinosa, Cornus officinalis, Dioscorea opposita, Alisma orientalis, Paeonia suffruticosa, Poria cocos, Citrus reticulate, Lycium chinensis, Albizia julibrissin, Ziziphus jujuba, Eclipta prostrata*, and *Ligustrum lucidum* and a cream containing *Dioscorea villosa, Linum usitatissimum, Pelargonium graveolens*, and *Salvia officinalis*, improvements were seen in both groups, although no intergroup differences were seen.

Phytoestrogens

Phytoestrogens are polyphenolic, nonsteroidal plant compounds with estrogen-like biological activity. Based on their chemical structure, they can be classified into three main groups: flavonoids, lignans, and cunestrans. These compounds structurally resemble estradiol and are shown to have weak estrogenic activity. The major dietary isoflavones, genistein and daidzein, are to be found in soy (*Glycine max*) and to a lesser extent the herbal medicine red clover (*Trifolium pratense*).

Soy (*G. max*)

Epidemiological studies suggest that in Asian nations where phytoestrogen consumption is generally much higher than in the West, perimenopausal symptoms are less prevalent. Thus soy preparations have been promoted
for perimenopausal symptoms. There are numerous RCTs investigating the
effect of soy on vasomotor symptoms of menopause. These trials are quite
varied in the severity of symptoms experienced by participants, dosage and
format of soy isoflavones, length of study, and outcome measures. However
a recent review concludes that there is some evidence for the efficacy of soy
preparations for perimenopausal symptoms but that the heterogeneity of
studies makes it difficult to make a definitive statement. Adverse event data
from clinical trials suggest that there are no serious safety concerns with soy
products in short-term use. However a recently published five-year-long
study by Unfer et al. suggests that long-term use may lead to an increase
in risk of endometrial hyperplasia.

**Red Clover (T. pratense)**

This herbal medicine is a source of isoflavones and supplements containing
extracts of this plant have become popular for menopausal symptoms.
There are five RCTs measuring the effect of red clover isoflavones on
vasomotor symptoms in menopausal women. The first two trials, published
in 1999 by Baber and Knight, involved 51 and 37 menopausal women,
respectively, who were experiencing three or more hot flushes daily. The
Baber study ran for 30 weeks and women were randomized to either one
tablet of Promensil® (40 mg isoflavone) or identical placebo. The study by
Knight et al. ran for 12 weeks with the women being randomized to either
one or four Promensil tablets daily or placebo (1). Both studies used the
Greene Menopause symptom score. No differences were seen between
treatment and placebo groups. Two further studies in 2002 investigated
the possible effect of Promensil in menopausal women with five or more
hot flushes daily. In the Van der Weijer et al. trial, 30 women were rando-
mized to either two tablets of Promensil or placebo for 12 weeks with a
four-week placebo run in. The study by Jeri involved 30 women randomized
to one tablet of Promensil or placebo for 16 weeks. In both trials, there was
a significant reduction of hot flushes (>40%) with Promensil versus placebo

However, the most recent RCT by Tice and coworkers involved 252
women with 35 or more hot flushes weekly. The women were randomized
to a daily dose of red clover isoflavones (82 or 57 mg) or identical placebo
for 12 weeks with a two-week placebo run in. There were no significant dif-
fers in any of the menopausal measures with the red clover isoflavones
compared with placebo.

**SUMMARY**

The vast majority of trial data are concerned with herbal medicine or sup-
plements. There is some evidence to suggest that black cohosh, soy, and
red clover may be effective for reducing menopausal symptoms.
FURTHER READING


REFERENCE

Androgen Therapy for Women

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INTRODUCTION

Androgen therapy for women is a subject of growing scientific and public interest. This interest has been stimulated by studies of androgen production and metabolism in women, greater understanding of the biological actions of androgens, recognition of the clinical significance of androgen insufficiency, especially in surgically menopausal women, and the development and clinical testing of a variety of androgens as well as new modes of androgen administration. The use of androgens in women is controversial with ongoing concerns about efficacy and safety.

ANDROGEN PRODUCTION IN WOMEN

Although five different androgens are produced in women, testosterone is the most studied. Ovaries and adrenal glands produce about half the daily serum testosterone with the remainder derived from circulating androstenedione. Testosterone levels peak when women are in their 20s and gradually decline over the remainder of their lives. By menopause, levels are about half the levels of women in their 20s. There is no marked change in testosterone levels during the menopause transition. The post-menopausal ovary continues to produce testosterone although, by the time women are in their 60s, the androgen levels are about half the levels...
at the time of menopause. Surgically menopausal women, whose ovaries have been removed, show an immediate decrease in serum testosterone of about 50%.

Sex steroids are primarily transported in women’s bodies attached to binding globulins with only a small percent free or bioavailable for induction of cell actions. At the time of natural menopause, there is a decline in estrogen production and a significant decline in sex steroid hormone-binding globulin (SHBG). As a result, free testosterone levels rise across the menopausal transition. Oral estrogen therapies increase SHBG, leading to a fall in free testosterone levels.

**BIOLOGICAL MECHANISMS OF ANDROGEN ACTIONS**

Androgens act through specific steroid receptors, which have been identified in many tissues of the body including the liver, kidney, brain, bone, breasts, muscle, skin, cardiovascular system, and throughout the reproductive tract. Androgens are metabolized into biologically active estrogens with estradiol derived from testosterone and estrone from androstenedione. Local estrogen synthesis from androgens, in particular estradiol derived from testosterone, has been proposed as a major cellular mechanism in bone and in the brain. In addition, androgens suppress sex steroid–binding globulin. As a result, androgen administration can lead to greater availability of free estrogens and androgens.

**ANDROGEN REPLACEMENT THERAPIES**

In 2001, an international conference was held at Princeton University, and the proceedings concluded that women with low androgens did experience signs and symptoms of hormone deficiency including loss of sexual desire and decreased bone density, but these signs and symptoms could be due to estrogen deficiency. Therefore, a consensus was reached with regard to the indications for androgen therapy with three criteria to be met:

1. That clinical symptoms of androgen insufficiency are present. Symptoms include unexplained fatigue, change in sexual function including decreased sex response and desire, and a diminished sense of well-being or dysphoric mood.
2. That the symptoms are persistent despite adequate estrogen therapy.
3. That serum free testosterone levels should be at or below the lowest quartile of the reference range for women during their reproductive years.

   - Androgen therapies are available as injectables, orals with and without estrogen, subcutaneous implants, and transdermals.
**Androgen Therapy for Women**

Different routes of androgen therapy

<table>
<thead>
<tr>
<th>Method</th>
<th>Agent</th>
<th>Dosage/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injectables (IM)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nandrolone decanoate</td>
<td>25–50 mg</td>
<td>Deca-durabolin</td>
</tr>
<tr>
<td>Testosterone enanthate</td>
<td>25–50 mg</td>
<td>Delatestryl</td>
</tr>
<tr>
<td><strong>Orals (daily)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyltestosterone</td>
<td>1.25–2.5 mg</td>
<td>Estratest h.s.-Estratest</td>
</tr>
<tr>
<td>Testosterone undecanoate</td>
<td>40–80 mg</td>
<td>TU undestor</td>
</tr>
<tr>
<td><strong>Subcutaneous and transdermal</strong></td>
<td></td>
<td></td>
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<tr>
<td>Testosterone implants</td>
<td>50 mg q 6 mos</td>
<td></td>
</tr>
<tr>
<td>Transdermal patch</td>
<td>150–300 μg q3.5 d</td>
<td>Unapproved</td>
</tr>
<tr>
<td>Testosterone gel</td>
<td>1 mg/d</td>
<td>Androgel</td>
</tr>
</tbody>
</table>

*Abbreviations: IM, intramuscular; TU, testosterone undecanoate (undestor); d, day.*

Effective treatment of hot flashes with oral or injectable androgen therapy in surgically menopausal women has been reported. It is currently suggested that androgen therapy be added for women receiving estrogen therapy who have persistent vasomotor symptoms. Other symptoms evaluated in these studies, which show response to androgen plus estrogen therapy beyond that of estrogen alone, include fatigue, sleep, and mood disturbances.

Studies using androgens plus estrogens in surgically menopausal women show greater effects on bone metabolism and bone mineral density (BMD) than treatment with estrogens alone. Generally positive correlations have been observed between androgens and BMD in premenopausal women. Androgen therapy added to estrogen therapy is especially helpful for the younger women undergoing hysterectomy and oophorectomy.

Sexual dysfunctions including decreased sexual desire, decreased response, and dyspareunia have been related to estrogen deficiency and do respond to estrogen therapy. Androgen therapies are reported to be helpful for women still sexually dissatisfied after taking estrogens, and this appears to be particularly true for women after surgical menopause. Two major studies have been completed using the testosterone patch. Although the Food and Drug Advisory Committee agreed the treatment was efficacious, approval of the patch was withheld as the Committee stated that more time was needed to provide safety data. A number of unapproved androgen preparations are in current clinical use in the United States. Dehydroepiandrosterone (DHEA), reported to improve sexual function in women with adrenal insufficiency, has not been shown to improve sexual function in women with normal adrenals. DHEA is widely used as a “nutritional supplement” despite the fact that DHEA is readily metabolized to estradiol and testosterone. Inconsistency in the content and purity of DHEA products is but one of the issues in using a nonapproved preparation. Androgen
gel has been approved for treatment of male sexual dysfunction but a preparation that women can use is still unapproved in the United States although it is available elsewhere. Other testosterone preparations for female sexual dysfunction, which may or may not be approved in the future, include a gel, a lotion, a spray, and a vaginal ring. Efficacy and safety remain the outstanding issues for all of these products.

ADVERSE EFFECTS

Concerns about the safety of androgen therapy in women include cardiovascular effects, virilization, hepatotoxicity, and cancer of the breast and endometrium. A recent review of this literature concludes: “The adverse effects . . . are generally mild.”

Oral androgens, among which most studied is methyltestosterone, lower high-density lipoprotein-cholesterol. Significantly, androgens also lower total cholesterol and triglycerides and have a neutral effect on low-density lipoprotein-cholesterol. Testosterone delivered by a transdermal patch appears to be lipid neutral. Effects on endothelial function appear to be beneficial with the addition of androgen to estrogen treatment showing an increased vasodilator response and blood flow. Androgens added to estrogen in women appear to decrease viscosity coincident with a significant decline in triglycerides despite a concomitant increase in fibrinogen levels. Coagulation effects have only been determined in a single study using hormone implants. Over a two-year time period, all clotting factors were in the normal reference range. Androgens stimulate erythropoiesis. Although no case of polycythemia has been reported in studies of physiological replacement of androgens in women, monitoring of the hematocrit is recommended in women receiving androgens.

The transdermal testosterone studies have shown no changes in fasting plasma insulin or glucose levels. While these findings are encouraging, further studies of the effects of androgens on insulin resistance are needed.

Acne, hirsutism, and virilization are relatively uncommon in women receiving low-dose androgen or androgen–estrogen therapy. Transdermal patch, testosterone implant, and intramuscular testosterone studies have shown no worsening of acne or hirsutism scores. In contrast, higher scores have been reported in women taking a combination of oral esterified estrogens (1.25 mg) and methyltestosterone (2.5 mg).

Hepatotoxicity has been reported with high doses of alkylated androgens but has not been seen in any of the androgen therapy trials in women.

An adverse effect on mood leading to an increase in anger and hostile outbursts was reported by Sherwin and Gelfand in women receiving 200 mg of intramuscular testosterone enanthate. Although unreported, we also observed an increase in anger reactions in our study at Yale of oral esterified estrogens (1.25 mg) and methyltestosterone (2.5 mg).
To date, no case of endometrial cancer has been reported in postmenopausal women taking physiological doses of androgens. However, endometrial hyperplasia in women receiving estrone (E) + methyltestosterone (MT) or subcutaneous estradiol–testosterone implants has been reported.

Hyperandrogenemia has been associated with breast cancer including metastatic disease, and 50% to 90% of breast tumors contain androgen receptors. However, to date, no report has described an increase in breast cancer in women receiving physiological doses of androgen therapy. Barrett-Connor et al. obtained baseline mammograms and repeat studies at 12 and 24 months in women receiving esterified estrogens plus methyltestosterone, which showed no significant changes in the androgen group.

CONCLUSIONS

Androgen therapy has been available for women for more than 50 years. Almost all studies of androgen efficacy and safety have been in women also receiving estrogens and very few prospective, randomized clinical trials have been conducted. Nevertheless, it does appear that adding androgens to estrogen therapy can be beneficial, especially for oophorectomized women and still-symptomatic women receiving estrogen therapy. Most studied are the effects on sexual function and these support the use of androgen–estrogen therapy for sexual dysfunction in postmenopausal women. Positive effects on other symptoms including fatigue, sleep, and mood disorders and on bone density also support the use of androgen therapy as indicated. Adverse effects, a current concern, do not appear to be clinically significant in women receiving physiological doses of androgens, although more safety studies are needed.

REFERENCES


INTRODUCTORY DESCRIPTION OF THE DISORDER IN QUESTION

Menopause brings about changes in the health of a postmenopausal woman that may have a major impact in her life. Until recently, estrogens in various formulations and combinations have been used to relieve menopausal symptoms in these women (1). The loss of bone mass and osteoporotic fractures can be effectively prevented by hormonal replacement therapy (HRT). However, initial enthusiasm about long-term benefits of HRT has been brought into question with two large, prospective randomized trials, the heart and estrogen/progestin replacement study and the Women’s Health Initiative study. Long suspected risks associated with estrogen replacement in postmenopausal women including breast cancer and deep vein thrombosis were also confirmed. The conclusion is that the balance between benefits and risks of long-term HRT in healthy postmenopausal women may not be advantageous after all. There is, therefore, a need to develop new therapies related to estrogen that can ideally provide significant benefits without the negative side effects associated with the use of estrogen.
DESCRIPTION OF THE CLASSES OF DRUGS INVOLVED, AND THEIR LICENSED AND COMMERCIAL NAMES

Selective estrogen receptor modulators (SERMs) are a new class of drugs that manifest estrogen receptor (ER) agonist activity in some tissues but oppose estrogen action in others. Tamoxifen (Tamifen®, Oestrifen®, Emblon®, Fentamox®, Tamofen®, Soltamox®, and Nolvadex®) is the first SERM initially developed as an antiestrogen for treatment of advanced breast cancer and ultimately as a breast cancer preventive. Initial observation showed that tamoxifen was bone protective in rodents and did not cause skeletal deterioration in women, as would be expected of an antagonist. Subsequent placebo-controlled trials demonstrated that tamoxifen could function as an estrogen by increasing lumbar spine bone mineral density and hence reduced the incidence of hip fractures (2). The potential use of tamoxifen to treat postmenopausal osteoporosis was however hampered by the undesirable endometrial stimulation secondary to an estrogen agonist effect. Nevertheless, the beneficial effect of tamoxifen on bone mass has established the SERM concept and stimulated a new search for an ideal compound that will have a selectivity in its estrogenic actions that approaches the desired profile for long-term therapy in the postmenopausal women. Raloxifene (Evista®) emerged as a result.

BRIEF MECHANISM OF ACTION

The exact mechanism of action of SERMs is still an issue under active research. The classical model of estrogen action involves the binding of a ligand to ER-α, which then promotes the displacement of the receptor from its inhibitory complex, allows receptor dimerization, and facilitates its interaction with specific estrogen response elements located within target gene promoters. Depending on the cellular and promoter context, the DNA-bound promoter can either positively or negatively regulate target gene transcription (3). The discovery of ER-β suggested that differential affinity of ligands for each of these receptors, coupled with tissue-specific differences in their expression, could explain some of the observed, different biologic activities of the same compound in different cells.

However, the unique properties of SERMs lie in their bulky side chain, which prevents helix 12 of the ER from relocating over the ligand-binding pocket as it will if estrogen is bound. This blocking effect in turn prevents key coactivators from interacting with the receptor and thus prevents activation (4). The further difference seen between tamoxifen and raloxifene in relation to their estrogenic and antiestrogenic properties relates to the ability of the raloxifene side chain to interact closely with aminoacid 351, thus further influencing the function of the ER.
DETAILS OF WHEN AND HOW TO USE

The initial dose-finding study on raloxifene showed that daily treatment with 30, 60, or 150 mg for two years reduced biochemical markers of bone turnover and improved bone mineral density at the lumbar spine, hip, and total body as compared to placebo. The increases in bone mineral density at most sites were greatest in the group that received 150 mg raloxifene except in the total hip, where the greatest increase was in the 60 mg group (5). In the subsequent large-scale randomized–controlled trial, the multiple outcomes of raloxifene evaluation (MORE) study, the bone mineral density at the lumbar spine and hip improved by 2% to 3% and the risk of vertebral fracture was reduced by 30% to 50% after three-year daily treatment with either 60 or 120 mg raloxifene. The decreased risk was marginally greater in the women with prevalent vertebral fractures, who were in the 120 mg raloxifene group, compared with those who were in the 60 mg group. The incidence of nonvertebral fractures did not show any significant decrease. Hot flashes were more frequent with 120 mg as compared to 60 mg raloxifene group (6,7). This study established 60 mg as the optimal daily dose for prevention and treatment of postmenopausal osteoporosis, which was approved by the Food and Drug Administration in 1999. An analysis over the full four-year duration of this trial further confirmed that the bone effect was maintained. Because of the adverse effect on hot flashes, raloxifene should not be used in women in the first two years of menopause, when the perimenopausal symptoms are at their worst.

BENEFITS

Apart from the beneficial effect on bone mass, the MORE study also demonstrated a 70% reduction in the incidence of breast cancer in the raloxifene-treated group (6,7), an effect similar to that reported for tamoxifen in the Breast Cancer Prevention Trial. In the uterus, raloxifene behaves as a classic, competitive estrogen antagonist and did not cause any endometrial stimulation like that of tamoxifen. None of the women treated with raloxifene in the MORE study were found to have endometrial hyperplasia or endometrial carcinoma. The incidence of vaginal bleeding was the same in the raloxifene-treated and placebo groups. Raloxifene has been shown to lower serum low-density lipoprotein-cholesterol and serum fibrinogen. Unlike estrogen replacement, raloxifene does not induce elevation of serum triglycerides and C-reactive protein. Among women at high risk of coronary heart disease, those taking raloxifene had significantly fewer cardiovascular events and stroke (8). These findings need to be confirmed by an adequately powered randomized trial using these cardiovascular events as the primary endpoint. A large-scale study is currently underway to address this issue.
SIDE EFFECTS

The most serious adverse effect related to raloxifene is venous thromboembolic events, including deep-vein thrombosis and pulmonary embolism. The relative risk for venous thromboembolic events was approximately three, which is comparable to that reported with estrogen therapy. Hot flashes, leg cramps, and peripheral edema are the most common nonserious adverse events. The lack of estrogen in the postmenopausal years has been considered one of the causal factors for atrophy of the pelvic floor and the subsequent development of pelvic-floor relaxation. Earlier studies have indicated negative effect of two SERMs on pelvic-floor integrity and urinary incontinence. A recent evaluation of the frequency of surgery for pelvic-floor relaxation has shown that patients on raloxifene had a reduced risk for pelvic-floor surgery (9). An apparent protective effect on pelvic-floor function with raloxifene awaits further investigation.

LIMITATION AND ALTERNATIVE THERAPIES

Unlike estrogen, raloxifene does not alleviate vasomotor symptoms. On the contrary, it may aggravate hot flash, which is a very common complaint in the perimenopausal period, making it unsuitable for use in this group of women. Alternatively, perimenopausal women with vasomotor symptoms can be offered estrogen therapy or tibolone. History of thromboembolic events constitutes a contraindication for raloxifene use. The use of raloxifene in treatment of postmenopausal osteoporosis is also limited by its lack of efficacy in preventing nonvertebral fractures, making it less attractive in women with a high fracture risk. Bisphosphonates may be considered for those with previous, confirmed venous thromboembolism or osteoporotic fracture.

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INTRODUCTION

The bisphosphonates have made a major contribution to how clinicians manage osteoporosis and are regarded as first-line therapy in the treatment of osteoporosis. Their chemical structure is characterized by two phosphate groups linked through a central carbon atom, with the various members of the class distinguished by the two side chains that bind to the central carbon atom. Two classes of bisphosphonates are often distinguished on the basis of their side chains: those that contain a nitrogen atom (e.g., alendronate, risedronate, ibandronate, and zolendronate), and those that do not (e.g., etidronate and clodronate).

MECHANISM OF ACTION

The bisphosphonates act mainly by blocking bone resorption. They are deposited on the surface of bone and remain there for a considerable time, usually months to years. They become incorporated into the bone crystal as bone is remodeled and are ingested by osteoclasts when these cells resorb bone. Within the osteoclast, nitrogen-containing bisphosphonates inhibit the enzyme farnesyl diphosphate synthase, a key enzyme in the mevalonate pathway.

Bisphosphonates lead to reduction in bone turnover resulting in an increased lifetime of the bone tissue, providing a longer time in which the secondary mineralization of bone can proceed. This results in an increase
in mineral density, which may contribute to the greater strength of bisphosphonate-treated bone, as may the preservation of trabecular thickness and trabecular connectivity. Meta-analyses of clinical trials suggest that bisphosphonate-induced changes in bone mineral density (BMD) alone do not account for all the reduction in fracture risk, suggesting that other factors, such as preservation of architecture, are also important.

ALENDRONATE

Alendronate, in doses of 5 to 10 mg/day, reduces bone resorption from postmenopausal levels to values in the lower half of the premenopausal range. These changes are maximal within a few months of initiating treatment and remain stable after that time. These declines in bone resorption are accompanied by increases in BMD. In the spine, BMD increases by about 5% after three years on treatment with 5 mg/day, and by about 9% with 10 mg/day. With continuation of therapy, there is a gradual increase in BMD, reaching 14% above baseline after 10 years with 10 mg/day.

In those studies powered to assess fracture rates, alendronate has been associated with decreases in fracture rates. The phase III trial and both arms of the Fracture Intervention Trial showed an approximately 50% decrease in vertebral fractures, and the pooled estimate from all the alendronate trials was a relative of risk of vertebral fracture of 0.52 (95% CI 0.43–0.65).

There is also evidence that alendronate decreases the risk of nonvertebral fractures in women with osteoporosis. The pooled relative risk for osteoporotic women estimated by Cranney was 0.49 (95% CI 0.36–0.67).

More recent studies have demonstrated that alendronate administered once weekly (70 mg) produces the same effects on bone turnover markers and BMD as once daily therapy. However, there are no fracture data other than with daily regimens of alendronate.

RISEDRONATE

In general, the suppression of bone resorption with risedronate is slightly less than that for alendronate. This is reflected in slightly smaller increments in BMD, typically about 5% at the lumbar spine after three years of therapy and less than 3% at the hip. Despite this, risedronate reduces vertebral fractures with a pooled relative risk across all studies of 0.64 (95% CI 0.54–0.77). Osteoporotic women without prevalent fractures also have a reduced risk of vertebral fracture on risedronate. Risedronate also reduces nonvertebral fractures. When available data on nonvertebral fractures are meta-analyzed, the relative risk after treatment with risedronate is 0.73 (95% CI 0.61–0.87). Pooling of data from the risedronate studies indicates that reductions in both vertebral and nonvertebral fractures are apparent within six months of starting this drug.
In a two-year extension to one of the risedronate studies, the double-blind and original randomization was maintained. The risk of new vertebral fractures was reduced by 59% in four and five years ($p = 0.01$) compared with a 49% reduction in the first three years. Continuation of risedronate for a further two years appears to be associated with maintenance of low fracture rates. As with the long-term alendronate data, suppression of markers is maintained with long-term treatment, and BMD changes tend to increase, though at a slower rate that in the early years of treatment.

Like alendronate, risedronate is now typically used in a once-a-week dose of 35 mg, rather than the 5 mg/day on which the fracture data are based. As with alendronate, equivalence of efficacy of this dose has been demonstrated only for bone turnover and BMD and there are no fracture data other than with daily regimen.

The relationship between fracture incidence and bone resorption in the risedronate studies has recently been analyzed by Eastell et al. Analysis of the data after pooling the placebo and risedronate groups indicated that suppression of markers of bone resorption of 40% achieved maximal fracture risk reduction and further decreases in bone resorption were not associated with further reductions in fracture risk. At this point, the fracture incidence appeared to plateau. In other words, a threshold of reduction in bone resorption existed below which no further decrease in vertebral fracture risk was observed. The number of individuals reaching this level of bone turnover was relatively small, so this analysis needs to be treated with caution and repeated with other bisphosphonates to determine whether there truly is an optimal bone turnover rate in patients with postmenopausal osteoporosis.

**IBANDRONATE**

Ibandronate was first studied in osteoporosis as an intravenous injection and showed beneficial effects on BMD. However, ibandronate 1 mg intravenously every three months did not result in a reduction in fracture numbers, possibly because this regimen did not stably suppress bone resorption markers over the between dose interval and did not increase BMD as much as other potent oral bisphosphonates. However oral ibandronate, given either continuously in a dose of 2.5 mg/day or intermittently (in a dose of 20 mg every other day for the first 12 doses followed by nine weeks without active drug) produced changes in BMD comparable to those found with oral alendronate or risedronate. Both the daily and intermittent oral regimens have now been shown to reduce vertebral fractures by about half. Intravenous ibandronate 2 mg, three monthly produces similar changes in BMD but its antifracture efficacy is less clear.

**ZOLEDRONATE**

In a 12-month phase II trial involving 350 women with low BMD, participants were randomized to placebo or various zoledronate dosage regimens. Three of
these regimens involved the use of a three-month dose interval, one a six-month dose interval, and one a single annual dose at the beginning of the study. While BMD and markers of bone turnover were stable in the placebo group, these indices changed in a similar fashion in the five zoledronate groups, suggesting the regimens were therapeutically equivalent. The changes in both markers and BMD were comparable to those seen with standard daily regimens of oral bisphosphonates where there are proven antifracture efficacy. This finding suggests that annual administration of zoledronate may prevent fractures and the results of phase III trials currently underway are awaited with interest.

BISPHOSPHONATES IN THE PREVENTION OF POSTMENOPAUSAL BONE LOSS

Bisphosphonates also have positive effects on BMD in women who do not yet have osteoporosis. For example, in a study of recently menopausal women, alendronate treatment for seven years increased spine and trochanter BMD by 3% to 4%, while femoral neck BMD was maintained. A two-year study with risedronate produced similar results.

ADVERSE EVENTS

Randomized controlled trials suggest little or no increase in the risk of upper gastrointestinal problems if bisphosphonates are administered weekly compared to daily. Occasionally patients also experience muscle or bone pain, which is usually transient.

CONCLUSIONS

The bisphosphonates are considered first line in the management of osteoporosis. There is an increasing diversity of agents and regimens, and evidence for their safety and efficacy continues to accumulate. Generic formulations are becoming available and this is likely to reduce drug costs. Questions still remain as to the optimal duration of therapy, and whether excess suppression of bone turnover with currently used regimens is associated with adverse long-term outcomes.

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INTRODUCTION

Although most of the bone strength (including bone mass) is genetically determined, other nutritional, environmental, and life style factors may influence bone health. Nutrition is one of the important and modifiable factors in the accrual and maintenance of bone mass and the prevention and treatment of osteoporosis. The nutrients of most obvious importance to bone health are calcium (Ca) and phosphorus (P), since they comprise roughly 80% to 90% of the mineral content of bone. Ca is a limiting mineral because its intake is inadequate and below recommendations in women across all age groups, according to numerous population surveys in the United States, the most recent one from the National Health and Nutrition Examination Survey (NHANES) data set (1). Therefore, Ca has been studied most extensively in relation to bone health. However, other minerals and trace elements are also crucial in carrying out reactions and metabolic processes in bone but have been studied in less extent (2).

This chapter reviews Ca and some other nutritionally essential minerals and their possible role in bone health in postmenopausal women. Essential minerals comprise only around 4% of total body weight, but they play a major role in numerous physiological processes. They are commonly divided into macro and micro categories (3). Each mineral is discussed
separately; however, many are codependent and may interact not only among themselves but also with other genetic and environmental factors influencing bone health. The complexity of these interactions is probably the reason why many studies have controversial or inconsistent findings regarding the effect of a single or a group of minerals in bone health.

MACROMINERALS

Calcium

The adult human body contains about 1000 to 1500 g of Ca (depending on gender, race, and size of the body) of which 99% is found in the bones in the form of hydroxyapatite (3). Dietary Ca requirement is determined mostly by skeletal needs, and it exerts a threshold behavior.

When evaluating the effect of Ca on bone mineral density (BMD) in older women, it is important to distinguish early from late postmenopause, given the large impact of estrogen withdrawal on bone during the early menopausal period. For the most part, interventional studies conducted during the early postmenopausal period (first 5–8 years after menopause) demonstrate that the effects of supplemental Ca are relatively small and appear to be confined to cortical, rather than trabecular bone. A meta-analysis in early postmenopausal women included 49 separate, mostly cross-sectional studies (4). There was a positive correlation between BMD and Ca intake, such that for each 500 mg increase in dietary Ca, there was a 0.5% to 1% less cortical bone loss, but not trabecular. As expected, the effect was greatest when the baseline Ca intake was low, supporting the threshold hypothesis.

In general, the effect of dietary Ca on bone loss in late postmenopausal women is more pronounced than during the early postmenopausal period. There are several studies documenting an increase or maintenance in BMD in mid to late postmenopausal women when additional Ca was given either as a food or supplement. Again, the largest improvement was observed when the baseline Ca intakes were the lowest. Additionally, the combination of other bone antiresorptive agents, including estrogen and/or bisphosphonates with Ca, was shown to be more effective than either treatment alone. Conversely, it is quite clear that the bone loss observed in untreated postmenopausal women is exacerbated by Ca deficiency. Cross-sectional studies are also convincing in presenting positive association between Ca and BMD of various skeletal sites in postmenopausal women (5).

Although the increase in BMD from additional Ca intake is encouraging, the most important outcome variables are bone fractures. There are several studies showing around 30% reduction in fracture risk in postmenopausal women taking 1000 mg Ca supplement per day. In a meta-analysis of 16 observational studies of dietary Ca and hip fractures, there was a small but consistent reduction of fractures (6). The data suggest
that 1 g of dietary Ca per day is associated with a 24% reduction in the risk of a hip fracture. It needs to be noted that some of the studies were done with simultaneous vitamin D supplementation, therefore, the benefits are probably due to the combined effects.

Overall, considering both the BMD and the fracture data, most of the studies are consistent and support the public health policy for increasing Ca intake in younger and older adults. However, the discrepancy between recommendation and actual intake is apparent and persistent. Table 1 presents the current recommendation for Ca intake in the United States for women across the age groups and actual intake as surveyed recently (1).

**Magnesium**

There is approximately 25 g of magnesium (Mg) in the human body, two-thirds of which is in the skeleton and the rest in soft tissue (3). Mg deficiency alters Ca metabolism resulting in hypocalcemia and vitamin D abnormalities due to impaired parathyroid hormone (PTH) secretion (7), caused by defect in second messenger system generating cyclic adenosine monophosphate (AMP) and phospholipase C.

Epidemiological studies in premenopausal women showed positive relationship between spine and forearm BMD, as well as with the rate of
change in spine BMD and Mg intake. However, in postmenopausal women, cross-sectional and longitudinal studies are less conclusive, particularly in early postmenopausal period where acute estrogen deficiency might mask the effects of a subtle dietary factor as is Mg.

In general, the effect of Mg supplementation in humans is poorly understood because there have been only a few well-controlled clinical trials.

**Phosphorus**

As an inorganic element, phosphorus (P) is second to Ca in abundance in the human body with around 85% incorporated into the skeleton. Although P is an essential nutrient, there is concern that excessive amounts typically consumed in U.S. population (Table 1) may be detrimental to bone (8).

**Sodium**

A positive relationship between urinary sodium (Na) (reflecting Na intake) and urinary Ca excretion has been shown in animals and humans of all age groups. This interaction becomes more important when considering the trends in intakes of each; Ca intake is lower than recommendations and Na intake remains consistently high (Table 1). While the hypercalciuric effect of Na is well established, the habitual excess of Na on bone mass and fracture incidence is still unclear.

**MICROMINERALS OR TRACE ELEMENTS**

**Copper**

Deficiency of copper (Cu) is rare as Cu is present in nearly all foods. Because Cu influences collagen maturation, it could influence bone composition and structure (9).

**Iron**

Iron (Fe) may play an important role in bone formation, acting as a cofactor for enzymes involved in collagen synthesis. A recent study indicated that Ca and Fe influence on change in BMD during one year in postmenopausal women was dependent on hormone use; that is, higher Fe intake was associated with the positive change in BMD in women on hormone replacement therapy (HRT), while higher Ca intake was associated with positive change in BMD in women not on hormone replacement therapy HRT (10).

It is worth noting that Fe absorption may be inhibited by the high intakes of other minerals, particularly Ca. However, when Ca consumption occurs separately from the meal containing Fe, the effect is less clear. It is also not clear to what extent, if any, higher Ca intake might influence Fe stores in population and what would be the consequences of lower Fe stores.
on bone health. On the opposite note, Fe might act as a toxin to bone cells and contribute to osteoporosis or other bone diseases in people with impaired Fe metabolism and Fe overload.

**Zinc**

The human body contains 1 to 2 g of zinc (Zn) and it plays an important role in connective tissue metabolism, acting as a cofactor for several enzymes, such as alkaline phosphatase and collagenase (3). Zn deficiency results in impaired DNA synthesis and protein metabolism that lead to negative effects on bone formation.

**ULTRATRACE MINERALS**

**Fluoride**

Fluoride (F) occurs in minute amounts in food and water supplies and is readily absorbed in the gastrointestinal tract by passive diffusion and incorporated into the teeth and bones. Essentiality of F has not been proven. Hagenauer et al (11) evaluated 11 randomized clinical trials including 1429 patients, followed for either two or four years, and found that F treatment significantly increased spinal BMD and did not change the rate of vertebral fractures, compared with nontreatment. Additionally, the low-dose F treatment was augmented by the concurrent HRT use. The authors concluded that although F increases vertebral BMD without changing the fracture rate, it still should not be considered as a first choice for osteoporosis therapy, in view of other drugs (namely, bisphosphonates) that are shown to also reduce vertebral fractures.

**CONCLUSIONS**

Osteoporosis is a multifactorial disorder and despite the considerable influence of heredity, bone health depends on the whole range of other nutrients and foods as well as the environmental factors. Therefore, a substantial effort is being made toward understanding the effect of various nutrients on bone accretion during youth and bone loss during aging. A wealth of new knowledge is now available, and our understanding of nutrients and other components affecting bone health continues to grow.

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INTRODUCTION

Anovulation is a relatively common cause for infertility accounting for about 25% of all cases, the treatment of which is highly successful. Ovulatory disorders could be due to either hypothalamic-pituitary ovarian axis dysfunction or other endocrine diseases. Hypothalamic-pituitary ovarian anovulation is further classified into three categories including hypogonadotrophic hypogonadism [World Health Organization (WHO) Group I], normogonadotrophic anovulation (WHO Group II), and hypergonadotrophic hypogonadism (premature ovarian failure, WHO Group III). Other endocrine causes of ovulatory disorders include hyperprolactinemia, thyroid disorders, and adrenal diseases such as Cushing’s syndrome and adult onset congenital adrenal hyperplasia (CAH). By far, the most common cause of anovulatory infertility is polycystic ovarian syndrome (PCOS) (WHO Group II), which affects about 6% to 8% of women of reproductive age and accounts for approximately 80% of all cases of anovulation. It refers to a heterogeneous group of disorders with a varied combination of clinical
(obesity, oligo/amenorrhea, and hirsutism), biochemical [elevated serum concentrations of luteinizing hormone (LH) and androgens], and ultrasonographic (bilaterally enlarged polycystic ovaries) features.

Successful ovulation induction in anovulatory patients depends on accurately identifying the underlying cause of the ovulatory disorder. Several drugs are available for ovulation induction, the choice of which depends on the cause of anovulation:

1. WHO Group I (hypogonadotrophic hypogonadism): ovulation induction can be achieved with gonadotropin releasing hormone (GnRH) or gonadotropins [follicle-stimulating hormone (FSH) + LH] therapy.
2. WHO Group II (essentially PCOS): the first-line treatment for ovulation induction is clomiphene citrate (CC), which is an antiestrogen compound. Clomiphene-resistant PCOS patients can either be treated with gonadotropin: human menopausal gonadotropin (hMG) or FSH (purified or recombinant), metformin (an insulin sensitizing agent), or laparoscopic ovarian diathermy (LOD).
3. Hyperprolactinemia: ovulation induction can be achieved with dopamine agonists such as bromocriptine or cabergoline.
4. In other endocrine disorders, ovulation induction could be achieved by correcting the underlying endocrine dysfunction. For instance, in adult onset CAH, the use of a small dose of corticosteroid such as dexamethasone will result in ovulation.

In this chapter, the various classes of oral drugs used for ovulation induction will be described. Their mechanism of action, indications, method of administration, benefits, side effects and limitations, and alternative therapies will be discussed.

CLOMIPHENE CITRATE

CC is an antiestrogenic compound that is licensed for the treatment of anovulatory infertility. The simplicity of use, low cost, and relative safety made CC the first choice drug for ovulation induction. Since its introduction in 1967, it has been the most extensively used drug for treatment of infertility. It is mainly used for ovulation induction in infertile women with normogonadotropic anovulation (WHO Group II). Most of these women have PCOS. CC can achieve an ovulation rate of about 75% and a pregnancy rate of 40%.

Pharmacology

CC is a nonsteroidal synthetic estrogen, known as triphenylchloroethylene, which is a derivative of triphenylethylene. It is related to the synthetic estrogen, diethylstilboestrol, and is known for its antiestrogenic and weak estrogenic properties. Commercially, clomiphene is used as a racemic
mixture of two stereoisomers, enclomiphene (about 60%) and zuclomiphene (about 40%), which exhibit different estrogenic and antiestrogenic activities. In addition, there are differences between the two isomers in their biological half-lives with a faster absorption and elimination of the enclomiphene than the zuclomiphene. This results in accumulation of the zu isomer after repeated administration of the drug in consecutive cycles. When given orally, clomiphene is readily absorbed from the gastrointestinal tract, metabolized in the liver, and excreted slowly through the intestines in the feces. Clomiphene is known for its long duration of action with a half-life of five days, although it continues to be excreted in the feces for up to six weeks. This may explain why patients on CC may continue to ovulate regularly after discontinuation of the drug, due to its residual effects.

**Mechanism of Action**

CC exerts its antiestrogenic actions by competing with endogenous estrogens (mainly estradiol) for binding to the estrogenic receptor in the nucleus. Clomiphene also exerts a weak estrogenic activity by binding to the same receptors. In normal circumstances, in the presence of estrogen, clomiphene acts mainly as an antiestrogenic compound, while in estrogen-deficient conditions, clomiphene exerts mainly estrogenic activity.

By binding to the estrogen receptors at the hypothalamic-pituitary system, clomiphene blocks the negative feedback effect of estradiol on GnRH secretion thus resulting in an increase in the GnRH pulse amplitude. Increased GnRH pulsatility results in an increased gonadotropin secretion from the pituitary. The resultant increase of the FSH stimulus to the ovary triggers an ovulatory cycle. Binding of clomiphene to the estrogenic receptor is a long-lasting event that blocks both the negative and the positive feedback effect of estrogen on gonadotropin secretion. However, once a threshold level of the circulating estrogen has been exceeded during the follicular phase, a positive feedback effect will be resumed allowing an LH surge to occur.

Clomiphene has also been shown to exert antiestrogenic activity in other estrogen-dependent tissues, including the ovary, uterus, and vaginal mucosa via the same mechanism. This unwanted effect of CC may explain the discrepancy between the high ovulation and the low pregnancy rates achieved with this treatment. It may also explain why the pregnancy rates decrease with the higher doses of clomiphene due to the increased antiestrogenic activity. The prolonged antiestrogenic effects of CC on the uterus result in delayed endometrial maturation, poor quality cervical mucus, and alteration in uterine blood flow.

**When to Use CC**

CC is used in the treatment of infertility in the following situations: anovulatory infertility, luteal phase defects (LPDs), and unexplained infertility.
CC may also be used with intrauterine insemination (IUI) to improve pregnancy rates in unexplained infertility. Clomiphene has been given in conjunction with gonadotropins in in-vitro fertilization (IVF) programs. However, recently the use of CC in IVF has been abandoned.

Anovulatory Infertility

CC is mainly used for ovulation induction in infertile women with normogonadotropic, normoestrogenic, and normoprolactinemic anovulation (WHO Group II). The majority of women in this group have PCOS. This group also includes anovulation associated with obesity. As stated above, clomiphene acts as an antiestrogen only in the presence of normal circulating estrogen, and is therefore not suitable for women with hypogonadotropic hypogonadism (WHO Group II) who are estrogen deficient.

Luteal Phase Defects

LPD has been the subject of much debate among specialists in the field of reproductive endocrinology. The inadequate secretory transformation of the endometrium, resulting from deficient progesterone production due to a defective corpus luteum, has been implicated in both infertility and recurrent pregnancy loss. Possible causes of LPD include hypothalamic pituitary dysfunction (resulting in abnormal follicular development or abnormal luteinization), thyroid dysfunction, and hyperprolactinemia. The true incidence of LPD is unknown, previous studies have reported variable incidences: 3% to 20% of infertile patients, 5% to 60% of patients experiencing recurrent pregnancy loss, and 6% to 10% of fertile women. Clinically, LPD is characterized by short menstrual cycles ($\leq$26 days) or premenstrual spotting. Basal body temperature chart may show a luteal phase of less than 11 days in women with LPD. The diagnosis could accurately be made by taking an endometrial sample in the mid-luteal phase for histologic dating. The endometrium that lags behind the date of actual endometrial sampling by three days is said to be diagnostic of LPD. CC may correct LPD by improving folliculogenesis and the resultant luteal phase following ovulation.

Unexplained Infertility

Unexplained infertility accounts for about 20% of all cases of infertility. A diagnosis of unexplained infertility is made when the routine investigations of the subfertile couple, including semen analysis and tests for ovulation and tubal patency, yield normal results. Current evidence indicates that treatment with CC in women with unexplained infertility may increase the chance of pregnancy, but this should be balanced by the risk of multiple pregnancy (NICE, 2004). Recent research has shown that CC treatment in women with regular ovulatory cycles leads to recruitment of additional follicles, thus
increasing the number of preovulatory follicles available to ovulate at the time of LH surge. However, the relationship between the number of preovulatory follicles and the probability of conception remains to be elucidated.

**How to Use CC**

CC is given for five days in the early follicular phase usually starting any day between day 2 and 5 after a spontaneous menstrual period or withdrawal bleeding induced by progestogen administration. Starting the treatment on day 2 is preferred as it allows ovulation to occur earlier, which is closer to the physiological cycle. Ovulation occurs 5 to 10 days after finishing CC. The usual starting daily dose of CC is 50 mg. Higher doses are not recommended at the beginning because most of the pregnancies (~50%) occur at a dose of 50 mg. Furthermore, higher doses of CC may be associated with increased antiestrogenic effects on the genital tract, which may reduce the probability of pregnancy. In rare cases, if the patient overresponds to 50 mg (as indicated by multiple follicular development on ultrasound scan or a previous history of ovarian hyperstimulation), the dose could be reduced to 25 mg. If the patient does not respond to the starting dose, as indicated by a mid-luteal phase progesterone level, the dose is increased in a stepwise manner by 50 mg every cycle up to a maximum daily dose of 150 mg. In some cases, the response to CC is inconsistent with intermittent ovulation, in which case the dose should be increased to the next level. Doses higher than 150 mg are not recommended as conception only occurs rarely at these high doses. In addition, the incidence and severity of side effects increase with high doses of CC. Once ovulation is achieved on a certain dose, treatment is continued with that dose for 6 to 12 months. Provided that all other subfertility factors have been excluded, the cumulative conception rate with CC continues to increase until it reaches a plateau at treatment cycle 12. Prolonging clomiphene treatment beyond 12 cycles has been linked with an increased risk of borderline or invasive ovarian tumor. It is therefore advisable to limit CC to 12 cycles. Clomiphene should be discontinued if it fails to induce ovulation on the maximum dose “CC-resistance” or if it fails to achieve pregnancy after 6 to 12 cycles despite ovulation “CC failure.”

It is recommended that patients receiving CC should be monitored for follicular development with serial pelvic ultrasound scans at least in their first cycle of treatment. This is essential to exclude multifollicular development and to minimize the risk of multiple pregnancies. If multifollicular development is detected, then the couple should be advised to avoid intercourse and a lower dose of CC is given in the following cycle. Pelvic ultrasonography also allows accurate determination of the timing of ovulation, which could help in correct timing of intercourse. However, these benefits of pelvic ultrasonography should be weighed against the disadvantage of complicating an otherwise simple treatment, which could add to the stress of the infertile couple. If mono-ovulation is confirmed, then further CC cycles could just be monitored.
with a mid-luteal phase serum progesterone concentration. A progesterone level of greater than or equal to 25 nmol/L is indicative of ovulation.

Who Will Benefit from Clomiphene?

Ovulation

It is now well established that obesity increases ovarian resistance to CC. It is therefore universally agreed that women with elevated body mass index (BMI) (>30 kg/m²) should first be advised to undergo a weight loss program for six months before commencing CC treatment. This represents a major challenge to many clinicians because only a small minority of obese women manages to achieve a significant weight loss. Consideration should be given to other weight-reducing measures such as the lipase inhibitor orlistat or minimally invasive stomach surgery especially in morbidly obese women. In obese PCOS women, metformin (an insulin sensitizing agent) is increasingly used in many centers to help these women to reduce weight, although its effectiveness remains to be established. Other factors that may reduce the sensitivity of the ovary to CC include amenorrhea, marked hyperandrogenemia, and insulin resistance, which are frequently found in PCOS. However, further research is required to evaluate the importance of these factors in determining sensitivity to CC.

Conception

Once ovulation has been achieved with CC, the above factors do not seem to have any impact on the chances of conception. Age and duration of infertility are the most important factors determining the chances of conception. The younger the patient and the shorter the duration of her infertility, the higher are her chances of conceiving. Other important factors determining the probability of pregnancy are the dose and duration of CC. As stated above, most pregnancies (50%) occur with CC 50 mg and only about 10% occur with 150 mg. In properly selected patients, extending duration of CC treatment increases the cumulative pregnancy rates from 60% at six months to 90% at 12 months. It is therefore recommended that CC treatment should be extended beyond six months (up to 12 months) in women who are more likely to conceive before turning to more complicated treatment options. On the other hand, those who are less likely to conceive on CC (older patients, with longer duration of infertility and those on high dose CC) could receive a short course of CC.

Another factor that may affect the chances of conception in women who ovulated on CC is the pretreatment serum concentration of LH. Women with high LH levels are more likely to conceive than those with normal levels.

Clinical Outcomes of CC Treatment

CC induces ovulation in the majority of anovulatory patients belonging to WHO group II, with an ovulation rate of up to 80%, but the pregnancy
rate is much lower (about 40%). This discrepancy between ovulation and conception rates during clomiphene treatment has been attributed to its antiestrogenic mechanism of action, which has a negative effect on the quality and quantity of cervical mucus and on endometrial development. The lower-than-expected conception rate may also be related to other factors that are known to reduce the chances of pregnancy such as age and duration of infertility (see above).

The overall incidence of miscarriage in women conceiving on CC is about 20% (17–23%), which is not significantly higher than that (15%) of the general population. However, miscarriage rates of up to 40% have been reported in PCOS women conceiving with the help of CC. This is possibly due to the high serum levels of androgens and/or LH, which are commonly found in this condition.

The incidence of multiple pregnancies after CC treatment is 7% to 10%, mostly twins. Although rare with CC (<0.5%), triplets and higher order pregnancies occurred more after this treatment than after IVF.

**Side Effects/Safety**

**Ovarian hyperstimulation syndrome:** Ovarian hyperstimulation syndrome (OHSS) is rare with CC treatment, affecting less than 5% of cases and usually occurs in the mild form. It occurs a few days after consuming CC tablets and is characterized by some abdominal distension and discomfort, nausea, and diarrhea. The ovaries may enlarge up to 12 cm.

**Other Side Effects**

The most common side effects of CC are hot flushes, which occur in about 10% of cases. Other less common side effects include ovarian enlargement and cyst formation, abdominal discomfort, nausea, vomiting, breast tenderness, headache, intermenstrual spotting, menorrhagia, weight gain, rashes, and reversible hair loss. Central nervous system disturbances include dizziness, nervous tension, vertigo, insomnia, depression, and convulsions. Other rare but serious side effects are visual disturbances, which indicate the withdrawal of treatment. These include halos and steaks around light, blurring, and scotoma. These visual effects disappear in one to two weeks leaving no permanent eye damage.

**Teratogenicity:** The incidence of birth defects in pregnancies induced by CC is no different from that in the normal population. It is unlikely that a residual effect of a short duration treatment can adversely affect the pregnancy. However, clomiphene should be withheld if there is any possibility of pregnancy.

**Ovarian cancer:** Earlier reports indicated a small increase in the risk of ovarian cancer in later life of women receiving CC for more than one year. However, more recent data suggest that this increased risk is related to
infertility rather than the use of ovulation-inducing drugs. Therefore, the increased risk of ovarian carcinoma in the long term, in women receiving CC, is still open to debate. However, discussion about this matter should be included in counseling of women before starting treatment with clomiphene.

Alternative Therapies

CC complications: In women who develop significant side effects to clomiphene, e.g., visual disturbances, depression, or OHSS, an alternative treatment could be tamoxifen. This is an antiestrogen and is generally considered to increase fertility rates in a similar way to clomiphene. In contrast to clomiphene, however, tamoxifen does not increase follicular phase FSH and LH levels. It has, therefore, been postulated that tamoxifen improves follicular development by direct action on the ovary rather than through the hypothalamic-pituitary axis. It is usually given for six days in the early follicular phase usually starting from menstrual cycle day 2 to 7. The usual starting daily dose of tamoxifen is 20 mg, which can be increased to 40 mg if there is no response. When used for short periods, tamoxifen does not appear to be associated with any increased risk of either ovarian or endometrial malignancy. Early studies indicated similar success rates between tamoxifen and clomiphene. Tamoxifen may therefore prove to be an effective alternative when clomiphene fails to achieve ovulation or pregnancy. Some authorities have recommended tamoxifen as their first choice for women with PCOS. The argument has been that PCOS is associated with relatively high levels of LH and this seems to reduce the chance of conception and increase the chance of miscarriage. Unlike clomiphene, tamoxifen does not further increase LH levels.

CC resistance (failure to induce ovulation): All clomiphene-resistant patients who are overweight or obese should be advised to lose weight through lifestyle measures. It is well established that weight reduction in overweight women restores responsiveness to clomiphene possibly by improving insulin sensitivity. Once the targeted weight has been achieved, clomiphene can be restarted.

For nonobese non-PCOS women who are resistant to CC, the only alternative is gonadotropin ovarian stimulation. On the other hand, clomiphene-resistant PCOS patients could be offered LOD, metformin therapy (an insulin sensitizing agent) or gonadotropin injections (hMG or FSH).

Currently, LOD is widely accepted worldwide in many centers as the treatment of choice for clomiphene-resistant PCOS patients. High ovulation (>75%) and pregnancy (~60%) rates have been reported following this treatment. In addition, LOD has also been shown to render the ovaries more sensitive to clomiphene.

Another effective medical alternative in clomiphene-resistant PCOS women is gonadotropin therapy. Three preparations are used, including
hMG, purified FSH, and recombinant FSH. The commonly used regimen in PCOS patients is the low-dose step-up protocol, which has the advantage of reducing the risks of OHSS and multiple pregnancy, which are known to be more common in PCOS.

Many authors have recommended LOD in preference to gonadotropin therapy as a second-line treatment for clomiphene-resistant PCOS patients. LOD is at least as effective as gonadotropins for induction of ovulation in CC-resistant patients. It offers a number of advantages over gonadotropin therapy. It is less costly and does not require intensive monitoring and a single treatment leads to repeated physiological ovulatory cycles and potentially repeated pregnancies without the stress of frequent hospital visits and timed intercourse. Furthermore, it avoids the complications associated with gonadotropin treatment including OHSS and multiple pregnancies and reduces the risk of miscarriage. The main drawback of LOD is the need for general anesthetic and surgery. Other complications, such as adhesion formation and premature ovarian failure, are rare and appear to be of little clinical significance.

Recently, there has been a growing body of evidence indicating that insulin-sensitizing drugs such as the biguanide metformin may be effective, either solely or as an adjuvant to clomiphene, in inducing ovulation in PCOS patients, especially the overweight patients. Metformin acts by increasing insulin sensitivity and its administration has been shown to reduce the fasting serum insulin levels and thereby reducing the serum androgen concentrations. The current data suggest that metformin can induce ovulation or restore the ovulatory responsiveness to CC in about 50% of overweight/obese PCOS women. In addition, metformin may have the advantage of reducing the multiple pregnancy rates and OHSS. More recent data have shown that metformin may be superior to LOD in clomiphene-resistant PCOS women achieving better reproductive outcome. However, these data are in conflict with many other studies, which have shown more favorable outcome with LOD. Therefore, the exact role and effectiveness of metformin in PCOS women remain uncertain until the results of further larger trials become available.

**CC failure (failure to achieve pregnancy despite ovulation):** Anovulatory women who ovulate with clomiphene but fail to conceive after six cycles of treatment could be offered clomiphene-stimulated IUI (NICE, 2004). An alternative approach could be gonadotropin-stimulated IUI. In addition to these two options, PCOS women could also be offered LOD or metformin. In these cases, LOD allows the patient to ovulate spontaneously and avoids the antiestrrogenic effect of clomiphene on the genital tract. Also, LOD avoids the possible abnormal hormonal response to clomiphene (abnormally high levels of mid-follicular LH with premature luteinization), which may be responsible for clomiphene failure.
CONCLUSION

CC remains the standard first-line treatment for ovulation induction in infertile women with WHO group II anovulation/oligo-ovulation owing to its simplicity of use, low cost, relative safety, and efficacy. In properly selected patients, high ovulation and pregnancy rates could be achieved. The main factors that reduce the ovarian responsiveness to clomiphene are elevated BMI, hyperandrogenemia, and insulin resistance, while factors that reduce the chances of conception in clomiphene responders are older age of patients, long duration of infertility, short duration of treatment, and higher doses of clomiphene. Further research is needed to evaluate the use of CC in assisted reproduction. Clinical trials are also required to compare clomiphene with metformin and LOD. Such trials will lead to proper selection of patients for each treatment, which will lead to new approaches that will optimize the reproductive outcome of ovulation induction.

METFORMIN

A link between insulin resistance and PCOS has been well established and is thought to play a central role in the pathophysiology of this syndrome. The associated hyperinsulinemia may directly promote ovarian androgen secretion and abnormal follicular development, which ultimately leads to ovarian dysfunction. This link between insulin resistance and PCOS led many authors to consider insulin sensitizing agents for the management of this syndrome. These agents, which have been used for many years in Type 2 diabetes, have recently been increasingly used worldwide in women with PCOS. The most commonly used agent in clinical practice is metformin, which is the only currently available biguanide drug. Other agents include the thiazolidinedione group of drugs, of which the most widely used is troglitazone. However, hepatotoxicity of this drug has led to its withdrawal. Newer agents are now available, including rosiglitazone (Avandia®), pioglitazone (Actos®) and d-chiro-inositol. Although several reports have recorded a wide range of benefits in metabolic, reproductive, and clinical measures, the exact role of these agents in the management of PCOS remain to be determined.

Pharmacology

The chemical name of biguanide is imidodicarbonimidic diamide and of metformin hydrochloride is N,N-Dimethyl-biguanide hydrochloride; chemical formula C4H11N5 (Fig. 1). The tablets contain 500, 850, or 1000 mg of metformin hydrochloride.

Pharmacokinetics

The absolute bioavailability of metformin given under fasting conditions is approximately 50% to 60%. Food decreases or slightly delays absorption of metformin. Studies have shown a lack of dose proportionality with increasing
doses, which is due to decreased absorption rather than an alteration in elimination. Metformin is negligibly bound to plasma proteins. At the usual clinical doses, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally less than 1 mg/mL and do not exceed 5 mg/mL, even at maximum doses. Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours with a half-life of approximately 17 hours. In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance. There are no differences between pharmacokinetics of metformin between patients with Type 2 diabetes and normal subjects.

**Mechanism of Action**

Despite its therapeutic benefits in PCOS, the mechanism of action of metformin in women with this syndrome remains uncertain. It improves insulin sensitivity by increasing peripheral glucose uptake in response to insulin at postreceptor level. This in turn results in correction of the associated hyperinsulinemia, which is responsible for the hypersecretion of ovarian androgens. In theory, the resulting decrease in androgen production improves the intraovarian microenvironment, which leads to normalization of ovarian follicular development. Metformin does not cause hyperinsulinemia and is therefore not associated with hypoglycemia. However, hypoglycemia could occur when caloric intake is deficient or when strenuous exercise is not compensated by caloric supplementation.

In women with Type 2 diabetes, metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and reduces adipose-tissue lipolysis. It is not known whether these effects occur in nondiabetic women.

**When to Use Metformin**

Although metformin is gaining increasing acceptance worldwide for use in women with PCOS, its exact role in this syndrome remains to be established.
The most common indication for metformin in PCOS is to induce ovulation in women seeking fertility treatment. Most gynecologists reserve metformin use to CC-resistant PCOS women; although an increasing number of reproductive medicine specialists use metformin as a first-line treatment for ovulation induction in overweight/obese PCOS women. If ovulation is not achieved after three months of metformin therapy, CC could be added.

The role of metformin in PCOS women undergoing IVF is unclear, although, some recent research has shown that the short-term use of metformin during IVF treatment may improve the pregnancy rates and reduce the risk of miscarriage and OHSS.

With respect to pregnancy, metformin is a category B agent, i.e., there is no evidence of animal or human fetal toxicity or teratogenicity. Current practice of most gynecologists is to stop metformin treatment once pregnancy has been established. Some preliminary research has suggested that metformin is safe during pregnancy and may have the benefit of reducing the risks of miscarriage and gestational diabetes.

Other potential uses of metformin in PCOS include androgenic symptoms (acne and/or hirsutism), obesity, and menstrual irregularities. Currently, there is no enough evidence to support a clinically significant effect of metformin on hirsutism/acne, and this drug should not be considered as first choice treatment for hyperandrogenism until more definitive evidence is available. Metformin is also increasingly used for PCOS women presenting with obesity. Current evidence suggests a small reduction (about 4%) in body weight after metformin treatment. As far as menstrual irregularity is concerned, combined oral contraceptives (COCs) remain the first choice to regulate cycles in PCOS women. However, metformin may be a useful alternative in PCOS women who are not able to take the COC either due to contraindication (e.g., obesity and high cardiovascular risk) or if they experience significant side effects to COC. In addition, COCs are known to exacerbate insulin resistance, which is common in PCOS. Although, the clinical relevance of this remains uncertain, this may make metformin a better option for PCOS women who present with menstrual irregularities.

**How to Use Metformin**

The effective dose range of metformin in women with PCOS remains to be determined. In current practice, there is no fixed dosage regimen for the management of patients with anovulatory PCOS with metformin. The dosage should be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose of 2550 mg. Metformin should be given in divided doses with meals. It should be started at a low dose, with gradual dose escalation, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required to achieve the desired effect, e.g., regular ovulatory cycles. The usual starting
The dose of metformin is 500 mg twice a day or 850 mg once a day, given with meals. Dosage increases should be made in increments of 500 mg weekly or 850 mg every two weeks, up to a total of 2550 mg per day, given in divided doses. Patients can also be titrated from 500 mg twice a day to 850 mg twice a day after two weeks. Doses above 2000 mg may be better tolerated given three times a day with meals. Overweight/obese women receiving metformin should be strongly encouraged to reduce weight through dieting and exercising. Patients should also be warned against excessive alcohol intake while receiving metformin because this could precipitate lactic acidosis (vide infra).

PCOS women receiving metformin should be monitored for gastrointestinal side effects and for achievement of the desired effect. Ovulation could be determined by keeping a record of the menstrual periods and by measuring the serum concentration of progesterone in the mid-luteal phase. If after three months of treatment, ovulation is not achieved, consideration should be given to increasing the dose of metformin (not exceeding the maximum dose), adding CC or changing to an alternative therapy. If metformin is to be given for a long duration (>1 year), initial and periodic monitoring of renal and hepatic functions should also be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, Vitamin B12 deficiency should be excluded.

Who Will Benefit from Metformin?

Very little is known about this important issue. Theoretically, metformin is expected to give the best results in PCOS women who are insulin resistant. However, literature data on this subject are conflicting. While some studies have shown better results in women with higher body mass index and plasma insulin concentration, others found that these parameters could not predict the response to metformin treatment. Therefore, the use of metformin should not be limited to a specific subgroup of PCOS women until further evidence is available on the impact of insulin resistance on the response to treatment.

Clinical Outcomes of Metformin Treatment

The exact success rates of metformin remain to be established. Most of the studies reported ovulation rates between 30% and 45% when using metformin alone; although more recent reports revealed higher ovulation (50–60%) and pregnancy (70%) rates with a miscarriage rate of about 15%.

Contraindications

Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast
materials such as intravenous (IV) urogram, IV cholangiography, angiography, and computed tomography scans with intravascular contrast materials. Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. It should be discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been reevaluated and found to be normal. Similarly, metformin therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient’s oral intake has resumed and renal function has been evaluated as normal. Other contraindications to the use of metformin include renal dysfunction, hepatic impairment, congestive heart failure requiring pharmacologic treatment, and known hypersensitivity to metformin hydrochloride. Impaired hepatic function has been associated with some cases of lactic acidosis, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

**Side Effects/Safety**

The most common adverse reactions (>5.0%) reported during metformin therapy include diarrhea (~50%), nausea/vomiting (~25%), flatulence (12%), asthenia (9%), indigestion (7%), abdominal discomfort (6%), and headache (5%). Diarrhea could lead to discontinuation of therapy in about 5% of patients treated with metformin. In addition, other less common adverse reactions occurring in less than 5% of patients receiving metformin include abnormal stools, hypoglycemia, myalgia, lightheadedness, dyspnea, nail disorder, rash, increased sweating, taste disorder, chest discomfort, chills, flu syndrome, flushing, and palpitation.

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation; when it occurs, it is fatal in approximately 50% of cases. The reported incidence of lactic acidosis during metformin therapy is very low (0.003%). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Excessive alcohol intake is also known to potentiate the effects of metformin hydrochloride on lactate metabolism.

The onset of lactic acidosis is often subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be
associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

CONCLUSION
Currently, metformin is increasingly used worldwide for ovulation induction in PCOS women seeking fertility treatment who are overweight and/or resistant to CC. It is usually started at a low dose, with gradual dose increments up to a maximum daily dose of 2550 mg, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required to achieve the desired effect. Further research is required to establish the exact role and the effective dose range of metformin in PCOS women.

AROMATASE INHIBITORS
Aromatase inhibitors have recently been investigated as potential alternatives to CC for induction of ovulation in patients with WHO group II anovulation. Letrozole [4,4′-(1H-1, 2, 4-triazol-1-ylmethylene)-bis-benzonitrile] is a specific, reversible, nonsteroidal aromatase inhibitor that reduces the estrogen produced by peripheral androgen aromatization. It is currently administered orally to postmenopausal patients with advanced breast cancer to suppress estrogen production. The disposition of letrozole is characterized by steady-state plasma concentrations in four to eight hours and a half-life of approximately 45 hours. The absolute systemic bioavailability of letrozole after oral administration is 100% compared with the same dose given intravenously.

It has been hypothesized that letrozole administration in the early follicular phase of the menstrual cycle would release the pituitary/hypothalamic axis from estrogenic negative feedback, similar to the effect of CC. The subsequent increase in gonadotropin secretion could trigger ovarian follicle development.

Theoretically, letrozole offers several advantages over CC. In contrast to CC, letrozole does not cause estrogen receptor downregulation. Letrozole treatment could therefore avoid the antiestrogenic adverse effects known to occur with CC on the quality and quantity of cervical mucus and on endometrial development. Consequently, letrozole treatment may overcome the problems associated with CC treatment including a discrepancy between ovulation and conception rates and a higher-than-expected incidence of miscarriage in conception cycles. In addition, unlike CC, which accumulates in the body because of its long half-life, letrozole is eliminated from the body rapidly. The rapid elimination and reversibility of letrozole may allow the endometrium to respond well to rising estrogen levels in the late follicular
phase. Some preliminary studies have shown the endometrium to be of adequate thickness during letrozole treatment supporting the notion that letrozole has no direct antiestrogenic effects on the endometrium. More recently, some preliminary data suggested that letrozole is associated with a significantly lower rate of multiple gestation compared with CC.

Letrozole has been used either as a single agent or as an adjuvant to FSH therapy in a daily dose of 2.5, 5, or 7 mg; although the optimal dose remains unknown. Side effects of letrozole are not common and include gastrointestinal disturbance, asthenia (fatigue), hot flushes, headache, and back pain. It has a wide therapeutic index (difference between therapeutic and toxic dosage is large).

Currently, only very limited clinical data are available on the use of letrozole. Therefore, letrozole cannot be recommended for use in clinical practice until further evidence from adequately designed clinical trials on its effectiveness and safety becomes available.

REFERENCES

INTRODUCTION

In the case of assisted reproductive techniques namely, stimulated intrauterine insemination (SIUI) and in vitro fertilization (IVF), the aim of gonadotropin therapy is to completely override the endogenous feedback mechanisms and induce multifollicular rather than monofollicular growth. The key to this is maintaining a subthreshold level of gonadotropins during the time of follicular recruitment thus overriding the process of selection of a single dominant follicle. Patients undergoing multifollicular stimulation for IVF or intracytoplasmic sperm injection (ICSI) also receive a concomitant gonadotropin-releasing hormone (GnRH) agonist, or more recently antagonist to block endogenous leutininising hormone (LH) production and LH surges. Finally when an appropriate follicular size is observed on ultrasound monitoring, final maturation of the follicles is achieved with exogenous human chorionic gonadotropin (hCG) administration. Detailed discussion of the use of gonadotropins in SIUI and IVF follows below.
IN VITRO FERTILIZATION

Which Gonadotropin to Use?

There is much debate over this subject, and individual centers frequently have strong preference for urinary (u) or recombinant (r) follicular stimulating hormone (FSH) preparations. In a randomised, controlled trial Ng et al. (1) found that human menopausal gonadotropin (HMG) was as good as recombinant human FSH in terms of oocyte and embryo quality. Similarly Dickey et al. (2) found the efficacy of purified urinary FSH to be equivalent to that of follitropin beta.

On the other hand, a recent meta-analysis by van Wely et al. (3) found that compared to r-FSH, the use of HMG results in a higher clinical pregnancy rate when used in a long protocol IVF/ICSI cycle. There was no difference between the two preparations in number of oocytes retrieved, miscarriage rate, or multiple pregnancy rate. In contrast, another meta-analysis by Daya et al. (4) showed that r-FSH produced higher pregnancy rates per cycle than u-FSH and the total gonadotropin dose required was lower.

However r-FSH does have a higher cost per ampoule than u-FSH, and until this issue is resolved with more studies, factors such as drug availability and cost effectiveness should govern the decision on which type of gonadotropin to give. The conclusion of the U.K. National Institute for Clinical Excellence review of treatments for infertile couples (5) was that:

Human menopausal gonadotropin, u-FSH and r-FSH are equally effective in achieving a live birth when used following pituitary down-regulation as part of IVF treatment. Consideration should be given to minimizing cost when prescribing.

What Regimen of Gonadotropins?

The main protocols for administration of gonadotropins in an IVF/ICSI cycle are the following:

1. Long protocol: Involves the use of a GnRH agonist for initial downregulation of the pituitary followed by administration of gonadotropins for follicular stimulation. The GnRH agonist is started usually in the luteal phase of the cycle preceding the IVF cycle.
2. Short protocol: This protocol is especially suited for poor responders to the long protocol and involves the use of a GnRH agonist to produce an initial flare of endogenous gonadotropins, followed by further stimulation with exogenous gonadotropins. The GnRH agonist is started in the early follicular phase of the stimulation protocol. The initial flare of LH increases the androsterone substrate available for conversion to estradiol by the granulosa cells and therefore results in higher estrogen levels. Continued
administration of the GnRH agonist during the stimulation cycle serves to prevent any premature LH surge from occurring.

3. GnRH antagonist protocol: GnRH antagonists offer an alternative approach to the management of superovulation in assisted conception. They produce a more acute and profound suppression of LH production than agonists. Accordingly in this protocol, endogenous LH production is achieved by administration of a GnRH antagonist after starting ovarian stimulation (usually day 6 of stimulation). According to a Cochrane review of agonist versus antagonist protocols, pregnancy rates are slightly lower with antagonist protocols (6). Antagonist protocols have identified several problems concerning patients scheduling and timing for ovum pick up, and require greater flexibility on the part of the IVF unit, with a need for six (or even seven) day working patterns and altered monitoring schedules (7). However, antagonist regimes are quicker than “long protocol” agonist regimes, and possibly carry a lower risk of ovarian hyperstimulation syndrome (OHSS). The initial two to three weeks of pituitary downregulation involved in the long protocol produce side effects of menopause, which are distressing to many women, and may discourage further attempts at IVF.

**Indications for LH Supplementation in IVF Protocols**

Excessive pituitary suppression in stimulation protocols is associated with adverse outcomes regarding the achieved pregnancy rates and higher rate of miscarriage. This is particularly important in patients with hypogonadotropic hypogonadism. In normogonadotropic patients however, pituitary downregulation will not result in absolute endogenous gonadotropin deficiency and as less than 1% of LH receptors need to be occupied to achieve a reasonable steroidogenic response, additional LH is not necessary in these patients (8). The general consensus is that endogenous LH levels should be 0.5–1.5 IU in long-term protocol situations.

**Factors Determining the Response to Gonadotropins in IVF Cycles**

1. Age
2. Basal level of FSH
3. Number of antral follicles
4. Body mass index.

These factors may be responsible for the variable response between patients and should be taken into consideration when choosing the dose and protocol for gonadotropin stimulation.

**Dose of FSH/IVF for IVF Cycles**

For patients below 40 years of age, the starting dose for stimulation lies in the range of 100–250 IU/day, with a trend toward use of lower doses of
gonadotropins to reduce risk of OHSS. Although higher doses are frequently given to older patients, the evidence that this practice is associated with higher pregnancy rates is unconvincing.

The Role of HCG/IVF Cycles

hCG is given to induce final follicular maturation in a dose of 5000–10,000 IU. Recent data suggest that Recombinant Human (rh)-LH may be an effective alternative to hCG in inducing follicular maturation and luteinization, while having the advantage of a lower risk of OHSS. A dose of recombinant LH between 15,000 and 30,000 IU has been found to be effective (9,10).

Gonadotropins and IUI

During the process of intrauterine insemination (IUI), timing is of the essence because the cervical factor is bypassed and this is greatly facilitated with the use of gonadotropins followed by hCG to stimulate ovulation.

Gonadotropins can be used in conjunction with IUI in the following situations:

1. To induce superovulation (growth of two to three follicles) in patients with unexplained infertility, mild-to-moderate male factor, and cervical factor of infertility.
2. To induce monofollicular development in anovulatory patients such as Polycystic Ovarian Syndrome (PCOS) or hypogonadotropic hypogonadism.

Which Gonadotropin to Use?

Gerli et al. (11) compared u-FSH to r-FSH during ovulation stimulation with IUI in PCOS patients. They found that u-FSH and r-FSH demonstrated the same effectiveness; however, the urinary preparation was more cost-effective due to the lower cost per IU.

Which Regimen of Gonadotropins to Use?

In cases of induction of monofollicular follicular growth, the usual protocol is a low dose step up protocol without pituitary downregulation. In cases where superovulation is needed such as in cases of unexplained infertility, a step-down protocol is usually used making use of the initial FSH flare produced by the administration of a GnRH agonist.

GnRH Agonists and Antagonists

Use of gonadotropins in modern assisted reproductive techniques and protocols is frequently combined with some form of pituitary downregulation
achieved by the use of GnRH agonists and antagonists. GnRH is a decapeptide secreted from the arcuate nucleus of the hypothalamus. GnRH is rapidly degraded by cleavage between of the bonds, between amino acids five and six, and six and seven. Consequently the half-life is only two to four minutes.

Substitution of the amino acid at position 6 results in the formation of GnRH agonists (12). More recently, complex aminoacid substitutions have resulted in the formation of GnRH antagonists.

GnRH agonists act by producing an initial flare of gonadotropin secretion, which is utilized as seen above in the early stages of follicular development. This is followed by a phase of downregulation and hypogonadism. GnRH antagonists on the other hand result in an almost immediate state of hypogonadism by competitive inhibition with the GnRH receptor.

Complications of Gonadotropin Treatment

1. OHSS: A potentially serious condition characterized by shift of fluid from the intracellular to the extracellular compartment. The exact mechanism for the condition is unknown. The syndrome varies in severity from mild-to-moderate to severe.
2. Local allergic reactions.
3. Exacerbation of gingival inflammation (13).
4. Venous thrombosis: It has been suggested that the use of r-FSH may precipitate the occurrence of venous thrombosis through increased coagulability. However in an open-label, randomized, controlled trial by Ricci et al. (14), the impact of u-FSH and r-FSH on hemostasis was studied. The study concluded that ovarian stimulation with r-FSH does not cause any significant alteration to coagulation or fibrinolysis. Moderate changes were observed but resolved within four weeks of stopping treatment.
5. Gastrointestinal system disorders: nausea, abdominal pain, and pelvic pain.
6. Breast pain and ectopic pregnancy have been reported with rh-LH use.

Contraindications to Gonadotropins

Contraindications are rare:

1. Hypersensitivity to gonadotropins or to any of the excipients.
2. Ovarian, uterine, or breast cancers.
3. Ovarian enlargement or cyst not due to polycystic ovarian disease.
4. Tumors of the hypothalamus and pituitary gland.
5. Pregnancy and lactation.
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PHARMACOLOGY AND PHARMACOKINETICS

Mifepristone, initially known with the name of RU486, is 17β-hydroxy-11β-(4-dimethylaminophenyl-1)-17α-(prop-1-ynyl)-estra-4,9-diene-3-one. It is a derivative of norethindrone, but it differs from norethindrone in the presence of a 4-dimethylaminophenyl group at the 11β position and a 1-propynyl chain at the 17α position. It is a progesterone antagonist at the receptor level. It binds to the progesterone receptor, with the same affinity as progesterone itself. It also binds to the glucocorticoid receptor but it does not bind to mineralocorticoid or oestrogen receptors.

The pharmacology of mifepristone has been reviewed previously (1,2). Mifepristone is orally active. After a single dose of mifepristone, serum mifepristone concentrations reach a maximum within one hour. There are two patterns of pharmacokinetics. After a low dose of mifepristone (50 mg), the disappearance of mifepristone follows first-order kinetics with a half-life of 20 to 25 hours. If a dose of 80 to 100 mg is administered, there is an initial redistribution phase of 6 to 10 hours followed by a plateau in the serum levels for 24 hours or more. With these doses, there is no significant dose-dependent difference in the serum concentrations within the first 48 hours. With lower doses of 2 to 25 mg/day, the pharmacokinetics of mifepristone are linear, unlike those seen following ingestion of higher daily doses. The nonlinear pharmacokinetics following ingestion of higher doses might
be due partly to the saturation of the specific serum transport protein for mifepristone, serum alpha-1-acid glycoprotein (orosomucoid). The protein becomes saturated at a serum concentration of approximately 2500 nmol/L of mifepristone. Therefore, after a single dose of 100 mg or more of mifepristone, the serum concentrations of mifepristone do not increase in accordance with the increase in dose. There is also no significant difference in the pharmacokinetics of mifepristone between pregnant and nonpregnant women. Mifepristone is excreted mainly in the feces with less than 10% in the urine.

MECHANISM OF ACTION

The exact mechanisms of action are still not entirely clear. Both progestins and antiprogestins bind to the progesterone receptors, which are ligand-activated transcription factors with domains for DNA binding, hormone binding, and transactivation. The binding of both progestins and antiprogestins will transform the progesterone receptors from a non-DNA-binding form to a form that will bind to DNA. This transformation is accompanied by a loss of associated heat-shock proteins and dimerization. The activated progestin receptor binds to progesterone-responsive genes and increases the rate of transcription of these genes producing agonist effects at the cellular and tissue levels. However, when the mifepristone–receptor complex binds to progesterone-responsive elements, these DNA-bound receptors are transcriptionally inactive, leading to the antagonistic action of mifepristone. A recent study suggests that under in vivo conditions, the antiprogestin–receptor complexes may not bind to progesterone response elements.

EFFECTS OF MIFEPRISTONE IN PREGNANT AND NONPREGNANT WOMEN

Effects on the Gravid Uterus

The blockade of the progesterone receptor will lead to necrosis of the capillary endothelial cells in the postovulatory endometrium. In early pregnancy, this will lead to increase in the synthesis of prostaglandins and a decrease in the concentration of prostaglandin dehydrogenase. The increase in endogenous prostaglandins will lead to the softening of the uterine cervix. It will also lead to the induction of regular uterine contractions. The study of Bygdeman and Swahn (3) showed that the administration of mifepristone also sensitizes the uterus to the action of exogenous prostaglandins. This has led to the development of the regimen of combination of mifepristone and a prostaglandin for medical abortion.

Effects of Mifepristone in the Nonpregnant Woman

When a single dose of mifepristone is given in the mid- or late-follicular phase, it may diminish or inhibit the luteinizing hormone surge. Continuous
daily administration of 2 mg or more of mifepristone will also lead to attenuation or delay of luteinizing hormone surge. A single dose of 200 mg of mifepristone in the early luteal phase will lead to significant retardation in the endometrial development. When mifepristone (50–800 mg) is given in the midluteal phase, there will also be significant changes in the endometrium and some women may have two episodes of bleeding.

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Pharmacology of Prostaglandins

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PHARMACOLOGY OF PROSTAGLANDIN ANALOGS USED IN FIRST TRIMESTER ABORTION

Prostaglandins (PGs) can stimulate myometrial contraction and cause cervical ripening and dilatation (1,2). Their receptors exist throughout all stages of pregnancy and thus, PGs and their analogues are effective in termination of first and second trimester pregnancy. The natural PGs, PG F$_{2\alpha}$ and PG E$_2$ were first investigated clinically for medical abortion but they were soon replaced by PG analogues because of their high incidence of gastrointestinal side effects when given parenterally or vaginally (3). Modification of the chemical structures of PGs to form various PG analogues makes them relatively resistant to metabolism and, hence, having prolonged action (1). The addition of a methyl group at the 15 position of PG F$_{2\alpha}$ forms 15-methyl PG F$_{2\alpha}$ (carboprost). It was used more often in second trimester abortion. The substitution of two methyl groups at the 16-position of PG E$_1$ results in gemeprost. Misoprostol differs structurally from PG E by the presence of a methyl ester at C-1, a methyl group at C-16 and a hydroxyl group at C-16 rather than at C-15. The PG E analogues are preferable as they have more selective action on the myometrium and cause fewer gastrointestinal side effects (3). The two most extensively studied and clinically useful PG E analogues for abortion are gemeprost and misoprostol.
Gemeprost

Gemeprost (16,16-dimethyl-trans-$\Delta_2$-PG E$_1$ methyl ester) (Cervagem$^\text{®}$) is available as 1 mg vaginal suppositories. It is approved for use vaginally for cervical dilatation prior to vacuum aspiration and second trimester medical abortion. Following vaginal administration of 1 mg gemeprost, the maximum plasma level was achieved after two to three hours to 100 and 300 pg/mL (4). The drug was detectable in plasma for at least six to eight hours. Gemeprost can be administered intravenously, but this route of administration is not commonly used in first trimester medical abortion.

The cervical priming effect of gemeprost was demonstrated by Greer et al. (5). The mechanical force required to dilate the cervix was measured using a tonometer and the collagen concentration was measured by optical densitometry after staining the polymerized collagen in the cervical biopsy with Picrosirius red and glycosaminoglycans with alcian blue using a MgCl$_2$ gradient. It was found that the mechanical force required to dilate the cervix and the collagen concentration were reduced after treatment with gemeprost. Gemeprost can also increase the baseline uterine tonus as measured by an increase in intra-amniotic pressure after administration of vaginal gemeprost. Uterine contractions developed after administration of 1 to 2 mg of vaginal gemeprost (6).

Misoprostol

Misoprostol (15-deoxy-16-hydroxy-16-methyl PG E$_1$) (Cytotec$^\text{®}$) is a synthetic PG E$_1$ analogue. It was developed for the treatment and prevention of peptic ulcer by Searle in 1973 because of its gastric acid anti-secretory properties and its various mucosal protective properties (7). It has become an important drug in gynaecological practice because of its uterotonic and cervical priming action. It was discovered that it could be used off-label as an abortifacient. It has several advantages over the other PG analogues. Firstly, it is cheap compared to other PG analogues. It is stable at room temperature and therefore does not require refrigeration. Because it is licensed for the treatment and prevention of peptic ulcer, it is widely and easily available in many developing countries.

EFFECT ON FEMALE GENITAL TRACT

Uterus

The data in the literature concerning the effect of misoprostol on the female genital tract was scarce although it has been used widely in obstetrics and gynaecology. The uterotonic and cervical softening effect on the female genital tract was considered as a side effect rather than a therapeutic effect when misoprostol was first introduced. However, these effects also make
misoprostol a versatile and useful drug in the daily practice of obstetrics and gynecology nowadays.

The effect of misoprostol on uterine contractions was well studied by Danielsson et al. and Aronsson et al. (8,9). Intrauterine pressure was recorded using a Grass polygraph connected to a pressure transducer, which was inserted extra-amniotically through the cervical canal up to about 1 to 2 cm below the uterine fundus. The typical effect of a single dose of oral misoprostol is an increase in uterine tonus (8). It is only following repeated treatment that regular uterine contractions appear. This may be explained by the fact that a sustained plasma level of misoprostol is required for the development of regular contractions. Regular contractions are essential for the manifestation of many of its clinical effects in medical abortion and induction of labor. Clinical studies showed that misoprostol could be administered vaginally, which was more effective compared to oral administration (10,11). The effect of vaginal administration of a single dose of misoprostol on uterine contractility was initially similar to that of oral administration: an increase in uterine tonus. However, after one to two hours, regular uterine contractions appeared that lasted at least for up to four hours after the start of misoprostol (8). The development of regular contractions after vaginal administration may explain the better clinical efficacy compared to oral administration, as found in many studies (10,11). Recently, a new route of sublingual administration of misoprostol was studied and it was effective for medical abortion in the first and second trimester (12). Aronsson et al. (9) compared the effects of misoprostol on uterine contractility following different routes of administration. It was found that the increase in uterine tonus following oral and sublingual treatment was more rapid and more pronounced than that following vaginal treatment. The mean time to increase in tonus was between 7.8 and 11.5 minutes for oral and sublingual administration. The mean time to maximum tonus was also significantly shorter for oral and sublingual misoprostol compared to vaginal administration, respectively. After one to two hours of misoprostol, the tonus began to decrease, and following vaginal and sublingual treatment, regular uterine contractions developed slowly. This was not the case for oral treatment. The regular uterine contractions after vaginal administration were sustained for a longer period when compared to sublingual treatment.

Cervix

There are many clinical studies that have demonstrated the cervical priming effect of misoprostol in the pregnant state. Misoprostol has been used extensively for its cervical softening effect before induction of labor and surgical evacuation of the uterus. Studies have demonstrated that less force was required for mechanical dilatation of the cervix if misoprostol was given before the procedure (13,14). While this softening effect on the cervix may
be secondary to the uterine contractions induced by misoprostol, it is more likely to be due to the direct effect of misoprostol on the cervix.

The uterine cervix is essentially a connective tissue organ. Smooth muscle cells account for less than 8% of the distal part of the cervix. The exact mechanism leading to physiological cervical ripening is not known. The biochemical events that have been implicated in cervical ripening are (i) a decrease in total collagen content, (ii) an increase in collagen solubility, and (iii) an increase in collagenolytic activity. The extracellular matrix of the cervix can change very quickly. The changes in extracellular matrix components during cervical ripening were described as similar to those of an inflammatory response (15). Indeed, during cervical ripening there is an influx of inflammatory cells including macrophages, neutrophils, mast cells, and eosinophils into the cervical stroma. It has been proposed that these cells produce cytokines and PGs that have an effect on extracellular matrix metabolism. PGs have been implicated to play an important role in cervical ripening. Studies have shown that various PG analogues could decrease the hydroxyproline content of the pregnant cervix (16).

The histochemical changes on the pregnant cervix after misoprostol were studied using electron microscopy and proline uptake assay. The mean proline incorporation per microgram protein and collagen density, estimated by light intensity was significantly less than the control. The diameter of the collagen fibres was smaller in the misoprostol group although the difference was not statistically significant. This indicated that the action of misoprostol appeared to be mainly on the connective tissue stroma with evidence of disintegration and dissolution of collagen (13).

PHARMACOKINETIC PROPERTIES OF MISOPROSTOL

Earlier studies only concentrated on pharmacokinetic properties after oral administration because this drug was licensed for oral use for treatment of peptic ulcer. After oral administration, misoprostol is rapidly and almost completely absorbed from the gastrointestinal tract. However, the drug undergoes extensive and rapid first-pass metabolism (de-esterification) to form misoprostol acid, the principal and active metabolite of the drug. It was shown by clinical studies that vaginal administration was more effective than oral administration in medical abortion (10,11). Zieman et al. (17) performed a pharmacokinetic study comparing oral and vaginal routes of administration. Various pharmacokinetic properties including the peak concentration, time to peak concentration, and the area under the serum concentration versus time curve were compared after 400 mg of misoprostol was given either vaginally or orally. Following a single dose of oral administration, the plasma misoprostol levels increased rapidly and peaked at about 30 minutes. However, the plasma levels declined rapidly by 120 minutes and remained low thereafter. In contrast, after vaginal administration,
the plasma concentration gradually increased, reaching maximum levels after 70 to 80 minutes, and slowly declined with detectable levels present after six hours. The peak concentration achieved following oral administration was higher than that following vaginal administration. The area under the plasma concentration versus time curve (AUC) represents the bioavailability of misoprostol. The AUC was significantly greater following vaginal than following oral administration. The greater bioavailability of vaginal misoprostol may help to explain why vaginal administration was more effective in medical abortion. However, it was shown in the same study that the coefficient of variation of the AUC was greater for vaginal than that of oral administration. This meant that the absorption of misoprostol through the vaginal route was less consistent compared to the oral route. Recently, it has been shown that misoprostol could be given sublingually. A pharmacokinetic study has compared the absorption kinetics of oral, vaginal, and sublingual routes of administration of misoprostol. It was found that sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration and the greatest bioavailability as measured by the AUC, as compared to other routes. It was shown that the peak concentration was achieved 20 minutes after sublingual administration, whereas vaginal misoprostol took an hour to reach peak concentration (18).

The distribution, elimination, and excretion have been studied after oral administration. The free acid of misoprostol is approximately 85% serum protein bound, and this binding is independent of the concentration of misoprostol. The reports on the metabolism and elimination of misoprostol in man were scanty. Following de-esterification there is β-oxidation of the α side chain and ω-oxidation of the β side chain and reduction to PG F analogues (19). Studies in animals and healthy volunteers have identified biphasic elimination of misoprostol metabolites. The fast phase has a half-life of about 1.5 hours in humans. The slow phase elimination half-life has been reported at 144 to 177 hours in man. After a single oral 200 mg dose of tritiated misoprostol there was 90% excretion within eight hours. Renal excretion accounted for 64% of the total radioactivity and 15% was eliminated in the faeces (20,21). There was no published study on the elimination and excretion of misoprostol following vaginal administration.

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Drugs Used in First Trimester Termination of Pregnancy

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THE USE OF PROSTAGLANDIN ANALOGS IN FIRST TRIMESTER ABORTION

Medical Abortion

Preabortion Assessment

The initial assessment of any women who requested termination of pregnancy in the first trimester is the same as that of surgical abortion. It is important to ascertain that the woman is pregnant and the pregnancy is intrauterine. An ultrasound examination should be done if ectopic pregnancy is suspected. The woman’s history should be taken and a physical examination including bimanual pelvic examination should be done. If the duration of pregnancy cannot be confirmed with history and physical examination, an ultrasound examination should be performed. This is because the complete abortion rate of regimens used in medical abortion is related to the gestational age. It is also important to know the hemoglobin level before medical abortion because heavy bleeding can sometimes occur during the abortion process. It is advisable to check the rhesus blood group and immunize all Rh-negative women with Rh-immunoglobulin within 72 hours of abortion.

Mifepristone: The regimens using a combination of mifepristone and prostaglandin analogues have been shown to be the most effective medical
method of termination of pregnancy in the first trimester up to nine weeks of gestation. The regimen involves the use of mifepristone 200 to 600 mg given 48 hours before the administration of a prostaglandin analogue. The registered dose of mifepristone used for medical abortion in the first trimester is 600 mg. However, it has been shown that 200 mg was as effective as 600 mg for this purpose (1). Recent studies have shown that the interval between the administration of mifepristone and misoprostol can be shortened to 24 hours without affecting the efficacy of the regimen (2).

**Mifepristone and Gemeprost:** Gemeprost 0.5 to 1 mg given 48 hours after mifepristone has been shown to be effective for medical abortion less than nine weeks gestation. The complete abortion rate was more than 90% in most studies (3).

**Mifepristone and Misoprostol:** Misoprostol is currently the commonest prostaglandin analogue used for the purpose of medical abortion in the first trimester. It has the advantages of being cheap and stable at room temperature compared to gemeprost. Misoprostol is licensed for oral use. The complete abortion rate with 400 μg oral misoprostol, when combined with mifepristone, declines with increase in gestational age. The complete abortion was 92%, 83%, and 77% for gestational age of less than 49 days, 50 to 56 days, and 57 to 63 days, respectively (4). Therefore, the combination of mifepristone and oral misoprostol is not an optimal regimen for medical abortion for gestational age greater than 49 days of gestation. Later, it was found that misoprostol could be administered vaginally. This route of administration was more potent when compared to oral treatment and the side effects were also less frequent (5). The complete abortion rate achieved by using mifepristone followed by 48 hours later 800 μg of vaginal misoprostol was 95% to 98% up to 63 days of gestation. Sublingual administration has been shown to be effective for first trimester medical abortion less than nine weeks gestation. It was shown that the 800 μg sublingual misoprostol could achieve a similar complete abortion rate when compared to a similar dose of vaginal misoprostol administered 48 hours after mifepristone for pregnancy less than nine weeks (6). There was no ongoing pregnancy in the sublingual arm in this study compared to three ongoing pregnancies in the vaginal arm. However, the incidences of side effects were slightly higher for sublingual misoprostol. Further studies using a larger sample size are required to compare these two routes of administration of misoprostol.

A randomized trial comparing 0.5 mg vaginal gemeprost with 800 μg vaginal misoprostol, after pretreatment with 200 mg mifepristone, showed that vaginal misoprostol was superior to gemeprost with a higher complete abortion rate, fewer incomplete abortions, and ongoing pregnancy. The incidences of side effects were similar. Therefore, misoprostol is currently the prostaglandin analogue of choice for medical abortion in the first trimester (7).
**Misoprostol-Alone Regimen:** Misoprostol-alone regimen has been investigated for first trimester medical abortion. Investigators have used various regimens of repeated doses of misoprostol with different dosing intervals. A regimen of 800 μg of misoprostol administered vaginally every 24 hours for up to three doses achieved complete abortion rates in 88% to 91% of women less than eight weeks pregnant (8,9). This regimen takes several days to complete and is therefore, inconvenient and expensive. Another regimen using 800 μg of misoprostol vaginally as an initial dose followed by 400 μg of misoprostol vaginally for three to four doses achieved complete abortion rates in 70% to 85% of women (10,11). The complete abortion rate of repeated doses of misoprostol is certainly not comparable to the combined mifepristone and misoprostol regimen. However, it may be an alternative for women who do not want surgical abortion in countries where mifepristone is not available.

**Medical Abortion Between Nine and Thirteen Weeks**

The complete abortion rate of the regimen, using mifepristone followed by a single dose of prostaglandin analogue, decreases with increase in gestational age. Medical abortion has been reported using mifepristone followed by repeated doses of misoprostol (12). The first dose of 800 μg of misoprostol is given vaginally. A maximum of two further doses of 400 μg of misoprostol will be given orally or vaginally (depending on the amount of vaginal bleeding) at three-hourly intervals if abortion does not occur. A median of two to three doses of misoprostol is required. The incidence of side effects is expected to be higher. The complete abortion rate is over 94%.

**Follow-Up Procedure and Postabortion Contraception**

Confirmation of abortion is important because of the potential teratogenic effects of the drugs used in medical abortion. The passage of tissue mass following the application of prostaglandin analogues is the most useful clinical indicator of abortion. If complete abortion cannot be ascertained before the woman leaves the clinic on the day of prostaglandin analogue, she should be followed-up about two weeks later to confirm that the abortion has been completed. It is expected that the vaginal bleeding may last for two weeks or sometimes more. Every woman should be informed that she may get pregnant in the month immediately after abortion. Advice on contraception should be given to every woman after medical abortion. Oral contraception and injectables can be started immediately after medical abortion.

**Cervical Priming Before Surgical Evacuation**

The procedure of vacuum aspiration is associated with complications such as excessive hemorrhage, incomplete abortion, cervical tear, and uterine perforation. The risk is increased when difficulty is encountered during cervical
dilatation at vacuum aspiration, especially in nulliparous patients. Cervical priming ahead of surgical abortion may reduce the complications of cervical injury, uterine perforation, hemorrhage, and incomplete abortion (13). One large, multicenter randomized trial has shown that the routine cervical priming with a prostaglandin significantly reduced the risk of short-term complications of first trimester vacuum aspiration (14). Various methods have been used for cervical priming before vacuum aspiration including laminaria tent, mifepristone, and prostaglandin analogues. Nowadays, vacuum aspiration is often performed as day-patient surgery. Laminaria tent has to be inserted for 12 hours and mifepristone has to be taken for 36 to 48 hours to have adequate cervical priming effect. Therefore, they are less convenient for day-patients. Prostaglandin analogues are the cervical priming agents of choice and both misoprostol and gemeprost have been studied for this purpose (15). It was found that 400 μg misoprostol given three hours before the procedure was the optimal dose for vaginal application (16). However, oral administration is more convenient. It can avoid a vaginal examination in a busy day-patient surgery admission clinic and is more acceptable to women (17). Recently, it has been shown that oral administration of 400 μg misoprostol three hours before the vacuum aspiration is as effective as a similar regimen of vaginal misoprostol (18). Sublingual misoprostol 400 μg given three hours prior to surgical evacuation has recently been shown to be as effective as a similar dose of vaginal misoprostol for cervical priming purpose (19). Sublingual misoprostol is more convenient and easier to administer than vaginal misoprostol especially in a busy day-surgery setting. Gemeprost is also effective for cervical priming. However, it has been shown that it was less effective when compared to misoprostol and the incidence of preoperative side effects was also higher (20). Therefore, misoprostol is the drug of choice for cervical priming before surgical evacuation because it is also less expensive and stable at room temperature. Oral, vaginal, and sublingual routes are effective ways of giving misoprostol. However, sublingual routes may represent the most convenient route for cervical priming.

Side Effects, Complications, and Acceptability
Side effects of prostaglandin analogues are usually mild and self-limiting. Gastrointestinal side effects such as diarrhea and vomiting are the commonest reported side effects. Fever, chills, and rigor are usually associated with repeated doses. Prolonged vaginal bleeding is a common problem after medical abortion. Most women bleed for a median of 14 days. The bleeding is usually not heavy. Despite these side effects and prolonged duration of bleeding, most of women in trial of medical abortion found this method acceptable and would choose it again in future. Serious side effects are rare with gemeprost and misoprostol.
OTHER PHARMACOLOGICAL AGENTS USED IN FIRST TRIMESTER ABORTION

Mifepristone is expensive and is not available in every country. Methotrexate is an antimetabolite. It can kill rapidly growing cells including trophoblastic cells of the placenta. Thus, it has been used for treatment of gestational trophoblastic disease, ectopic pregnancy, and medical abortion. Methotrexate has been studied in combination with misoprostol for medical abortion in the first trimester. It was compared to mifepristone in combination with misoprostol for medical abortion in the first trimester in a randomized study. Although the complete abortion rates were comparable, the group of women using methotrexate took a longer time to have complete abortion. About 20% of the women using methotrexate aborted after day 8 (21,22). Thus, the acceptability of methotrexate was not as good as mifepristone. In addition, there is a four to six days of waiting time between methotrexate and misoprostol as compared to 36 to 48 hours for mifepristone. In conclusion, mifepristone should be the drug of choice if it is available.

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Drugs for Second Trimester Termination of Pregnancy

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INTRODUCTION

Abortion-related mortality and morbidity rise in relation to increasing gestation (1,2). In most countries in Western Europe and North America, two-thirds of complications occur during termination of pregnancy after 12 weeks, which only account for 10% to 15% of abortions. Lots of efforts have been made to formulate a safe and effective regimen in order to reduce the abortion-related complications. Medical methods involving the use of synthetic prostaglandin (PG) analogues alone or in combination with mifepristone have become the most widely adopted regimens nowadays. Surgical method by dilatation and evacuation (D and E), preceded by cervical preparation, is also proven to be safe and effective for second trimester termination of pregnancy when undertaken by experienced specialists with access to the necessary instruments (3). Again, mifepristone and synthetic PG analogues are the useful cervical priming agents prior to the procedure (4–6).

MEDICAL TERMINATION OF PREGNANCY

Gemeprost-Alone Regimen

Gemeprost (16,16-dimethyl trans-2 PGE1 methyl ester) is a PGE1 analogue. It is the only PG licensed in the United Kingdom for induction of abortion.
Vaginal gemeprost-only regimen gave a complete abortion rate of 88% to 96.5% in 48 hours (7–10). The commonest regimen is 1 mg every three hours for five doses in 24 hours. It is repeated if abortion does not occur. The median induction to abortion interval ranged from 14 to 18 hours. It was subsequently shown that increasing the dosing interval to every six hours did not compromise the abortion rate or the induction–abortion interval (11). The advantages of the revised regimen were the reduction in the number of pessaries and lower incidence of side effects. However, gemeprost is expensive; it requires refrigeration for storage. These make its use practical only in the developed countries.

**Misoprostol-Alone Regimen**

Although misoprostol was originally licensed for the oral route, most of the misoprostol-only regimens used in second trimester abortion involved vaginal administration, as the systemic bioavailability of misoprostol after vaginal administration was greater than that after oral administration (12). Jain and Mishell first described the use of misoprostol for second trimester termination of pregnancy. They compared the efficacy of 200 μg of vaginal misoprostol administered every 12 hours to the PGE2 (Prostin, Upjohn, Kalamazoo, Mich.) regimen (20 mg intravaginally every four hours). The induction-to-delivery intervals and the 24-hour success rates were comparable between the two treatment groups (13). When using misoprostol as a single medication, the success rates varied from 73% to 92% (9,10,14,15). The average induction-to-abortion interval was 13 to 35 hours. These disparate results are probably related to the difference in dosing regimens and the administration routes. The reported dosing regimens range from 100 μg q12 hours to 400 μg q3 hours. Wong et al. showed that vaginal misoprostol (400 μg every three hours for a maximum of five doses) was more effective than gemeprost (1 mg vaginal gemeprost every three hours for a maximum of five doses) for second trimester abortion (9). Recently, the sublingual route was also studied, because the sublingual area was the most vascular area of the buccal cavity. It avoids the first-pass effect through the liver. The discomfort caused by vaginal administration can be avoided at the same time. Tang and Ho achieved 100% abortion rate with a median induction-to-abortion interval of 11.6 hours by using 400 μg sublingual misoprostol every three hours for a maximum of five doses (16). The induction-to-delivery interval was shorter than a similar dose regimen of vaginal misoprostol alone (15.2 hours), but was slightly longer than a similar dose regimen of vaginal misoprostol in combination of mifepristone (nine hours) (15). Further randomized studies are required to compare the efficacy and acceptability of the sublingual versus the vaginal route.

**Mifepristone and PG Regimen**

Mifepristone is the antiprogesterin that is approved for induction of abortion. It increases the sensitivity of the uterus to PGs. Pretreatment with mifepristone,
prior to PG administration, reduces the induction–abortion interval as well as the analgesia requirements and the total dose of PGs required (17,18) when compared with PG-only regimens. It is also more effective than the laminaria tent in shortening the induction–abortion interval (19). In the United Kingdom, mifepristone, in a 600 mg dose in combination with PGE1 analogue, gemeprost, has been licensed for second trimester medical abortion since 1995 and is increasingly used at all gestations. However, randomized studies have indicated that a reduced dose of 200 mg of mifepristone is equally effective for termination of pregnancy in the second trimester (20). Similarly, the dosage of gemeprost can be decreased to 0.5 mg every six hours without jeopardizing the abortion rate and induction to abortion interval (21). Women (<1%) might abort with mifepristone before the administration of PGs. They should be counseled about the possibility of abortion at home prior to PG treatment, and early seeking of medical help is advised if excessive bleeding occurs.

Following pretreatment with mifepristone, vaginal misoprostol has been shown more effective than oral misoprostol for second trimester termination of pregnancy, although the oral route is more acceptable to patients (6). Women preferred oral misoprostol to vaginal administration because it was less painful, gave more privacy, and was more convenient (6,21). Thus, a combination of vaginal and oral route evolved, aiming to improve both the efficacy and the patients’ acceptability. El Refaey and Templeton showed that as long as the first dose was given vaginally, subsequent oral administration was as effective as the vaginal administration (600 μg vaginal misoprostol + oral or vaginal 400 μg every three hours). The abortion rate (97%) and the induction to abortion interval (6.5 hours) were similar to those with similar doses of vaginal misoprostol (22). The results were confirmed later by a larger series of patients using a slightly higher initial dose of vaginal misoprostol (800 μg). It was thought that vaginal misoprostol as the first dose could lead to more effective cervical priming, and there was no advantage in giving the subsequent doses vaginally (23). Ashok et al. published the largest review of 1002 consecutive medical termination of pregnancy at 13 to 21 weeks gestation. The combination of mifepristone 200 mg and misoprostol (800 μg vaginal misoprostol followed by 400 μg oral misoprostol at three-hour intervals, to a maximum of four doses) was considerably less expensive and at least as effective as regimens using mifepristone and gemeprost (24). The success was related to age and previous live birth with younger women and those with a previous live birth more likely to have a successful abortion.

SURGICAL METHODS OF SECOND TRIMESTER TERMINATION OF PREGNANCY

Cervical Priming

D and E of the uterus is the favored method for second trimester termination of pregnancy in the United States and in the non-National Health
Service abortion sector in the United Kingdom (25). This procedure generally involves the use of suction aspiration in combination with larger-bore (14–16 mm diameter) cannulae, large diameter tubing, evacuation of fetal parts and placenta with specially designed forceps (Sofer, Bierer). Cervical preparation is critical to the success of the procedure, as rapid mechanical dilatation of the cervix carries a significant risk of cervical laceration with immediate attendant morbidity and the possibility to remote complications such as cervical incompetence. The World Health Organization recommended that cervical preparation should precede all abortion induced after 14 weeks (26). The laminaria tent has been used for this purpose; it takes 4 to 12 hours to act, and trained medical staff is required for insertion. Complications including uterine perforation, infection, and breakage in the cervix or migration to the uterine cavity have been reported. Recently, the administrations of buccal misoprostol were found to be as effective as the laminaria tent for cervical preparation (27). The efficacy and acceptability need to be further confirmed by a larger trial.

Use of PG with Scarred Uterus

Termination of pregnancy with previous uterine scar is always challenging. No matter what method is used, there are higher risks of uterine rupture than those without a scar. The risk of rupture of uterus at the time of medical termination was higher in women presenting with a previous uterine scar than that of an intact uterus (3.8% vs. 0.2%) (28,29). Uterine scar rupture has been reported in both gemeprost and misoprostol regimens (30–32). No well-controlled study has shown any method better than the others. A small study has shown the efficacy of misoprostol in second trimester termination in scarred uterus. There is not enough data to show that misoprostol is safe but at least it may be an alternative. With the rising cesarean section rate, there will be an increasing number of women undergoing termination of pregnancy with a previous uterine scar. Women should be appropriately counseled about the risks and consequences. The optimum chance for a successful outcome is provided by the informed and alert clinician who appreciates the potential risks of the procedure and who is prepared to deal with those risks, and the clinician should be fully aware of the presentation and management of scar rupture.

SIDE EFFECTS AND COMPLICATIONS

Between 1988 and 1996, there were nine maternal deaths in the United Kingdom related to legal abortion, of which five followed second trimester abortion and three followed D and E of the uterus. However, there is no recent randomized study to compare the safety and efficacy of current medical versus D and E for second trimester abortion. In general, the use
of PGs, gemeprost, and misoprostol, with or without mifepristone, is a safe and effective method of medical abortion in the second trimester. Side effects including nausea, vomiting, diarrhea are characteristics of PG administration and are due to PG’s stimulatory effect on the gastrointestinal tract. Diarrhea is more common in women using gemeprost, whereas fever is more common with misoprostol. Serious complications including uterine rupture, major hemorrhage, and cervical tear are rare. Cases of uterine rupture have been reported to occur with both gemeprost and misoprostol, and the use of mifepristone did not exclude this possibility. The incidence of uterine rupture was estimated to be 0.5% in the second and third trimester using mifepristone and gemeprost. Risk factors of uterine rupture include previous cesarean section, grand multipara, advance gestation, prolonged PG therapy, and use of oxytocin in addition to PGs. Cardiovascular complications are uncommon with gemeprost and misoprostol. Long-term complications associated with medical abortion in the second trimester using gemeprost and misoprostol with or without mifepristone are rarely reported. There is no known association with subsequent infertility or miscarriage after medical abortion using the oral or vaginal route with PG analogues.

CONCLUSION

The combination of mifepristone with misoprostol or gemeprost is a safe and effective method for second trimester termination of pregnancy. PG analogue-alone regimen is also effective if mifepristone is not available. Side effects of PGs are mainly due to their effect on the smooth muscles and are dose related. Misoprostol seems to have several advantages when compared with gemeprost. It is considerably cheaper and does not require special storage conditions. Although misoprostol is not licensed for induction of abortion in second trimester pregnancy, experience is accumulating by “off license” use that it is as effective and safe as the licensed product. Both mifepristone and PGs analogue are effective for cervical priming prior to D and E in second trimester abortion.

REFERENCES

21. Ngai SW, Tang OS, Ho PC. Randomized comparison of vaginal (200 μg every 3 h) and oral (400 μg every 3 h) misoprostol when combined with mifepristone in termination of second trimester pregnancy. Hum Reprod 2000; 15:2205–2208.
INTRODUCTION

Both surgery and radiotherapy are useful treatment modalities for localized cancers. Once the cancer has spread beyond the primary organ, chemotherapy represents the only treatment option that may cure the disease.

Modern chemotherapeutic regimens for treatment of gynecologic malignancies use agents with different chemical properties and mechanisms of action. These agents have different actions at different pathways controlling cell metabolism and at different stages of the cell cycle controlling cell proliferation and death. They are usually classified by their chemical origin, including antimetabolites, alkylating agents, antibiotics, plant alkaloids, taxanes, and hormonal agents (Table 1).

The choice of drug or regimen is determined by a number of factors. Apart from the mechanism of action, pharmacokinetic properties of these agents have to be considered by the oncologist in choosing the appropriate drugs for a particular patient, including absorption, distribution, metabolism, and excretion. Apart from the drug itself, natural history of the malignancy, patient characteristics and probability of achieving a response or cure (treatment intent) are important considerations.
<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of action</th>
<th>Examples of drugs</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolites</td>
<td>Structural or chemical analogs of metabolites in the synthesis of purines, pyrimidines, and nucleic acids. Phase-specific agents.</td>
<td>Methotrexate, Hydroxyurea, 5-Fluorouracil, 6-Mercaptopurine</td>
<td>CHAMOC, EMA, CO, MAC in GTD</td>
</tr>
<tr>
<td>Alkylating agent</td>
<td>Formation of DNA adducts, leading to single or double strand breaks or cross-links</td>
<td>Cyclophosphamide, Hosulam, Melphalan, Carboplatin, Chlorambucil, Thiopeta</td>
<td>CAP, DDP/CTX in EOC; Ilospamide/DDP in sarcomas</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>DNA intercalation, leading to inhibition of DNA transcription and RNA translation</td>
<td>Dactinomycin, Bleomycin, Doxorubicin, Mitomycin C, Mitoxantrone</td>
<td>VAC, BEP, VP/P in germ cell tumors; MTX/Act D, EMA-CO in GTD; Adr/DDP in sarcomas</td>
</tr>
<tr>
<td>Plant derivatives</td>
<td>Disturbance of normal assembly, disassembly, and stabilization of intracellular microtubules</td>
<td>Vinblastine, Vincristine, Etoposide, Paclitaxel, Topotecan, Irinotecan</td>
<td>CP in EOC, VP/DDP in neuroendocrine tumor</td>
</tr>
<tr>
<td>Hormones</td>
<td>Direct antiprotein effects, estrogen antagonist</td>
<td>Megestrol acetate, Tamoxifen</td>
<td>ESS, CA corpus</td>
</tr>
</tbody>
</table>

**Abbreviations:** MAC, actinomycin-D; methotrexate, cyclophosphamide; GTD, gestational trophoblastic disease; CAP, cyclophosphamide, adriamycin and platinum; DDP/CTX, cisplatinum; EOC, epithelial ovarian cancers; AUC, area under the curve; VAC, vincristine, actinomycin-D, cisplatinum; BEP, bleomycin, etoposide, cisplatinum; ESS, endodermal stromal sarcoma; CA, carcinoma.
It is important to note that except for a few cancers, a single drug used in standard dose does not cure cancer. Multiagent chemotherapy accomplishes three important advantages over single-agent treatment (1).

- It provides maximal cell kill within the range of toxicity tolerated by the host for each drug as long as dosing is not compromised.
- It provides a broader range of coverage of resistant cells lines in a heterogenous tumor population.
- It prevents or slows the development of new resistant lines.

Selection of drugs in a combination regimen should follow these principles:

1. Only drugs known to be effective against the tumor when used alone.
2. When several drugs of a class are available and are equally effective, a drug should be selected on the basis of toxicity that does not overlap with the toxicity of other drugs to be used.
3. Drugs should be used in their optimal dose and schedule.
4. Drug combination should be given at consistent intervals.

For drug-sensitive cancers, the factor limiting the capacity to cure often is proper dosing (2). The dose–response curve in biologic systems is usually sigmoidal in shape, with a threshold, lag phase, a linear phase, and a plateau phase. The dose–response curve for anticancer drugs is usually steep with a narrow therapeutic margin. Large tumor burdens may also shift the dose–response curve to the right resulting in lower therapeutic effect.

Dose reductions, which are not uncommon in patients who develop significant toxicity during chemotherapy, are likely to be associated with significantly fewer therapeutic effects (2). A dose reduction in the linear phase of the dose–response curve results in a loss of the capacity to cure the tumor before there is a diminution in the response rate. That is, complete remissions will continue to be observed, but with dose reduction as small as 20%, the last few residual cells may not be eliminated, and relapse is inevitable. On the average, a dose reduction of approximately 20% leads to a loss of 50% of the cure rate (3,4). A positive relation between dose intensity and response rate has been demonstrated in advanced ovarian cancers and in other solid tumors.

Chemotherapy is used in a variety of situations in gynecologic oncology. The best known is in the treatment of gestational trophoblastic disease and germ cell tumors in which chemotherapy is highly effective. However, these diseases are uncommon. The most common use of chemotherapy in gynecologic oncology is in the treatment of epithelial ovarian cancers. In cervical cancer, chemotherapy is usually reserved for selected cases of relapsed disease. Recently, this is also used concomitantly with radiotherapy as a primary treatment for locally advanced cervical cancer and vulval cancer (Table 2).
ADJUVANT CHEMOTHERAPY FOR EPITHELIAL OVARIAN CANCER

Early Stage Ovarian Cancer

Approximately 30% of patients with ovarian cancer are diagnosed with early stage disease. However, 10% to 50% of these patients develop recurrent disease after surgery and may die from ovarian cancer.

Since the prognosis of adequately staged patients with stage Ia or stage Ib grade 1, nonclear cell ovarian carcinoma is extremely good, surgery alone can be curative, and adjuvant chemotherapy is not indicated (Table 3).

For patients with stage Ia, Ib, grade 2–3, stage Ic and IIa, and all stages I to IIa with clear cell tumors, platinum-based adjuvant chemotherapy has been found to improve both the overall and recurrence-free survivals in the international collaborative ovarian neoplasm trial I (ICON1) (5) and the pooled analysis of the ICON1 and the European organization for research and treatment of cancer collaborators-adjuvant chemotherapy in ovarian neoplasm (EORTC-ACTION) studies (6). However, one should note that majority of patients in these studies were not adequately staged.

In the EORTC-ACTION Trial, no differences in overall and recurrence-free survivals could be demonstrated in patients who were optimally staged. However, the number of patients in the subgroup analysis was small, and patients were not prospectively stratified according to the surgical staging categories. Further studies are required to confirm the role of adjuvant chemotherapy in these patients with optimally staged early stage ovarian cancer.

Given that the majority of centers in the ICON1 study used single-agent carboplatin (the second most commonly chosen regimen in the ACTION study), this becomes the treatment of choice. Alternatively, a combination of carboplatin and paclitaxel may be considered for those with poor prognostic factors such as clear cell tumors.

For patients with stage IIb or higher, adjuvant chemotherapy should be given. The current standard first-line chemotherapy is a combination of carboplatin and paclitaxel.

Table 2 Use of Chemotherapy in Gynaecological Oncology

<table>
<thead>
<tr>
<th>Use of Chemotherapy in Gynaecological Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant and neoadjuvant treatment in ovarian cancer</td>
</tr>
<tr>
<td>Primary treatment of gestational trophoblastic disease</td>
</tr>
<tr>
<td>Relapsed ovarian cancer</td>
</tr>
<tr>
<td>Advanced or relapsed cervical cancer</td>
</tr>
<tr>
<td>Chemoradiation in cervical and vulval cancer</td>
</tr>
<tr>
<td>Advanced and relapsed endometrial cancer</td>
</tr>
<tr>
<td>Sarcomas and nonepithelial ovarian tumors</td>
</tr>
</tbody>
</table>
Advanced Stage Ovarian Cancer

About 70% of patients with ovarian cancer were stage III or IV at the time of diagnosis. The current standard regimen for first-line chemotherapy in ovarian cancer is a combination of platinum and paclitaxel. Both the Gynecologic Oncology Group (GOG-111) (7) and the European–Canadian Intergroup (Ov10) trials (8) have demonstrated optimum response rates with this drug combination, and it has come to be accepted as the “gold standard” for treating ovarian cancer. While this regimen has resulted in prolongation of progression-free times, overall survival has not significantly improved with this treatment strategy.

It has been found in a number of trials that carboplatin and cisplatin have similar efficacy when used in combination with paclitaxel. Given the toxicity profile and ease of administration, carboplatin has become the platinum of choice in the first-line chemotherapy for ovarian cancer.

Recently, important questions about the clinical value of platinum/taxane combinations have been raised by the results of the large ICON3 study involving 2074 ovarian cancer patients (9). The data from this trial suggest that there was no benefit, in terms of either progression-free or overall survival, from the use of paclitaxel/carboplatin compared with carboplatin alone or cyclophosphamide/doxorubicin/cisplatin. Furthermore, the incidences of alopecia, fever, and sensory neuropathy were significantly higher in the taxane treatment arm compared with carboplatin alone. However, this needs to be interpreted with caution, as about one-third of patients on carboplatin in the control group received taxane at some stage.

Although overall clinical responses can be achieved in up to 80% of patients with suboptimally debulked stages III and IV disease after primary debulking surgery and aggressive chemotherapy (defined as at least six cycles of platinum plus paclitaxel chemotherapy), the proportion of patients with pathological complete remission as defined by second look laparotomy constitutes less than 50% of the clinical complete responders. Even among those with pathological complete response, almost half will subsequently progress. With a view to improving long-term results, consolidation therapy has therefore been investigated after initial surgery and chemotherapy.

Table 3  First-Line Chemotherapy for Ovarian Cancer

| Stage Ia, Ib, grade 1, nonclear cell tumor | No further chemotherapy |
| Stage Ia, Ib, grade 2–3 or clear cell tumor; or stage Ic and IIa, nonclear cell tumor | Single-agent Carboplatin (AUC of 5.0–7.5) every 3 wk for 6 cycles |
| Stage Ic and IIa, clear cell tumor; stage IIb or higher | Combination chemotherapy with Carboplatin (AUC of 5.0–7.5) or cisplatin (100 mg/m²) plus paclitaxel (175 mg/m² over 3 hours) every 3 wk for 6 cycles |

Abbreviation: AUC, area under the curve.
A number of different options for consolidation therapy in ovarian cancer are available, including radiotherapy, cytotoxic therapy, and intraperitoneal therapy. Studies of consolidation with radiotherapy suggest that it is associated with considerable toxicity, and no significant benefit in terms of improvement in survival (10–12). The overall results from the randomized studies suggested a lack of overall survival benefit of consolidation conventional-dose chemotherapy even for those patients with minimal or no residual disease.

In summary, there is no proven efficacy with consistent high levels of evidence to support the routine use of consolidation therapy after adequate (usually six cycles) chemotherapy comprising paclitaxel plus either cisplatin or carboplatin for surgically debulked stages III/IV ovarian cancer.

NEOADJUVANT CHEMOTHERAPY FOR ADVANCED STAGE OVARIAN CANCER

Several studies have shown that aggressive cytoreduction of stage IV disease is feasible and offers a survival advantage from being maximally surgically cytoreduced at initial laparotomy (13). However, there is no randomized data supporting this. Young patients with good performance status, pleural effusion as only site of disease outside abdominal cavity, small volume metastases, and no major organ dysfunction should be considered for surgery.

For patients with poor performance status or with advanced stage disease in whom the chance of optimal debulking is low, neoadjuvant chemotherapy by giving chemotherapy first with delayed primary surgery after three or six cycles of treatment may be considered as an alternative treatment option. Several retrospective studies suggest that the same survival can be obtained with neoadjuvant chemotherapy compared with primary cytoreductive surgery. In addition, the subsequent surgery may be technically easier than if primary surgery is to be performed, with less operative morbidity (14–16). Patients may also have better quality of life. Recently, a prospective phase II study has demonstrated that higher tumor resection rate and longer median survival could be achieved by the use of neoadjuvant chemotherapy compared with conventional therapy (17). The strategy of neoadjuvant chemotherapy and delayed primary surgery needs to be confirmed by randomized trial. The ongoing EORTC 55971 trial is currently addressing this issue.

The decision on neoadjuvant chemotherapy should be individualized. Patients may be selected to receive neoadjuvant chemotherapy based on the extent of disease on the abdominopelvic computed tomography (CT) scan. For patients with CT scan findings of attachment of the omentum to the spleen or disease greater than 2 cm on the diaphragm, liver surface or parenchyma, pleura, mesentery, gall bladder fossa or the suprarenal para-aortic nodes, the chance of optimum cytoreduction will be about 33% (18).
PRIMARY TREATMENT OF GESTATIONAL TROPHOBLASTIC NEOPLASIA

Early and appropriate treatment is essential to the successful treatment for gestational trophoblastic neoplasia (GTN). Single-agent chemotherapy is recommended for low-risk GTN. The two most active drugs are methotrexate with or without folinic acid rescue (19,20) and actinomycin D. Other drugs include etopside, which has been shown to have an increased risk of secondary malignancy, and 5-fluorouracil. Treatment of the intermediate risk group is controversial. Some centers treat the intermediate risk group as low risk using a single agent while others treat it as a high risk using multiple agents. Still others use two agents only. Treatment of the high-risk group is by combination multiple chemotherapy. Common regimens used include etopside, methotrexate, actinomycin-D/cyclophosphamide, vincritine (21), cyclophosphamide, hydroxyurea, actinomycin-D, methotrexate, vincritine, folinic acid, adriamycin, and actinomycin-D, methotrexate, cyclophosphamide. In patients with brain metastasis, intrathecal methotrexate or whole brain irradiation in addition to systemic chemotherapy may improve survival (22).

REFRACTORY OR RECURRENT OVARIAN CANCER

The majority of ovarian cancer patients develop recurrent disease within a relatively short period, including 50% to 75% of patients who have a complete response to initial treatment. The site of recurrence is usually the pelvis and abdomen, although 20% of patients may have recurrences in the retroperitoneal nodes. The median survival after disease recurrence ranges from 12 to 24 months. As a general rule, the later the recurrence, the better the prognosis for survival duration.

The goals of treatment in relapsed ovarian cancer include prolongation of survival and maintenance of quality of life. It is also important to control disease-related symptoms and minimize the side effects of treatment. Generally, it is considered that maintaining stable disease with a good quality of life is a reasonable goal in continuation of therapy, providing there is no cumulative toxicity.

A number of different strategies may be employed in the management of patients with relapsed ovarian cancer, including retreatment with platinum or salvage therapy with a variety of other agents, either alone or in combination. For the selection of the optimal chemotherapy regimen at first relapse, patients are usually characterized according to their degree of sensitivity or resistance to the initial treatment, depending on the interval between initial response and first relapse regimen (Table 4).

The response to platinum retreatment in patients with relapsed ovarian cancer is strongly influenced by their treatment-free interval after initial therapy with a platinum combination. Those who progress under
platinum therapy are defined as platinum refractory, those who relapse within six months are defined as platinum resistant, and those who relapse after six months or more are defined as platinum sensitive. Response rates to platinum retreatment in platinum-refractory patients tend to be around 10%, compared with approximately 28% in platinum-sensitive patients. The number of responders in the 6- to 12-month category is thought to be in the 25% to 30% range, slowly increasing to a rate of 60% to 70% at two years (23,24).

Studies to date suggest that combination regimens for salvage therapy may improve response rates compared with single-agent therapy, but with increased toxicity and no apparent improvement in survival. However, results from the ICON4/Arbeitsgemeinschaft gynaekologische onkologie–ovarian cancer trial 2.2 study (phase III randomized trials of paclitaxel plus carboplatin or cisplatin versus conventional platinum-based chemotherapy in relapsed ovarian cancer) has suggested that paclitaxel combined with platinum chemotherapy confers survival and progression-free survival advantages compared with conventional platinum-based chemotherapy (25).

Special consideration should be given to those patients with recurrent disease between 6 and 12 months, especially for those with severe side-effects during the previous platinum chemotherapy. With comparable response rates, topotecan may be considered as an alternative option.

For patients with platinum-refractory or platinum-resistant tumors (no response or relapse within six months, respectively), and for subsequent relapses, topotecan, liposomal doxorubicin, gemcitabine, etoposide, docetaxel, or oxaliplatin might be used. These have all shown a response ranging between 10% and 15%.

### Table 4  Chemotherapy for Recurrent Ovarian Cancer

<table>
<thead>
<tr>
<th>Platinum-sensitive tumor</th>
<th>Treatment-free interval between 6 and 12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single-agent Carboplatin (AUC of 5.0–7.5) or combined with Paclitaxel (175 mg/m² over 3 hr) every 3 wk</td>
</tr>
<tr>
<td></td>
<td>Topotecan (1.25 mg/m² for 5 days every 3 wk)</td>
</tr>
<tr>
<td>Treatment-free interval of more than 12 mo</td>
<td>Single-agent Carboplatin (AUC of 5.0–7.5) or combined with Paclitaxel (175 mg/m² over 3 hr) every 3 wk</td>
</tr>
<tr>
<td>Platinum-resistant tumor</td>
<td>Paclitaxel (175 mg/m² over 3 hr) every 3 wk, if not previously used</td>
</tr>
<tr>
<td></td>
<td>Topotecan (1.25 mg/m² for 5 days every 3 wk)</td>
</tr>
<tr>
<td></td>
<td>Liposomal Doxorubicin (40–50 mg/m² every 4 wk)</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine (800–1000 mg/m² D1, 8 and 15 every 4 wk)</td>
</tr>
<tr>
<td></td>
<td>Etoposide (50–100 mg/m² daily for 21 days every 28 days)</td>
</tr>
<tr>
<td></td>
<td>Docetaxel (60–100 mg/m² every 3 wk)</td>
</tr>
<tr>
<td></td>
<td>Oxaliplatin (59–130 mg/m² 20 min or 2 hr infusion every 3 wk)</td>
</tr>
</tbody>
</table>
Topotecan has demonstrated efficacy in relapsed ovarian cancer and has shown antitumor activity in both platinum-sensitive and platinum-resistant disease, with generally higher response rates in platinum-sensitive tumors (19–33%) than in platinum-resistant tumors (14–18%). The main toxicity associated with topotecan when used in the standard five-day dosing schedule is myelosuppression, which is usually predictable, reversible, and noncumulative. Nonhematologic toxicity is generally mild to moderate and is not associated with significant end-organ toxicity. It has been shown to be better tolerated in terms of myelosuppression in less heavily pretreated patients; it might therefore be beneficial to use it early in the treatment sequence.

Comparative trials have shown that topotecan is associated with tumor response rates and survival benefits that are similar to those seen with paclitaxel and liposomal doxorubicin. Follow-up data extending to four years indicate that the survival benefit persists in long-term therapy, and an analysis of data from five different trials has shown that treatment for more than six cycles may be associated with longer survival and no cumulative toxic effects. Long-term treatment with topotecan is feasible in some patients and that there is a potential for both late response and survival benefit in responding or stable patients who continue topotecan therapy for seven cycles or more.

Liposomal doxorubicin is an encapsulated doxorubicin in a polyethylene-glycol-liposome, which allows delivery of high local levels of doxorubicin, within a small volume of distribution, accompanied by a prolonged circulation time. The risk of cardiomyopathy is significantly reduced. The most significant toxicity is a plantar-palmar erythrodysesthesia. This can generally be ameliorated by prolonging the treatment interval to four weeks and/or by dose reduction (26).

Gemcitabine is active as a single agent in the treatment of recurrent ovarian cancer. It is extraordinarily well tolerated. It has the advantage of being able to be given as a short infusion. Studies have demonstrated activity in platinum-resistant, as well as paclitaxel-resistant, patients. Gemcitabine toxicity is generally mild, transient, and noncumulative. It includes myelosuppression (which is dose limiting), flu-like symptoms, fatigue, fever, peripheral edema, proteinuria, cutaneous reactions, and respiratory and gastrointestinal effects. There have been rare reports of hemolytic uremic syndrome and cardiac dysfunction, including myocardial infarction, congestive heart failure, and atrial fibrillation. The myelosuppression is easily managed by lowering the dosage.

Apart from systemic chemotherapy, hormonal therapy with agents such as Tamoxifen may also be considered. So far, only observational data from women treated with tamoxifen have been reported. In a meta-analysis (27), 60 of 623 women (9.6%) treated with tamoxifen achieved an objective response and this varied from 0% to 56% in different studies. Stable disease, for variable periods of four weeks or more, was observed in 131 of 411 (31.9%) women.
There were not enough data to assess duration of response, survival, or the palliative effect of tamoxifen on symptom control or quality of life.

This is no conclusive evidence that secondary debulking surgery confers a survival advantage to patients with recurrent disease, because a randomized trial would not be possible. All retrospective and one prospective study report a statistically significant increase in disease-free survival of one or two years in patients who are able to achieve optimal redebulking (28). Suitable candidates include those with disease-free interval of more than 12 months, previous response to cisplatin therapy, and isolated resectable nodules.

The optimal management of a patient with relapsed or progressive ovarian cancer requires a careful assessment of the patient’s condition. Any physical condition that may immediately affect the patient’s survival or quality of life, such as intestinal obstruction, ascites, pleural effusions, or organ failure should be attended and adequate treatment should be given.

It is important for the patient to realize that chemotherapy responses do not necessarily mean survival prolongation. The patient’s family may be involved in the decision making. Their wishes should be respected.

CHEMORADIATION IN LOCALLY ADVANCED CERVICAL CANCER

The recommended treatment is radiation therapy with concurrent cisplatin-based chemotherapy (29–33). The optimal regimen, dose and schedule of concurrent chemotherapy have not been confirmed.

Suggested dose of radiation is 85 to 90 Gy to point A and 55 to 60 Gy to point B. Cisplatin is given in a dose of 40 mg/m² weekly during external beam therapy and at the time of brachytherapy (Table 5). In patients with para-aortic nodal disease, extended field radiation or adjuvant chemotherapy after concurrent chemoradiation may be considered. However, there is little data on the toxicity associated with concurrent chemotherapy and extended field irradiation.

**Table 5** Concurrent Chemoradiation

<table>
<thead>
<tr>
<th>Pelvic irradiation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard field</td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>External irradiation to 40–50 Gy/4–5wk</td>
</tr>
<tr>
<td></td>
<td>Brachytherapy boost 80–85 Gy for small tumor and 85–90 Gy for large tumor</td>
</tr>
<tr>
<td><strong>Total duration</strong></td>
<td>6–7wk</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>Cisplatin 40 mg/m² weekly during ERT and at each brachytherapy</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>Cisplatin 75 mg/m² every 4 wk for 3 courses</td>
</tr>
</tbody>
</table>
Radical hysterectomy or pelvic exenteration may be considered in cases with poor response to concurrent chemoradiation or with persistent disease after chemoradiation.

ADVANCED OR METASTATIC CERVICAL CANCER

The disease should be considered incurable and palliative and supportive care is indicated. The aim of palliative care is to maintain and improve quality of life and the whole person should always be considered. It is important to provide both optimum relief from symptoms and to maintain their social and psychological well-being (Chapter 3).

Chemotherapy has a limited role in prolonging survival or improving quality of life. Transient pain relief may be achieved. There is no evidence to suggest that combination therapy is better than single-agent therapy. Cisplatin is the most active drug with response rate of about 30% at the dose of 100 mg/m² (34). Other drugs with reported response include carboplatin, ifosfamide, and epirubicin.

CHEMORADIATION IN VULVAL CANCER

Where possible, the management of vulval cancer is usually surgical. Chemotherapy, using 5-fluorouracil, cisplatin or both, in combination with radiotherapy, has been used in patients unfit for surgery or in those in whom exenterative surgery would have to be performed in order to achieve complete resection. With this approach, response rates of 50% to 90% have been reported. In cases where complete response has been achieved, surgical excision of the primary tumor may not be necessary (35).

Preoperative chemoradiation may also reduce the need for radical primary surgery in patients with locally extensive tumors, for example leading to preservation of the anal sphincter and avoiding the necessity for major plastic reconstructive procedures (36).

ADVANCED AND RELAPSED ENDOMETRIAL CANCER

Treatment is individualized and is often palliative in intent. Systemic metastasis is a major problem but no chemotherapeutic agent has any apparent prophylactic value in endometrial cancer. Cytotoxic chemotherapy is only of palliative value and doxorubicin appears to be the most active agent.

Progestagens have an established place in the palliative treatment of women with advanced disease. However, meta-analysis based on the currently available good quality trials failed to demonstrate that adjuvant progestagen therapy has a significant beneficial effect on endometrial cancer-related deaths (37). The available evidence points toward the conclusion that progestagens have no role in the primary treatment of endometrial cancer.
Meta-analysis of the currently available published trials demonstrated that the overall survival of patients with endometrial cancer may be adversely affected by adjuvant progestagen therapy. This may be due to an adverse effect on deaths from intercurrent disease. Progestagens are associated with a reduction in the level of high-density lipoproteins. Because high-density lipoproteins are considered to be a protective factor against cardiovascular disease, an increase in cardiovascular-related deaths might be expected in the treatment group. However, adjuvant progestagen therapy was not apparently associated with an increased incidence of cardiovascular deaths. Moreover, in the two trials by MacDonald (38) and De Palo (39) in which long-term therapy was used, there was similar risk of such deaths in the treatment and control groups.

Serous papillary carcinomas have a poor prognosis even in the absence of deep myometrial invasion. They disseminate widely and usually recur in the upper abdomen. There is no consensus regarding adjuvant treatment after surgery in these patients. Trials regarding this are ongoing in various centers.

Similarly, clear cell carcinomas have a predilection for recurrence in the upper abdomen. There is some evidence that if serous papillary or clear cell carcinomas are limited to the curettings with no adverse features in the hysterectomy specimen, the prognosis may not be impaired (40).

SARCOMAS

Theoretically, adjuvant chemotherapy may help to control subclinical distant disease. However, studies for its use in stage I or II uterine sarcomas failed to show any statistically significant survival benefits. Its use is not generally accepted or recommended.

For stages I and II uterine sarcoma, adjuvant doxorubicin is still the main choice, though there is no statistically significant difference in the recurrence rate, progression-free survival or overall survival. Ifosfamide is now under the phase II trial, and it is usually used in advanced or recurrent disease, especially in carcinosarcoma, but its use has been limited by its toxicity. Cisplatin is also another option, especially in the case of carcinosarcoma.

Comparison between combination chemotherapy and sequential single agents was also done in small prospective randomised trials for advanced disease and metastatic sarcoma. Again, it failed to show any survival benefit for aggressively dosed combination chemotherapy. In general, combination chemotherapy is used as neoadjuvant therapy to improve the overall objective response of the sarcoma, while in cases where no surgical resection is indicated or palliation being the overall plan, sequential single agent is advised.

GERM CELL TUMOR

Malignant germ cell tumors usually occur in the first two decades of life and may also be seen in the third decade. They account for about two-thirds of the ovarian malignancies in these young female populations. The patient
frequently presents with a palpable abdominal mass and abdominal pain. Because these tumors are highly chemosensitive, the prognosis of germ cell tumors is excellent with cure rates of 90% to 100% have been reported (41,42).

Germ cell tumors are staged in the same way as epithelial ovarian cancer. Because systemic chemotherapy can cure the majority of patients even with advanced disease, conservative surgery is the standard in all stages of all germ cell tumors (Table 6). Except for dysgerminoma and immature teratoma, a thorough surgical staging is not indicated because chemotherapy will be needed.

The chemotherapy regimen vincristine, actinomycin-D, cyclophosphamide appears to be the treatment of choice for most of the malignant germ cell tumors, including dysgerminoma, immature teratoma, endodermal sinus tumor, embryonal carcinoma, and mixed germ cell tumors. It is associated with similar cure rate but less toxicity when compared with bleomycin, etoposide, cis-platinum (BEP) (43,44). It can also be used for choriocarcinoma. Other chemotherapy regimens that may be used include BEP, vinblastine, bleomycin, cis-platinum, and cis-platinum, vincristine, methotrexate, bleomycin, -actinomycin-D, cyclophosphamide, etoposide (45).

**CARCINOSARCOMA**

Carcinosarcomas are very rare and account for only less than 1% to 2% of all malignant ovarian tumors. Histologically, it consists of a mixture of malignant epithelial and mesenchymal elements. These lesions are biologically aggressive and most patients have evidence of metastases. In general, the response to therapy and overall survival are poor with median survivals of 4 to 14 months (46–50).

The stage classification is the same FIGO system used for epithelial ovarian cancer. These patients should be treated by cytoreductive surgery.
and postoperative chemotherapy. Similar to epithelial ovarian cancer, significant survival benefit has been shown for women who have optimum cytoreduction after surgery (50). Although many patients die within a few months after surgery, a substantial proportion of patients who respond to chemotherapy may benefit with a better survival rate. The response rate to chemotherapy reported in the literature ranges from 35% to 47% (48-50). Many different chemotherapy regimens have been used, reflecting the uncertainty of treatment for this malignancy. The optimal chemotherapy has yet to be defined. Based on the experience on other female genital tract sarcomas, a combination of cisplatin and adriamycin is an option.

SMALL CELL CARCINOMA OF CERVIX

Small cell cancers have a higher frequency of lymph-vascular space invasion, a significantly higher rate of recurrence, particularly to extrapelvic sites, and a lower survival rate. Because of their propensity for early systemic spread, there is a need for primary therapy that addresses both regional and systemic sites. Chemotherapy is usually advocated in addition to surgery and/or radiation therapy.

A number of chemotherapeutic agents have been used with cisplatin as one of the most active agents. Several combinations of these agents have been shown to be able to achieve some level of response in the treatment of small cell carcinoma of the cervix. These combinations include: adriamycin and cyclophosphamide (51); cisplatin, doxorubicin, and etoposide (52); cisplatin, vincristine, methotrexate, doxorubicin, cyclophosphamide, and etoposide (53); cisplatin, etoposide, and concurrent radiation (54); and vincristine, adriamycin, and cyclophosphamide (55). Unfortunately, the large variety of treatment schemes used in the therapy of such a rare tumor does not allow comparison of their effectiveness.

Present aggressive therapy with surgery, radiation therapy, and chemotherapy has not significantly improved outcomes, though increases in progression-free survival have been noted. Continuing investigations with knowledge gained from treatment of small cell carcinoma of the lung are needed to find the best treatment option. A combination of cisplatin and etoposide has been shown to be the regimen of choice in small cell carcinoma of the lung (56). However, whether this regimen has the same level of effectiveness in the treatment of small cell carcinoma of the cervix remains to be proven.

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Drug Treatment for Sequelae After Gynecologic Cancer Treatment

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INTRODUCTION
Although there are a number of excellent gynecologic oncology textbooks available which discuss the treatment of various gynecologic cancers, many conditions that arise in the course and after cancer therapy have not been comprehensively discussed and contained in a textbook. This chapter focuses on the drug treatment for the prevention and treatment of sequelae after gynecologic cancer therapy.

COMPLICATIONS AFTER GYNECOLOGIC CANCER SURGERY
Infections
Infection is a major cause of morbidity and mortality in cancer patients. For patients with gynecologic malignancy, the most common source of bacteria that cause infection is the vaginal flora. Normally, this flora consists of a mixture of aerobes and anaerobes. The aerobes include gram-negative bacilli such as Escherichia coli, Klebsiella species, and Enterobacter species, and gram-positive cocci, including Streptococci and Enterococci. The anaerobes
include the Bacteroides and Prevotella species, the Clostridium species, and anaerobic Streptococci (1,2). Due to the proximity of the female genital tract to the urinary and colorectal systems, gynecologic cancer patients are prone to infections due to various reasons (Table 1).

Table 1  Infections in Gynecologic Cancer Patients

<table>
<thead>
<tr>
<th>Predisposing factor</th>
<th>Type of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor related</strong></td>
<td></td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>Peritonitis, septicemia</td>
</tr>
<tr>
<td>Ureteric obstruction</td>
<td>Pyelonephritis</td>
</tr>
<tr>
<td>Tumor necrosis</td>
<td>Abscess formation</td>
</tr>
<tr>
<td>Fistula formation</td>
<td>Urinary tract infection, skin infection</td>
</tr>
<tr>
<td>Cervical stenosis</td>
<td>Pyometra</td>
</tr>
<tr>
<td><strong>Treatment related</strong></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>Wound infection, infected lymphocyst, intra-abdominal sepsis</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Neutropenic sepsis</td>
</tr>
<tr>
<td>Radiation</td>
<td>Enteritis, wound infection, urinary tract infection</td>
</tr>
<tr>
<td><strong>Catheter related</strong></td>
<td></td>
</tr>
<tr>
<td>Transurethral or suprapubic catheter</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Percutaneous nephrostomy</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Intravenous catheter</td>
<td>Thrombophlebitis, septicemia</td>
</tr>
<tr>
<td>Intraperitoneal catheter</td>
<td>Peritonitis</td>
</tr>
</tbody>
</table>

include the Bacteroides and Prevotella species, the Clostridium species, and anaerobic Streptococci (1,2). Due to the proximity of the female genital tract to the urinary and colorectal systems, gynecologic cancer patients are prone to infections due to various reasons (Table 1).

Prophylaxis in Surgery

The overall operative site infection rate ranges from 6.7% to 44% (3–6). Prophylactic antibiotics are indicated for women undergoing pelvic surgery for malignancy, to reduce the chance of operative-site infections. The interpretation of prospective studies on this issue is limited by the small sample size of the studies. An overview of these studies showed that the overall incidence of pelvic infection and wound infection was significantly reduced by the administration of prophylactic antibiotics (7).

Combination regimens and prolonged administration do not appear to offer superior infection prevention when compared with that provided by a single-dose single-agent regimen. Moreover, a single-dose regimen has a theoretical advantage of being less likely to cause selection of resistant species (8). Cefazolin provides activity against gram-negative and gram-positive aerobic and anaerobic bacteria. It is an uncommon therapeutic agent and is comparatively inexpensive. A single dose of 2g given IV in the operating room is commonly used (9,10).

Bowel Preparation

Bowel preparation aims to reduce the colonic microflora and to decrease the chance of postoperative infection in case where colonic resection or
reanastomosis is needed. It can be mechanical or antimicrobial. Mechanical methods can only be used for patients with unobstructed bowel. Fleet phosphosoda in cold water the day before surgery is commonly used. Other regimens include whole gut irrigation with chilled polyethylene glycol and electrolyte therapy or a similar lavage solution given orally at a rate of approximately 1 L/hr until the rectal effluent is clear.

Antibiotic coverage to reduce the high bacterial count inside the lumen should include neomycin (1 g, oral) and erythromycin base (1 g, oral), each given three or four times the day prior to surgery. In addition, IV antibiotics should be given immediately before surgery.

**Urinary Tract Infection**

Many clinical situations predispose a patient to urinary tract infection (UTI), including prolonged bladder catheterization, pelvic irradiation, and urinary obstruction by tumor. Therapy should be based on the sensitivity pattern of the organism. In patients with pyuria and fever, empiric antibiotic therapy should be given while waiting for the urine culture results. For any gynecologic cancer patients without an explained predisposition to recurrent UTI, investigations should be performed to exclude obstruction as a cause.

Optimal duration of therapy in a patient with a urethral stent or a permanent indwelling catheter is often difficult to determine. It is virtually impossible to eradicate an infection in the presence of a foreign body, but removal of the stent or catheter is not always feasible. Chronic suppressive therapy may be needed. In general, among patients with gram-negative rods, chronic suppressive therapy may include ampicillin, trimethoprim–sulfamethoxazole, or ciprofloxacin. For gram-positive infections, amoxicillin–clavulanic acid, dicloxacillin, or carbenicillin indanyl sodium may be used.

**Wound Infection**

Many variables may influence the development of wound infection after surgery, including hospital flora, patient flora, operative technique and variables, patient nutrition, and immunocompetency due to prior chemotherapy or radiotherapy. Patient factors such as obesity and diabetes mellitus and surgical variables such as excessive inoculum at the operative site, excessive cautery, and suture materials are important risk factors for wound infections.

If wound infection is suspected, the wound should be explored, and aerobic and anaerobic cultures should be obtained. Foreign bodies such as suture or drain and necrotic tissues should be removed. The wound should be cleansed with dressing two to four times daily. Commonly used solutions include hydrogen peroxide, Salvon, or Hibitane solutions. Antibiotics are seldom necessary. These gaped wounds may be left open to heal by secondary intent, or they may be closed before discharge from the hospital after the margins are granulated. The optimal time for secondary closure is about fourth day after the institution of wound therapy.
Central IV Catheter-Related Infections

Indwelling central venous catheters are not uncommonly used in patients receiving chemotherapy or total parental nutrition. Catheter-related infections can cause considerable morbidity and occasional mortality (11,12).

Infections can be an exit-site or tunnel infection, and it can also be luminal with resulting bacteremias. An inflamed, tender area along the tunnel or purulence at the exit site should suggest infection. For luminal infection, the patient may complain of infusion-associated rigors and high fevers. Blood culture is essential to make the diagnosis, and this should be taken from both the peripheral and the central sites. Patients often require prolonged and frequent hospitalizations for antibiotic therapy, which should cover both gram-positive organisms and pseudomonas infection. Treatment should be continued for at least five to seven days after cultures become negative and for three to four weeks for pseudomonas infection. Sometimes, the catheter may have to be removed.

<table>
<thead>
<tr>
<th>Exit-site or tunnel infection</th>
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<tbody>
<tr>
<td>Vancomycin 1 g IV Q12H</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Catheter-related bacteremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticarcillin–clavulanic acid 3.1 g IV Q4H ± gentamicin</td>
</tr>
<tr>
<td>3–5 mg/kg/day in three divided doses</td>
</tr>
<tr>
<td>Vancomycin 1 g IV Q12H + gentamicin 3–5 mg/kg/day in three divided doses</td>
</tr>
</tbody>
</table>

Thromboembolic Disease

Gynecologic cancer patients are prone to develop thromboembolic complications as indicated by the Virchow trial, and this complication can be fatal. It is therefore essential to prevent this from happening, especially after pelvic surgery.

In choosing the methods for the prevention of thromboembolism (Table 2), the risk of hemorrhagic complications has to be weighed against the potential benefit achieved. For the physical methods, the hemorrhagic risk is negligible, but they are not sufficiently effective on their own. On the other hand, the pharmacological methods carry a risk of bleeding that is usually proportional to the intensity of the preventive effect (13).

Unfractionated heparin is either given in a fixed dose, which is usually 5000 U, starting from two hours before surgery and repeated every 8 to 12 hours, or in a dose, which is adjusted postoperatively to maintain a slight prolongation of the activated partial thromboplastin time (APTT) (13). The use of low-dose heparin resulted in a 67% to 75% risk reduction for deep vein thrombosis (DVT) and a 64% reduction of fatal pulmonary embolism from 0.9% to 0.3% (14).

The use of low-molecular-weight (LMW) heparins has mainly been compared with unfractionated heparins. They were found to have similar
efficacy in thromboprophylaxis. Owing to the almost complete bioavailability of LMW heparins after subcutaneous injections and a predictable dose–response relationship, there is no need for monitoring with a weight-adjusted dose. It also has a longer half-life, allowing for once daily injections in most situations and outpatient treatment (15,16). Moreover, there is a lower risk of heparin-induced thrombocytopenia than with unfractionated heparin.

Dextran is a branched polysaccharide and has been used in thromboprophylaxis. It is expensive and may cause anaphylactic reactions and volume overload. It is inferior to unfractionated and LMW heparin in the prevention of DVT (17).

It is crucial to anticoagulate in established venous thromboembolism (18). Unfractionated heparin given as IV infusion or subcutaneous injections is effective. Monitoring is required to verify adequate prolongation of the APTT to two to three times of the control value. During the past decade, a substantial number of trials and several meta-analyses have demonstrated that LMW heparins are effective and safe in the treatment of DVT (19–23). It has also been shown that LMW heparin is equally effective and safe in symptomatic, submassive pulmonary embolism.

When the initial treatment for venous thromboembolism is not accompanied by secondary prophylaxis, the risk of an early recurrence is high, and a recurrence rate of 32% during the first year has been reported. Maintenance prophylaxis is usually provided with vitamin K antagonists, aiming at an international normalized ratio of 2.0 to 3.0. The prophylaxis may be discontinued after six weeks in patients with calf vein thrombosis and an identified temporary risk factor, such as surgery (24). In all other groups, the risk of recurrence is reduced to half, if the prophylaxis is prolonged from six weeks to six months, with no appreciable increase in the risk of hemorrhage. For the

Table 2 Methods for Thromboprophylaxis

<table>
<thead>
<tr>
<th>General measures</th>
<th>Discontinuation of oral contraceptives a month before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Appropriate perioperative fluid substitution</td>
</tr>
<tr>
<td></td>
<td>The use of local or regional anesthesia rather than general anesthesia</td>
</tr>
<tr>
<td></td>
<td>Atraumatic surgical technique</td>
</tr>
<tr>
<td></td>
<td>Early mobilization after surgery</td>
</tr>
<tr>
<td>Physical Methods</td>
<td>Graduated compression stocking</td>
</tr>
<tr>
<td></td>
<td>Intermittent pneumatic compression</td>
</tr>
<tr>
<td>Pharmacological methods</td>
<td>Unfractionated heparin</td>
</tr>
<tr>
<td></td>
<td>Low molecular heparin</td>
</tr>
<tr>
<td></td>
<td>Heparinoids, e.g., dextran</td>
</tr>
<tr>
<td></td>
<td>Vitamin K antagonists</td>
</tr>
</tbody>
</table>

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patients who discontinue the anticoagulation after six weeks, there is a rapid accumulation of recurrent events up to six months (25).

**Bladder Dysfunction After Radical Hysterectomy**

During radical hysterectomy, part of the parasympathetic nerves to the bladder would be damaged while taking the uterosacral ligaments. It is a usual practice to continuously drain the bladder for few days to two weeks after operation so as to allow resting of the bladder and recovery of bladder function subsequent to the nerve injury. Majority of patients are able to void spontaneously, though a few may suffer from bladder dysfunction with difficulty in complete emptying of the bladder. Although not well proven by randomized studies, the use of cholinergic agents such as distigmine (5 mg daily) may be helpful.

**Chemotherapy-Related Complications**

**Chemotherapy-Induced Emesis**

Effective treatment and prophylaxis of chemotherapy-induced emesis requires an appreciation of the timing of onset of nausea and vomiting in relation to the administration of chemotherapy. The three main categories observed are acute, delayed, and anticipatory nausea and vomiting.

Most common is acute vomiting, beginning within one to two hours after dosing, reaching a peak at 4 to 10 hours, and usually resolving within 12 to 24 hours. Delayed nausea and vomiting can occur up to five days after administration of chemotherapy, being most common between 48 and 72 hours (26, 27). It is usually less severe but of longer duration than the acute type. Anticipatory emesis is a conditioned response, in which the occurrence of nausea and vomiting precede a scheduled dose.

There are five classes of drugs commonly used to treat chemotherapy-induced emesis. Their use and side effects are summarized in the Table 3. Combination regimens using drugs from different classes, with different mechanisms of action may increase the efficacy of treatment and may sometimes be necessary for cases refractory to single-agent therapy (28). Examples include the use of dexamethasone with metoclopramide or with ondansetron. Drug combinations may also be used to prevent specific side effects; for example, diphenhydramine can be added to prevent the extrapyramidal side effects associated with metoclopramide.

Chemotherapy-induced emesis is more easily prevented than treated. Therefore, antiemetics should be used prophylactically and continued for a duration characteristic of the chemotherapeutic agent used. Good initial response to therapy should be documented, and the same drugs should be used again on future occasions. Patient preference should be respected, because this usually reflects successful control.
Table 3  Antiemetics Used in Chemotherapy-Induced Vomiting

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Indication</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine antagonists</td>
<td>Acute and delayed nausea and vomiting. Moderate to severe emetic challenges</td>
<td>Sedation, diarrhea, extrapyramidal side effects</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT3 receptor antagonists</td>
<td>Severe emetic challenges</td>
<td>Headache, constipation, somnolence</td>
</tr>
<tr>
<td>Ondansetron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granisetron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Moderate emetic challenges. Combined with other agents in severe emesis</td>
<td>Increased appetite, mood elevation, reduced metoclopramide-associated side effects, somnolence, insomnia</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Moderate emetic challenge. Failed antiemetic treatment. Not suitable for patients with psychiatric disorder</td>
<td>Tachycardia, conjunctival injection, orthostatic hypotension, syncope, exacerbation of mania, depression, and schizophrenia</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>As an adjunct in anticipatory nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: HT: Hydroxytryptamine

Attention to patient’s psychological needs is critically important. Chemotherapy-induced emesis, especially if there is an anticipatory component, may benefit from psychological interventional measures such as cognitive behavioral therapy and the use of an adjunctive sedative or amnestic agent such as lorazepam.

Electrolyte Imbalance Associated with Chemotherapy

Potassium Disturbance

In gynecologic oncology, common causes of hypokalemia include diarrhea, intestinal or biliary fistulas, ileal conduits, vomiting, and diuretic therapy. Hypokalemia may be secondary to magnesium depletion, because magnesium is required for the membrane pumps in the renal tubules (29).

Normally, symptoms do not occur until the serum potassium is below 3.0 mmol/L. Replacement of potassium can be given orally or IV. In most cases, parenteral replacement is usually more effective and has faster actions. An increase of 1–1.5 mmol/L potassium can be achieved with a replacement at 0.7 mmol/kg of lean body weight over two hours. Most hospital protocols
prevent administration of more than 10–15 mmol/hr, but in cases of severe hypokalemia (below 2.0 mmol/L), 80–100 mmol of potassium can be administered over one hour with special precautions.

Hyperkalemia may be due to a number of causes including metabolic acidosis, renal impairment, adrenal insufficiency, or drugs [e.g., angiotensin-converting enzyme (ACE) inhibitors, non-steroid anti-inflammatory drugs (NSAIDs), or heparin]. Calcium gluconate is utilized in the treatment of acute hyperkalemia by antagonizing the effects of potassium in the central nervous system and heart. The duration of action is approximately one hour, and other measures to lower serum potassium level should be instituted concurrently. By exchanging sodium for potassium and inducing diarrhea, the use of ion-exchange resin/laxative combination (kayexalate and sorbitol) helps to maintain serum potassium less than 6 mmol/L. Insulin combined with dextrose infusions can also lower serum potassium level acutely, but this effect is transient, because it does not promote potassium clearance from the body. Hemodialysis is the most effective way to normalize the serum potassium until correction of the underlying process can be accomplished, but requires the placement of shunts, with associated complications.

Magnesium Disturbance
A major problem when diagnosing magnesium imbalances is the uneven distribution within the body. Less than 0.5% of magnesium is present in the serum. Serum magnesium may be normal even with magnesium depletion or excess (30). Low magnesium level may contribute to postoperative ileus or impaired respiratory motor function. Patients treated with platinum chemotherapy are prone to hypomagnesemia. Maintenance of adequate magnesium is important for muscle function. Replacement can be readily achieved via the oral, IV, or IM route.

Neutropenia
Cancer patients undergoing chemotherapy frequently develop transient low white cell count (neutropenia). The severity and duration of neutropenia are variable and depend on the drugs, the dose, the schedule, and the patient’s previous radiation and chemotherapy. Neutropenia predisposes to bacteremia. Pathogens implicated in these infections are gram-negative bacteria, including *Pseudomonas aeruginosa*, gram-positive bacteria, and fungi. During the past decade, there have been changes in the organisms that cause infection. While the incidence of gram-negative infections has declined, gram-positive organisms now account for between 60% and 70% of microbiological-documented infections in neutropenic patients (31,32).

In the absence of preventive measures, between 48% and 60% of neutropenic patients who become febrile have an infection, and around 20% or more of the patients with profound neutropenia (<100/mm³) have bacteremia (33–35). A number of strategies have been used to prevent the
occurrence of febrile neutropenia. These include isolation of the patient, granulocyte (G) transfusion, active or passive immunization, acceleration of G recovery, and prophylactic use of antibacterial agents. However, many of these approaches have fallen out of favor for various reasons (36).

**Antimicrobials:** Antibiotics and colony-stimulating factors (CSF) given in different schedules have been tested in clinical trials. The use of antibiotics given immediately after the chemotherapy has been tested (37), but no significant effect can be demonstrated. Another approach, by using antibiotics only after neutropenia develops, but before fever starts, has proven effective according to a meta-analysis (38). However, there are concerns about the emergence of antibiotics resistance (37), which lead the Infectious Diseases Society of America (39) to recommend against the routine use of antibiotics in afebrile neutropenia.

Febrile neutropenia is a potentially life-threatening situation and requires prompt medical intervention (40). The patients commonly do not have obvious sources of infection, with subtle clinical signs and symptoms. Usually the only manifestation of infection in such patients is fever (40,41). Management of these patients requires early aggressive antibiotic therapy prior to identification of the causative pathogen(s) or their susceptibilities. If antibiotics are not given in timely manner, mortality level can be as high as 47% and even up to 75%, depending on the type of pathogen (41).

However, there is no consensus as to which antibiotics or combinations of antibiotics are best for these patients. Numerous regimens are effective, and their use should be determined according to the sensitivity patterns for *P. aeruginosa* at the individual hospital (Table 4).

A recently published meta-analysis of 46 trials suggested advantages to broad-spectrum beta-lactam monotherapy over beta-lactam-aminoglycoside combination therapy (42), including (i) a similar survival, (ii) a significantly lower treatment failure rate, (iii) comparable secondary infection rates, and (iv) a lower rate of adverse side effects such as aminoglycoside-associated nephrotoxicity. Monotherapy should, therefore, be the preferred regimen.

Treatment should be modified in patients not responding to the initial antibiotic regimen. This usually includes vancomycin to cover resistant gram-positive bacteria and/or amphotericin B to treat fungal infections (31).

Although gram-positive infections currently dominate, empirical treatment does not cover these pathogens. In the Center for Disease Control recommendations, the empirical use of vancomycin for febrile neutropenic patients is specifically discouraged (43). This is because gram-positive infections are usually less rapidly fatal, permitting initiation of specific antibiotic treatment when such an infection is documented (44). Administration of vancomycin may be associated with adverse effects, especially when combined with aminoglycosides or other nephrotoxic agents. Moreover, the use of vancomycin has been associated with emergence of vancomycin-resistant enterococci, and
lately with *Staphylococcus aureus* resistant to vancomycin and other glycopeptides (45,46). Finally, the use of glycopeptides may increase the risk for fungal super infections, a feared complication with persistent neutropenia.

In patients with clinically suspected serious catheter-related infections, known colonization with gram-positive bacteria resistant to beta-lactams, positive blood cultures for gram-positive bacteria prior to final identification and susceptibility testing, or hypotension, the addition of vancomycin may be prudent.

Apart from gram-positive infections, cancer patients treated with chemotherapy also have an increased risk of acquiring fungal infections. Such infections can be life threatening, particularly in those with neutropenia. Antifungal drugs are therefore often given prophylactically to such patients, or when they have a fever. The rationale is to start therapy before it is too late, that is, before death is inevitable, because it is difficult to diagnose an invasive fungal infection with certainty (47). However, prophylactic or empirical treatment with antifungals was found to have no statistically significant effect on mortality (48).

IV amphotericin B is the only antifungal agent for which there is evidence suggesting that it might reduce mortality. It should therefore be preferred when antifungal therapy in cancer patients with neutropenia is considered indicated. Amphotericin B should be given under optimal circumstances, with premedication to reduce infusion-related toxicity, slow infusion, and with potassium and magnesium supplements to prevent nephrotoxicity.

**Granulocyte-colony-stimulating factors:** G-CSF regulates the production of neutrophil lineage. Its administration results in a dose-dependent increase in circulating neutrophils, due mainly to a reduced transit time from stem cell to mature neutrophil. Among the most used G-CSFs are filgrastim

---

### Table 4 Antibiotic Regimens for Neutropenic Patients

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Intravenous beta-lactam antibiotic given as monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antipseudomonal carboxy-penicillins or ureidopenicillins ± beta-lactamase inhibitor</td>
</tr>
<tr>
<td></td>
<td>Piperacillin, piperacillin/clavulanate, ticarcillin–clavulanate, azlocillin, mezlocillin</td>
</tr>
<tr>
<td></td>
<td>Cephalosporins</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime, ceftriaxone, cefoperazone, cefoxitin, cefuroxime, cefepime, ceftiraxone</td>
</tr>
<tr>
<td></td>
<td>Carbapenems</td>
</tr>
<tr>
<td></td>
<td>Imipenem/cilastatin, meropenem</td>
</tr>
<tr>
<td></td>
<td>Combination dualtherapy of an intravenous beta-lactam antibiotic with one of the following aminoglycosides given intravenously</td>
</tr>
<tr>
<td></td>
<td>Gentamicin, tobramycin, amikacin, netilmicin</td>
</tr>
</tbody>
</table>

---
and lenograstim. The recommended dose is 5–10 μg/kg/day by subcutaneous injection. Therapy should begin at least 24 hours after chemotherapy and continue daily until the expected nadir is past, and the neutrophil count is about $1.0 \times 10^9/L$. The next course of chemotherapy should not be given until at least 48 hours after the last dose of G-CSF because there will be a 50% drop in neutrophil count within 48 hours of discontinuing the G-CSF. Common side effects include bone, joint pain, and flu-like syndromes.

Prophylactic G-CSF has been found to be effective in reducing the incidence of febrile neutropenia when given immediately after chemotherapy (49,50). However, the use of G-CSF would be cost-effective only if more than 40% of patients are expected to develop febrile neutropenia (51,52).

Alternatively, G-CSF may be used after the development of neutropenia while patients are still afebrile. One randomized study of G-CSF against no therapy in these patients concluded that this therapy was ineffective (53), but another two randomized studies reached the opposite conclusion (54,55). The use of G-CSF has also been studied in patients with febrile neutropenia. These studies were limited by their small sample sizes. A meta-analysis suggested that the use of G-CSF does not affect overall mortality, but reduces the amount of time spent in hospital and the neutrophil recovery period (56). Based on the findings of these findings, the American Society of Clinical Oncology does not recommend the routine use of G-CSF in neutropenic patients (52,57).

Peripheral Neuropathy

A few of the commonly used chemotherapeutic drugs such as cisplatinum, vincristine, and taxol have side effects on the peripheral nerves leading to peripheral neuropathy. The first symptom is paresthesia, needling sensation of the fingers and toes described as “glove and stocking” distribution. This may progress to impairment of vibration sensation, loss of reflex, and weakness of muscle. In severe cases, the responsible chemotherapeutic agent may have to be stopped. It is, however, unfortunate that symptoms tend to persist with slow recovery over months or even years. Amitriptyline may provide some relief in symptomatic patients. Protective agents such as amifostine have been tested, and no significant protective effect against neurotoxicity has been identified (58,59). The role of oral vitamin B6 is also limited.

Radiation-Associated Side Effects

The gastrointestinal tract can be particularly sensitive to radiation damage. The actively mitotic cells of the gastrointestinal tract, especially the mucosal layers, are susceptible to acute toxicity. Chronic radiation effects appear late following irradiation, often after many months and are commonly attributed to the radiation-induced vascular injury with progressive ischemia. Acute radiation effects on tissue typically correlate with the daily dose (dose rate) and the total
dose delivered, whereas chronic effects are generally determined by the total dose and volume of tissue included in the radiation field (60).

Radiation-associated side effects can be classified according to the time following radiation. Acute effects can be defined as that occurring during or within one month of radiation therapy. Side effects that appear between one and three months following radiation are often termed “subacute,” whereas chronic effects appear more than three months following treatment. Often acute and subacute complications are grouped together and are considered distinct from chronic toxicity.

**Acute or Subacute Complications**

Acute effects such as nausea, vomiting, abdominal cramps, and diarrhea are commonly observed during abdominal and pelvic radiation. These symptoms are generally self-limited and usually resolve after the completion of therapy. Anticholinergic medication and opiates often can provide symptomatic relief. Those patients with symptoms unresponsive to these agents may benefit from cholestyramine and bile salt–sequestrating agents. Change in dose rate and in the volume irradiated can also relieve the acute symptoms. Decreasing the daily dose rate by as little as 10% can improve symptoms.

Radiation injuries of the large bowel can cause rectal bleeding in addition to nausea, vomiting, cramps, and diarrhea. This injury is most commonly in the rectum due to its fixed position and its proximity to the female genital tract. Like other acute effects, the symptoms of acute radiation proctitis usually subside shortly after the completion of radiation therapy and require no therapy for the small amount of bleeding. However, marked continuous bleeding may occur and require medical treatment of the proctitis, with periodic blood transfusion. Medical treatment for this condition includes the use of stool bulking agents, softeners, antidiarrheal agents, antispasmodics, and steroid enemas. Continued bleeding despite these measures requires more aggressive treatment such as endoscopic laser photocoagulation.

**Chronic Complications**

**Radiation Proctitis**

Late effects may occur in the rectosigmoid or terminal ileum, leading to bleeding, stricture, obstruction, fistulas, or perforation. Among these complications, chronic radiation proctitis is relatively more common, with a prevalence of 5% to 10%. Presently, there is no recommended standard management. This is, in part, due to the difficulties in recognizing and establishing the diagnosis and also because some of the biological changes may not be reversible. The outcome of both medical and surgical management for this condition can be disappointing.

A number of treatment options have been suggested, including low-residue or elemental diets, pain control, and replacement transfusion. Other
therapies are of variable benefit in controlling symptoms and are summarized in Table 5. With the episodic and variable nature of late radiation proctitis in mind, placebo-controlled studies are required to assess whether these treatments are effective (61).

Although the use of certain interventions (e.g., rectal sucralfate, adding metronidazole to the anti-inflammatory regime and heater probes) have been associated with clinical improvement for radiation proctitis, the interpretation of these results has been limited by the small sample sizes and the lack of placebo control in these studies.

Table 5 Nonsurgical Treatment for Radiation Proctitis

<table>
<thead>
<tr>
<th>Nonsurgical treatment options</th>
<th>Mechanism</th>
<th>Examples and route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminosalicylic acid derivatives</td>
<td>Anti-inflammatory</td>
<td>Sulfasalazine and mesalazine, given orally</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Anti-inflammatory</td>
<td>Hydrocortisone or betamethasone, given orally or as rectal enema</td>
</tr>
<tr>
<td>Sucralfate preparations</td>
<td></td>
<td>Sucralfate, given orally or rectally</td>
</tr>
<tr>
<td>Short-chain fatty acid preparations</td>
<td>To optimize the method of delivery of nutrients direct to the colonocyte to accelerate tissue repair</td>
<td>Rectal administration</td>
</tr>
<tr>
<td>Formalin application</td>
<td>Reduce and stop bleeding from radiation-induced telangiectasia or neovascularature</td>
<td>Rectal application or irrigation</td>
</tr>
<tr>
<td>Thermal coagulation therapy</td>
<td>Control rectal outlet bleeding</td>
<td>Argon laser and endoscopic coagulation therapy</td>
</tr>
</tbody>
</table>

Radiation Cystitis

Late radiation cystitis represents a spectrum of symptoms and clinical features occurring by definition, at least three months after completion of pelvic radiotherapy. Due to the proximity of the organs in the pelvis,field arrangements that produce late radiation toxicity in the bladder often occur with similar changes in the rectum. This may cause urinary problems including pain, blood in the urine, and reduced bladder capacity. A cycle of bleeding, infection and, occasionally, life-threatening complications can occur.

In such a relatively rare condition, there are obvious difficulties in identifying sufficient patients to participate in a randomized controlled trial.
Moreover, documentation of toxicity is often inconsistent, making evaluation of responses to treatments difficult.

The optimum treatment for this type of clinical problem is not defined, and the outcome of medical management can be disappointing (62). Treatment options include treating infections, blood transfusion, catheterization, and bladder irrigation. Other nonsurgical treatments include drugs instilled into the bladder (Table 6).

Apart from the above nonsurgical treatments for late radiation changes, there are other experimental treatment options (61,62). Analogues of the naturally occurring superoxide dismutase, which inhibit the production of free radicals (the basis of radiation effect), have been used in the treatment of radiation cystitis and proctitis. Pentoxyfilline may contribute to the healing of late radiation injury by improving blood flow in compromised tissue. The use of hyperbaric oxygen may increase vascular density and promote healing of radiation-damaged tissues through its angiogenic effect.

REFERENCES


**Table 6** Nonsurgical Treatment for Radiation Cystitis

<table>
<thead>
<tr>
<th>Treatment options</th>
<th>Mechanism</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravesical agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alum irrigation</td>
<td>Protein precipitation, alleviating capillary bleeding</td>
<td>It has no use in heavy bleeding</td>
</tr>
<tr>
<td>Formalin instillation</td>
<td>Reduce and stop bleeding from radiation-induced telangiectasia or neovasculature</td>
<td>Vesicoureteric reflux may produce a bilateral pyonephrosis with fatal sepsis</td>
</tr>
<tr>
<td><strong>Systemic therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d-glucosamine, a precursor of glycosaminoglycans</td>
<td>Adhere to the bladder surface supplementing the defective natural glycosaminoglycans layer</td>
<td></td>
</tr>
<tr>
<td>Estrogens</td>
<td>Stabilization of vascular fragility</td>
<td></td>
</tr>
</tbody>
</table>
Common Drugs Used in Palliative Phase in Advanced Gynecological Malignancy

K. K. Lam
Palliative Medical Unit, Grantham Hospital, HKSAR, Hong Kong, China

Y. M. Chan and Hextan Y. S. Ngan
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University of Hong Kong, HKSAR, Hong Kong, China

INTRODUCTION

Pain and symptom control is an essential component of palliative care. Drugs play a very important role in this aspect. Pain and symptom control must be based upon scientific evidence as far as possible. An absence of evidence does not mean that something is not effective but it means that we do not know. Patient and family wishes and preferences have to be considered and different options of treatment and explanations have to be offered to patient and family to enhance compliance with the treatment regimen.

The use of drugs in palliative medicine may sometimes be considered as unconventional in general medical fields. The information provided below is not exhaustive. Readers are advised to review the relevant palliative medicine and drug literatures or consult a specialist in palliative medicine in case of doubts.

PAIN MANAGEMENT

General principles of pain management should be followed. One should first identify the site of pain and assess the pain intensity, using numerical rating
scale (0–10) or visual analogue scale (mark on a scale from 0–100 mm), then assess the impact of pain on the patient’s psychological and functional aspects, sleep, and the meaning of pain for the patient. One should elucidate the etiology and pathophysiology of pain and prescribe drug treatment according to World Health Organization (WHO) three-step analgesic ladder (1) and pathophysiology of pain. WHO analgesic ladder includes three steps. Step 1 is nonopioids—e.g., paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs). Step 2 is weak opioids ± nonopioids, e.g., dextropropoxyphene. Step 3 is strong opioids ± nonopioids—e.g., morphine and fentanyl. If pain cannot be controlled by step 1, one should proceed to step 2, and then step 3 until the pain is adequately controlled, which means that the pain is no longer bothersome to the patient (Fig. 1).

The prescription of analgesic, besides by the ladder, should also be by the mouth as far as possible because it is the most convenient route and by the clock. All moderate-to-severe pain should be put on a fixed dose schedule around the clock and not on an as-needed basis and the patient should also be given “rescue doses” in addition to control any breakthrough pain.

Pain prescription should also be individualized because individual requirements for analgesics vary enormously, and the dosage of analgesics must be titrated against that particular patient’s pain. Adjuvant analgesics can be used in all steps of analgesic ladder if indicated, to enhance analgesic effects, e.g., antidepressants and anticonvulsants in neuropathic pain, or to control adverse effects of opioids, e.g., antiemetics and laxatives.

**Nonsteroidal Anti-inflammatory Drugs**

NSAIDs, e.g., diclofenac and naproxen, are indicated in mild-to-moderate pain as analgesic, especially if there is inflammation involved, e.g., soft-tissue infiltration or bone metastasis (2). Their main side effects are gastrointestinal.
They produce peptic ulcerations and gastric irritation. This risk is increased significantly with concomitant use of steroids. Misoprostol (0.2 mg b.d.) or high-dose H2 inhibitors (e.g., famotidine 40 mg b.d.) can prevent both gastric and duodenal ulcerations induced by NSAIDs with or without steroids. It can also induce renal failure if patient already has decreased circulating volume from any causes. NSAIDs cause fluid retention. They also cause reversible inhibition of platelet aggregation and increase bleeding time. Hypersensitivity reactions and skin rashes can also occur (Table 1).

**Weak Opioids**

In general, a weak opioid should be added to, not substituted for, a nonopioid (e.g., Dologesic: the weak opioid dextropropoxyphene is added to paracetamol). If a weak opioid is inadequate in pain control when given regularly, it should be replaced by a strong opioid. Opioids include all natural and synthetic drugs with morphine-like activity. The most commonly used weak opioid is dextropropoxyphene. Its common side effects are nausea, vomiting, drowsiness, and dry mouth, though less so than low-dose morphine. Distalgesic (or dologesic) contains paracetamol 325 mg and dextropropoxyphene 32.5 mg (Table 2).

**Strong Opioids**

Commonly used strong opioids are morphine and fentanyl.

**Morphine**

Morphine is the strong opioid of choice. It is the main pharmacologically active constituent of opium. It acts on specific opioid receptors. Side effects

<table>
<thead>
<tr>
<th>Oral drugs</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>50 mg b.d. to t.i.d.</td>
</tr>
<tr>
<td>Diclofenac slow release</td>
<td>100 mg to 150 mg q.d.</td>
</tr>
<tr>
<td>Naproxen</td>
<td>250 mg to 500 mg b.d., maximum dose 500 mg t.i.d.</td>
</tr>
</tbody>
</table>

**Table 1** Usual Dosage of Common Nonsteroidal Anti-inflammatory Drugs

<table>
<thead>
<tr>
<th>Oral drugs</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

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<table>
<thead>
<tr>
<th>Oral drugs</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distalgesic</td>
<td>1–2 tablets q.i.d., maximum is 12 tablets/day, including the p.r.n. doses (p.r.n. doses of tablet 1–2 q4h to q6h may be added)</td>
</tr>
</tbody>
</table>

*Limited by the liver toxicity caused by high dose of paracetamol.*
of strong opioids include sedation, myoclonus, itching, sweating, and dry mouth. Morphine (syrup) is well absorbed orally, given at four hourly dose intervals. Morphine slow-release tablets (MST) are usually given 12 hourly. It may need to be given in eight hourly dosing in some patients. Total daily dose of syrup morphine is equivalent to total daily dose of MST (Table 3).

The starting dose for pain control in adults not controlled on regular weak opioids is 10 mg four hourly morphine (syrup) or 30 mg q12h MST. For elderly, cachectic, or those not taking regular weak opioids, 5 mg four hourly morphine or 10 to 20 mg q12h MST may be more appropriate. Morphine is approximately twice as potent by subcutaneous injection (or infusion) and thrice as potent by intravenous (IV) injection (or infusion). Constipation is almost inevitable and is dose related. A laxative should always be prescribed when starting treatment with a strong opioid (senna with or without docusate). Nausea and vomiting may be relieved by an antiemetic (haloperidol or metoclopramide), but an initial nausea and drowsiness after starting morphine or escalating the dose will usually wear off after a few days.

The rescue dose may be given as often as required (every hour) and each dose is calculated as one-tenth dose of the total daily morphine prescribed (3). Once the patient is seen to tolerate the morphine, a double dose can be given at bedtime to omit the need for a dose in the middle of the night. When pain is controlled, continue either the morphine (syrup) as scheduled or convert to convenient MST dose. One should give the last dose of syrup morphine together with the first dose of MST, but continue to use morphine syrup for breakthrough pain. If the patient is vomiting or no longer able to swallow medication, use continuous subcutaneous infusion (CSCI) by a syringe driver. Active treatment of opioid toxicity is only necessary with severe respiratory depression (respiratory rate <8/min, with reduced conscious level) by using naloxone—a potent opioid antagonist. It is given by diluting 0.4 mg of it in 10 mL water and injecting IV 1 mL every

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Usual Dosage of Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Starting dosage</td>
</tr>
<tr>
<td>Oral syrup morphine</td>
<td>5–10 mg q4h</td>
</tr>
<tr>
<td>Oral morphine slow-release tablets</td>
<td>10–20 mg q12h</td>
</tr>
<tr>
<td>Continuous subcutaneous infusion morphine</td>
<td>Total daily oral dose divided by 2, given in 24 hr</td>
</tr>
</tbody>
</table>

*Note: Dose titration is increased by increments of 30–50%, e.g., 5-10-15-20-30-40-60-100-120-160-200 mg (for reference only). Very few patients will require more than 600 mg daily.*
50 to 60 seconds to prevent acute opioid withdrawal. Naloxone injection should be stopped immediately when respiration has returned to normal.

Fentanyl

Fentanyl (4) is a highly selective opioid mu-1 receptor agonist and causes fewer side effects than does morphine, especially constipation and dysphoric effects. Because its effect is more selective than morphine, it may be helpful in patients with morphine responsive pain who develop intolerable side effects. Due to its lack of effects on other opioid receptors, conversion from morphine to fentanyl may lead to withdrawal symptoms, e.g., colic, diarrhea, nausea, sweating, and restlessness. These can be treated by the smaller rescue doses of morphine. Fentanyl is indicated when increasing dose of morphine relieves pain but causes unacceptable side effects, e.g., drowsiness and severe constipation. It is also used in patients with renal impairment leading to accumulation of toxic metabolites resulting in toxicity, e.g., myoclonus and confusion. It is used when patients have swallowing difficulties, e.g., in patients with head and neck cancer. Fentanyl is not absorbed orally and is available as injection or transdermal patch.

Transdermal fentanyl patch provides continuous opioid delivery for up to 72 hours.

Conversion dose from syrup morphine to transdermal fentanyl shown in the table serves as a guideline (Table 4) (4).

When applying the patch, one should give three more doses of morphine syrup or give the last dose of MST because fentanyl reaches maximum blood levels in 12 to 24 hours. Morphine syrup should be continued if needed for withdrawal symptoms of morphine or breakthrough pain. The patch should be changed every 72 hours and applied to dry, noninflamed, nonirradiated, unshaven, and hairless skin on the upper arm or trunk. The rate of absorption of fentanyl from the patch may be increased in febrile patients or if the skin under the patch becomes vasodilated because of an external heat source nearby. Transdermal fentanyl is contraindicated in patients who need rapid titration of their analgesics for severe uncontrolled pain. Fentanyl will not relieve pain that is nonresponsive to morphine.

### Table 4 Conversion Table from Syrup Morphine to Transdermal Fentanyl Patch

<table>
<thead>
<tr>
<th>Daily oral morphine dose (mg)</th>
<th>Fentanyl patch dose q72h (µg/hr patch)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–134 (average 90)</td>
<td>25</td>
</tr>
<tr>
<td>135–224 (average 180)</td>
<td>50</td>
</tr>
<tr>
<td>225–314 (average 270)</td>
<td>75</td>
</tr>
<tr>
<td>315–404 (average 360)</td>
<td>100</td>
</tr>
</tbody>
</table>
ADJUVANT ANALGESICS USED IN NEUROPATHIC PAIN

Pain is classified generally as nociceptive or neuropathic. Nociceptive pain is the pain that is perceived to be commensurate with tissue damage associated with identifiable somatic or visceral lesion. It is usually opioid responsive. Neuropathic pain is the pain due to damage to or dysfunction of the nervous system itself. The working definition of neuropathic pain is pain in an area with abnormal or absent sensation, with associated characteristic features of neuropathic pain, e.g., dysesthesia—unpleasant abnormal sensation, with burning, prickling characteristics or paroxysmal, stabbing, shooting, or constricting pain, or allodynia, which is pain due to a stimulus that does not normally provoke pain (e.g., touch or cold). Neuropathic pain can be due to nerve compression or nerve injury. Nerve compression pain is usually responsive to opioid or steroid (e.g., dexamethasone 8 mg o.m. and noon). Nerve injury pain (neurogenic pain) is usually less responsive to opioid and may need adjuvant analgesic as an add-on therapy to control the pain. Commonly used adjuvant analgesics are antidepressants and anticonvulsants.

Antidepressants

Antidepressants act by blocking the reuptake of pain inhibitory neurotransmitters noradrenalin and serotonin (5). The prototype is amitriptyline, which is used for continuous dysaesthesia neuropathic pain. Side effects of amitriptyline are due to its antihistamine effects, e.g., drowsiness and tiredness and its anticholinergic effects, e.g., constipation, dry mouth, and urinary retention.

Anticonvulsants

Anticonvulsant (membrane stabilizer) is used in paroxysmal shooting or stabbing pain, which is caused by bursts of ectopic discharges from damaged nerves. Gamma-aminobutyric acid (GABA) is a principal neurotransmitter found in inhibitory interneurons in the dorsal horn of spinal cord. The anticonvulsant sodium valproate enhances GABA function and has been found effective in the treatment of trigeminal and postherpetic neuralgia. It is generally well tolerated. Its main side effects are sedation and nausea (6). The more expensive anticonvulsant drug gabapentin acts by inhibiting the release of excitatory neurotransmitters at N-methyl-D-aspartate (NMDA) and non-NMDA receptors. It may also enhance GABA function (7). Its side effects are somnolence and dizziness (Table 5).

Because neuropathic pain is partially opioid responsive and there is usually a mixed nociceptive and neuropathic pain in clinical situation, opioid and adjuvants are usually used together if neuropathic pain is suspected to be present. There is great interindividual variability in the response to adjuvant analgesics. Sequential drug trials may be necessary to find
out the best suitable drugs for the patient. Low initial doses and gradual dose escalation may avoid early side effects but may delay the onset of analgesia, and the patient must be forewarned of this possibility to improve compliance with therapy, otherwise the drugs may be stopped prematurely.

**NAUSEA AND VOMITING**

In the management of nausea and vomiting in advanced cancer, first find out the causes and treat or remove the reversible causes; then choose the most appropriate antiemetic according to the neurotransmitters involved in the vomiting pathway (8). The most commonly used antiemetics are discussed below.

**Class A**

Prokinetics are drugs that coordinate anteroduodenal contractions and accelerate gastrointestinal transit. The most commonly used prokinetic is metoclopramide. Metoclopramide also acts on the gut as peripheral dopaminergic antagonist to inhibit the dopaminergic brake in the myenteric plexus. It also acts on 5HT4 (serotonin) receptors in the gut to improve upper gastrointestinal transit (9). Its side effects are sedation, dystonia, and extrapyramidal. It can be given orally, intramuscularly, intravenously, or CSCI.

**Class B**

Central dopaminergic antagonist inhibits the chemoreceptor trigger zone (CTZ), which is activated by drugs, toxic metabolites, and biochemical abnormalities in the blood, thus decreasing afferent inputs from CTZ to the vomiting center. The most potent drug in this group is haloperidol. Its side effect is extrapyramidal.

**Class C**

Antihistamine inhibits the histamine receptors in the vomiting center and vestibular apparatus. This group of drugs, including cyclizine and meclizine, also has anticholinergic effects. Its side effects are dry mouth, drowsiness, and constipation. Drug combinations of different class (A, B, or C) may be more

### Table 5 Usual Dosage of Adjuvant Analgesics

<table>
<thead>
<tr>
<th>Adjuvant analgesic</th>
<th>Oral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>25–100 mg nocte</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>400 mg nocte to 1200 mg/day in 3 divided doses</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300–1800 mg/day in 3 divided doses</td>
</tr>
</tbody>
</table>
efficacious. One should not prescribe a prokinetic (which acts through cholinergic pathway) and an anticholinergic drug concurrently (e.g., cyclizine) (Table 6).

### Table 6: Usual Dosage of Antiemetics

<table>
<thead>
<tr>
<th>Antiemetic drugs</th>
<th>Oral dose</th>
<th>Continuous subcutaneous infusion dose over 24 hr (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide</td>
<td>10–20 mg q4h to q6h</td>
<td>60–240</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1.5 mg nocte to 5 mg/ day in 2 divided doses</td>
<td>5–20</td>
</tr>
<tr>
<td>Cyclizine or meclizine</td>
<td>25–50 mg q8h or t.i.d.</td>
<td>100–150 (for cyclizine only)</td>
</tr>
</tbody>
</table>

### INTESTINAL OBSTRUCTION

Distressing symptoms resulting from intestinal obstruction are common in patients with abdominal and pelvic cancers, e.g., ovarian, colorectal, pancreatic, or prostate cancer. Bowel obstruction is often multifactorial, with contributing factors also from inflammatory edema, fecal impaction, or administration of constipating drugs (10). The obstructive symptoms in advanced cancer are usually intermittent in nature. The main symptoms are intestinal colic, continuous abdominal pain due to distension, hepatomegaly or tumor mass, and vomiting.

Surgical treatment, aimed at restoring the continuity of the bowel lumen, should be considered for every patient. The goal of pharmacologic treatment is to relieve the distressing symptoms of intestinal obstruction until it subsides or till death. In the majority of cases, obstructive symptoms can be controlled, but a small group, mainly gastroduodenal or jejunal obstruction, may require nasogastric intubation or venting gastrostomy. CSCI using a portable syringe driver is the preferred route of drug administration in intestinal obstruction.

**Class A**

Morphine is used for control of continuous abdominal pain.

**Class B**

Antispasmodic is used to control the intestinal colic. The most common antispasmodic used, hyoscine butylbromide, is a naturally occurring belladonna alkaloid with smooth muscle relaxant and antisecretory properties. It does not cross the blood–brain barrier and therefore does not cause drowsiness. Its side effects are due to its antimuscarinic effects, e.g., dry mouth and urinary retention.
**Class C**

Antiemetic drugs, both haloperidol and cyclizine, are used as first-line treatment, either alone or in combination.

**Class D**

Laxatives—fecal softener laxatives (e.g., docusate) may be given to patients in whom colonic or rectal obstruction is suspected. Patients should be allowed to take small, low residue, mainly fluid meals according to their choice and pace when the vomiting is controlled. IV hydration is needed only if the patient is hypotensive due to dehydration. Pharmacologic treatment of intestinal obstruction in advanced malignancy is preferred to prolonged nasogastric suction and IV fluid. The nasogastric tube will interfere with cough and swallowing and may be associated with nasal cartilage erosion and aspiration pneumonia. It creates additional discomfort and distress to patients and the “drip and suck” is regarded as barriers between them and family members. The place of dexamethasone in intestinal obstruction is controversial (Table 7).

**CONSTIPATION**

Constipation is very common in palliative care patients (11). It occurs in 50% of patients with advanced cancer and in over 80% of patients receiving opioids. It is a frequent cause of severe distress, and may be associated with abdominal pain, flatulence, bloating, and nausea. The goal of pharmacologic therapy is to prevent constipation, and failing that, to treat it. For patients initiating opioid therapy, laxatives should be given as a routine preventive measure in general, and senna is the stimulant laxative of choice. Nonpharmacologic measures are also important to treat constipation, e.g., increased fluid or dietary fiber intake, increased mobility, abdominal massage or establish a regular bowel routine, especially after breakfast. Drugs commonly used as laxative are discussed below.

---

**Table 7** Usual Dosage of Drugs Used in Intestinal Obstruction

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Continuous subcutaneous infusion dose in 24 hr (mg)</th>
<th>Stat IMI or IVI dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>As needed</td>
<td>NA</td>
</tr>
<tr>
<td>Hyoscine butylbromide</td>
<td>60–120</td>
<td>20</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>5–15</td>
<td>NA</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>60–240</td>
<td>10</td>
</tr>
</tbody>
</table>

*Abbreviations: NA, not applicable; IMI, intramuscular injection; IVI, intravenous injection.*
Oral Laxatives

1. Surfactant laxative (docusate) acts as a detergent to increase water penetration of stool. It also promotes fluid secretion into the bowel. It is used as a stool softener. It may have an unpleasant aftertaste, which is minimized by drinking plenty of water.

2. Contact (stimulant) cathartics directly stimulate myenteric plexus to induce peristalsis. Senna is an anthranoid laxative that passes unabsorbed and unchanged through the small bowel and is hydrolyzed by bacterial glycosidases in the large bowel to yield the active agent. The usual starting oral dose is 15 mg nocte (Senokot tablet contains 7.5 mg/tablet). For patients receiving opioids, one should start with 15 mg b.d., and the dose can be increased up to 22.5 mg t.i.d. Patients with hard stool may require a combination of a stimulant laxative and a stool softener. The main side effect is colicky abdominal pain in some patients.

3. Osmotic laxative—lactulose—is a synthetic disaccharide and a combination of galactose and fructose, which is not absorbed by the small bowel. It exerts an osmotic effect in the small bowel to retain water in the lumen. It is then degraded by colonic bacteria flora to acetic acid and lactic acid, which stimulate peristalsis. It may take few days to have effects. Its side effects: abdominal colic, flatulence, bloating, and intolerance due to its sweet taste. Because it is much more expensive than senna and not more efficacious than senna with similar side effects, senna is more preferable and osmotic agents may not be needed in most cases (Table 8).

Rectal Laxatives

Rectal laxatives are used if oral laxatives are unsuccessful, either in the form of suppositories or enemas.

1. Glycerine suppositories promote defecation by softening and lubricating the feces as well as stimulating defecation.

2. Bisacodyl suppositories are polyphenolic stimulant rectal laxative which when applied to rectal mucosa, induce almost immediate powerful peristalsis.

<table>
<thead>
<tr>
<th>Table 8</th>
<th>Usual Dosage of Oral Laxatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral laxative</td>
<td>Dose</td>
</tr>
<tr>
<td>Senna (Senokot)</td>
<td>Tablet 2 nocte to tablet 3 t.i.d.</td>
</tr>
<tr>
<td>Docusate</td>
<td>100–200 mg b.d.</td>
</tr>
<tr>
<td>Lactulose</td>
<td>15 mL b.d.–30 mL t.i.d.</td>
</tr>
</tbody>
</table>
3. Sodium phosphate enema (Fleet enema) is used if suppositories are ineffective. It is an osmotic enema, which stimulates large bowel peristalsis. For very hard fecal impaction, manual rectal evacuation may be necessary, with pain medications or sedatives given prior to the removal procedure.

SYMPTOMS FROM MALIGNANT ASCITES

Ascites is defined as excessive accumulation of fluid (exudate) into the peritoneal cavity (12). It causes abdominal distension, pain, nausea, vomiting, and dyspnea. Cancer accounts for 10% of all causes of ascites, which occurs most commonly in ovarian, endometrial, breast, colonic, gastric, and pancreatic cancers. Twenty percent of malignant ascites has unknown primary tumors. Mechanical drainage of ascites provides rapid relief of symptoms in tense ascites if there is no contraindication, e.g., bleeding tendency. Drug treatment of malignant ascites is by diuretics. Oral diuretics are effective in about one-third of patients and it is difficult to predict which patients would respond, but they should be considered in all patients with malignant ascites. They may also be useful in the prevention of reaccumulation of ascites. The diuretic of choice is spironolactone, which is an aldosterone antagonist.

It acts by inhibiting the action of aldosterone on renal distal tubules. One should start with 100 to 150 mg/day, then gradually increasing the dose every three days, until a response is achieved or unacceptable side effects occur, up to about 400 mg/day.

It is important to monitor urea and electrolytes regularly. If hyperkalemia develops or response is not satisfactory, one can add frusemide instead of adding spironolactone. Once a satisfactory response is achieved, it may be possible to reduce the dose of diuretics for maintenance therapy (Table 9).

SYMPTOMS FROM HYPERCALCEMIA OF MALIGNANCY

Normal range of total plasma calcium concentration is 2.2 to 2.62 mmol/L. The total plasma calcium is affected by binding with plasma proteins. Adjusted plasma calcium level corrected for albumin level is calculated by measuring plasma calcium level + (40 - measured plasma albumin in g/L)× 0.025, assuming the normal plasma albumin is 40 g/L. The major mechanism and pathogenesis

<table>
<thead>
<tr>
<th>Table 9</th>
<th>Usual Dosage of Diuretics for Malignant Ascites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Oral dose (mg/day)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>100–400</td>
</tr>
<tr>
<td>Frusemide</td>
<td>40–80</td>
</tr>
</tbody>
</table>
of hypercalcemia in advanced malignancy is due to increased osteoclastic bone resorption, mediated by cytokines that is locally produced in response to metastases (13). Most hypercalcemic patients are dehydrated so that IV fluid 3 to 4 L/day of normal saline has to be given for rehydration first before the drug treatment. The most common drug used to treat malignant hypercalcemia giving rise to symptoms is the second-generation bisphosphonate, pamidronate disodium, which inhibits osteoclast activity. It is given as a single IV infusion in 500 mL of normal saline in four hours. The maximum effect is usually seen within 7 days and then the effect usually lasts for about 28 days. Its side effect is fever or flu-like symptoms occurring within two days of IV infusion. If the response is not satisfactory within seven days, repeated infusion with higher dose may be tried. IV potassium supplement has to be given if the serum potassium level is low before or after pamidronate infusion (Table 10).

THE USE OF STEROID IN ADVANCED CANCER

Dexamethasone is the chosen steroid because of its less salt-retaining properties compared with prednisolone (14). Common specific indications for starting steroid are epidural spinal cord compression, brain metastasis, lymphangitis carcinomatosis, and superior vena caval obstruction. The usual oral dose used is 8 mg o.m. and noon in order to reduce nighttime agitation and insomnia. Nonspecific indications of steroid are anorexia, low mood, pain, and weakness (Table 11).

The results of steroid should be assessed after one week and the drug can be stopped if there has been no therapeutic response. Stopping steroid abruptly is safe after a week if no more than dexamethasone 6 mg/day is given (15). Short courses of larger doses and longer courses of lower doses may suppress the hypothalamic-pituitary-adrenal axis for prolonged periods. Doses then have to be tapered more slowly over days and weeks.

Table 10  Intravenous Pamidronate Dose Escalation

| Starting dose | 30 mg |
|  | If unsatisfactory response after 7 days | 60 mg |
|  | If still unsatisfactory response | 90 mg |

*Single infusion in 500 mL of normal saline in 4 hr.

Table 11  Dosage of Dexamethasone Used in Malignancy

<table>
<thead>
<tr>
<th>Underlying conditions</th>
<th>Oral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific</td>
<td>8 mg o.m. and 8 mg noon</td>
</tr>
<tr>
<td>Nonspecific</td>
<td>4 mg q.d.</td>
</tr>
</tbody>
</table>
If there is improvement, try to reduce to minimal dose that maintains the benefit. The patients and families should be warned of the side effects of steroid therapy and the danger of stopping abruptly. The side effects of steroid, especially in long-term use (more than two weeks), are weight gain, change in facial appearance, acne, and sleep disturbances. More serious side effects including hyperglycemia, peripheral edema, susceptibility to infection (fungal infection of oral cavity and esophagus), proximal myopathy, peptic ulcer, and psychosis can also occur.

A decreased serum albumin level less than 2.5 g/dL will make the patients more prone to the toxicity of steroid therapy. Long-term steroid is however sometimes indicated if there is presence of steroid reversible neurologic deficits (Table 11).

REFERENCES

FURTHER READING


INTRODUCTION

Urogynecology encompasses problems of the lower urinary tract and genital tract in women, which, being in close proximity, often develop coexistent disorders. Although rarely life-threatening, urinary problems, such as incontinence, and pelvic organ prolapse cause distress to the individual or her carers, significantly impair quality of life, and impose a considerable financial burden on the health care budget of the nation. Sufferers may have to alter many of their routines and habits, to the detriment of their social lives, relationships, jobs, and psychological well-being. Problems are often hidden even from spouses, and social isolation and relationship problems may develop.

The role of the urogynecologist is different from that of the urologist—the urogynecologist is able to adopt a much more holistic approach to problems affecting women, bringing expertise in the management of pelvic pathology, such as uterine fibroids, ovarian cysts, or pelvic inflammatory disease and endometriosis. These conditions may not only coexist with problems of the lower urinary tract and genital tract, but can also be causative. Ongoing management of urogynecological problems through reproductive life, managing contraception, pregnancy, childbirth, and aging are vital to the well-being of women, allowing a continuum of care from the menarche to menopause and beyond.
Treatment ranges from simple lifestyle advice and behavioral modification, through physical and pharmacological therapies, to complex and potentially difficult surgical intervention. It is not always possible to cure, but much can always be done to improve or manage the problem.

Drugs may have a profound effect on lower urinary tract function, although there are no drugs which have specific effects on the bladder and urethra which do not affect other tissues or organs. Drugs can change the autonomic function of the bladder by affecting the cholinergic and adrenergic nerves. There are also many cotransmitters and local hormones which act on the lower urinary tract, including histamine, 5-hydroxytryptamine, substance P, endogenous opioids, vasoactive intestinal peptide, neuropeptide Y, and prostaglandins. The importance of these substances in the normal function of the bladder and urethra is not clear, but their effects can be blocked by anticholinergics and adrenergic blockers.

In this section, we will consider: the common drugs used in the management of both detrusor overactivity and urodynamic stress incontinence; drugs used in the management of voiding difficulty; the use of therapeutic and prophylactic antimicrobials in lower urinary tract infection (UTI); and the role of estrogen in the management of urinary incontinence and urogenital atrophy.

URINARY INCONTINENCE

Urinary incontinence, the "complaint of any involuntary leakage of urine" (1) is a common and distressing condition known to adversely affect quality of life (2). Although the prevalence of urinary incontinence has been found to vary widely depending on the definition used, a recent large-scale epidemiological study found that 25% of women complain of urinary leakage and 7% had significant incontinence that was bothersome (3). In economic terms, the cost is also considerable, $26 billion being spent per annum in the United States alone (4).

Drug treatment continues to be have an important role in the management of women with urinary incontinence, although many of the agents used have not been subjected to controlled clinical trials (5). From the number of preparations studied, it is clear that there are no ideal drugs and very often the clinical results have been disappointing, this being partly due to poor efficacy and side effects (6). Comparison of drug therapies for incontinence is compounded by a placebo effect of 30 to 40%, and as the response to any drug is only likely to be in the region of 60% any differences detected are likely to be small and thus require large-scale studies to demonstrate an effect.

DETRUSOR OVERACTIVITY

"Overactive bladder" (OAB) is the term used to describe the symptom complex of urinary frequency and urgency, with or without urge incontinence.
Recent epidemiological studies have reported the overall prevalence of OAB in women to be 16.9%, suggesting that there could be 17.5 million women in the United States who suffer from the condition. The prevalence increases with age, being 4.8% in women under 25 years to 30.9% in those over the age of 65 years (7). This is supported by recent prevalence data from Europe in which 16,776 interviews were conducted in a population-based survey (8). The overall prevalence of OAB in individuals of 40 years and above was 16.6% and increased with age. Frequency was the most commonly reported symptom (85%), whereas 54% complained of urgency and 36% urge incontinence. When considering management, 60% had consulted a physician although only 27% were currently receiving treatment.

The symptoms of OAB are due to involuntary contractions of the detrusor muscle during the filling phase of the micturition cycle (Fig. 1). This condition is called detrusor overactivity (1), and the detrusor contractions are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors (9).

Molecular cloning studies have revealed five distinct genes for muscarinic acetylcholine receptors in rats and humans, and it has been shown that five receptor subtypes (M₁–M₅) correspond to these gene products (10). Five pharmacologically defined muscarinic receptors, M₁–M₅, have been demonstrated within the bladder (11) although there is predominance of M₂ and M₃ (12). Although the ratio of M₂ to M₃ receptors is 3:1, the latter is the more pharmacologically active and is responsible for normal bladder contraction. The role of M₂ receptors in initiating bladder contraction is thought to be less important although they do oppose sympathetically mediated smooth muscle relaxation.

**Figure 1** Subtracted cystometry trace showing low compliance and systolic detrusor contractions during filling. **Abbreviations:** pAbd, abdominal pressure; pVes, vesical pressure; pDet, detrusor pressure.
mediated by β-adrenergic receptors (Fig. 2) (13). In addition, in certain disease states, such as neurogenic bladder dysfunction, the M2 receptors may become more important in mediating detrusor contractions (14).

Most women with Detrusor overactivity (DO) will require drug therapy, because this remains the mainstay of treatment. Many drugs have been tried over the years in the treatment of DO—none is completely satisfactory, and many have had to be abandoned due to lack of efficacy, or dangerous, or unpleasant, side effects. For many of the drugs, their clinical use is based on weak, open studies rather than randomized controlled trials (Table 1) (15). Even then, the placebo response is so large that clinical effect is difficult to distinguish (16). Drug effects in individuals, however, can vary markedly. Even those drugs presently in use are not without their problems. Most of these drugs exert their effect by acting on the acetylcholine receptors within the detrusor muscle; other drugs have central effects, act to reduce urine production, or raise the sensory threshold of the bladder. Because they are not without side effects, therapy is seldom continued indefinitely, and so must be considered as an adjunct to behavioral therapy.

The use of drugs in the frail, elderly, and infirm is contentious. Much lower doses of drugs should be used in the frail and elderly. Alcohol and medication use are major causes of acute incontinence in the elderly. Polypharmacy and the use of psychotropic medication are most prevalent in those aged 85 years or over with women predominating, and appear to be increasing (17), compounding the problem.
<table>
<thead>
<tr>
<th></th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimuscarinic drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolterodine</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Trospium</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Propantheline</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Atropine, hyoscamine</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td><strong>Drugs acting on membrane channels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel antagonists</td>
<td>Under investigation</td>
<td></td>
</tr>
<tr>
<td>Potassium channel openers</td>
<td>Under investigation</td>
<td></td>
</tr>
<tr>
<td><strong>Drugs with mixed actions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Propiverine</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Dicyclomine</td>
<td>3</td>
<td>C</td>
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<tr>
<td>Flavoxate</td>
<td>2</td>
<td>D</td>
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<tr>
<td><strong>Alpha blockers</strong></td>
<td></td>
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<tr>
<td>Alfuzosin</td>
<td>3</td>
<td>C</td>
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<tr>
<td>Doxazosin</td>
<td>3</td>
<td>C</td>
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<tr>
<td>Prazosin</td>
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<td>C</td>
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<tr>
<td>Terazosin</td>
<td>3</td>
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<tr>
<td>Tamsulosin</td>
<td>3</td>
<td>C C</td>
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<tr>
<td><strong>Beta agonists</strong></td>
<td></td>
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<tr>
<td>Terbutaline</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Clenbuterol</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>3</td>
<td>C</td>
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<tr>
<td><strong>Antidepressants</strong></td>
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<tr>
<td>Imipramine</td>
<td>2</td>
<td>C</td>
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<tr>
<td>Amitriptylline</td>
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<td>C</td>
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<td><strong>Prostaglandin synthesis inhibitors</strong></td>
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<td>Indomethacin</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>2</td>
<td>C</td>
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<td><strong>Vasopressin analogues</strong></td>
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<td>Desmopressin</td>
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<tr>
<td><strong>Other drugs</strong></td>
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<tr>
<td>Baclofen</td>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>C&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Resiniferatoxin</td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>C&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Botulinum</td>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>B&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Intrathecal use.  
<sup>b</sup>Intravesical.  
<sup>c</sup>Bladder wall.

*Source:* From Ref. 15.
Drugs That Have a Mixed Action

Oxybutynin

Oxybutynin is a tertiary amine that undergoes extensive first-pass metabolism to an active metabolite, N-desmethyl oxybutynin (18) that occurs in high concentrations (19) and is thought to be responsible for a significant part of the action of the parent drug. It has a mixed action consisting of both an antimuscarinic and a direct muscle-relaxant effect in addition to local anesthetic properties. The later is important when given intravesically but probably has no effect when given systemically. Oxybutynin has been shown to have a high affinity for muscarinic receptors in the bladder (20) and has a higher affinity for M₁ and M₃ receptors over M₂ (21).

The effectiveness of oxybutynin in the management of patients with detrusor overactivity is well documented. A double-blind, placebo-controlled trial found oxybutynin to be significantly better than placebo in improving lower urinary tract symptoms although 80% of patients complained of significant adverse effects, principally dry mouth or dry skin (22). Similar results have also been demonstrated in further placebo-controlled trials (23,24).

In addition, oxybutynin has been compared to other treatments for detrusor overactivity. It has been found to be significantly better than previous antimuscarinic agents such as propantheline in the treatment of detrusor overactivity (58% improvement vs. 45% improvement), although it is associated with a higher rate of adverse effects (63 vs. 44%) (16). More recently, a placebo-controlled, multicenter study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence has been performed. This showed oxybutynin to be as efficacious as propiverine although found it was associated with more severe adverse effects (25).

The antimuscarinic adverse effects of oxybutynin are well-documented and are often dose-limiting (26). Using an intravesical route of administration, higher local levels of oxybutynin can be achieved while limiting the systemic adverse effects. Using this route of administration, oxybutynin has been shown to increase bladder capacity and lead to a significant clinical improvement (27).

Rectal administration has also been shown to be associated with fewer adverse effects when compared to oral administration (28), but does not appear to be acceptable to patients in the long-term.

To maximize efficacy and minimize adverse effects, alternative delivery systems are currently under evaluation (Table 2). Extended-release preparations of oxybutynin (oxybutynin ER) have been developed, which utilize a novel delivery system to release the drug at a constant rate over 24 hours. This avoids the peaks and troughs that are associated with the immediate-release versions (Fig. 3). In a multicenter comparison of controlled versus immediate-release oxybutynin, although there was a similar reduction in urge incontinence episodes, there was a significant reduction in severe dry mouth symptoms (ER 25% vs. IR 46%; \( p = 0.03 \)) (29). Oxybutynin ER...
(10 mg/day) was compared with tolterodine (2 mg bd) in a 12-week, randomized, double-blind, parallel-group study, involving 378 women with OAB and known to be responsive to anticholinergics (30). Oxybutynin ER was found to be significantly more effective than tolterodine in reducing incontinence episode frequency, frequency of micturition, and total incontinence, at 12 weeks when adjusted for baseline, although the rates of dry mouth and other adverse effects were similar in both groups.

Transdermal oxybutynin has been investigated in a general population of subjects with OAB and urge or mixed UI (31). Five hundred and twenty adult subjects were randomized to 12 weeks of double-blind daily treatment with oxybutynin transdermal delivery system (TDS) or placebo administered twice

<table>
<thead>
<tr>
<th>Drug Plasma Concentrations</th>
<th>Frequency of Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once daily dosing</td>
<td>Oxybutynin Patch</td>
</tr>
<tr>
<td>Therapeutic Range</td>
<td></td>
</tr>
<tr>
<td>Toxic Level</td>
<td></td>
</tr>
<tr>
<td>Min Effective Concentration</td>
<td></td>
</tr>
<tr>
<td>No therapeutic effects</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3 Drug plasma concentrations with daily dosing and slow-release patch preparations.

### Table 2: Advantages and Disadvantages of Novel Drug Delivery Systems

<table>
<thead>
<tr>
<th>Drug Formulation</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended release (oral)</td>
<td>Efficacy maintained</td>
<td>Unsuitable for “PRN” use</td>
</tr>
<tr>
<td></td>
<td>Reduced side effects</td>
<td>Limited dose</td>
</tr>
<tr>
<td></td>
<td>Once daily dose</td>
<td>Good compliance</td>
</tr>
<tr>
<td></td>
<td>Good compliance</td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td>Efficacy similar to ER oral preparations</td>
<td>Patch site pruritis</td>
</tr>
<tr>
<td></td>
<td>Lowest incidence of side effects in trials</td>
<td></td>
</tr>
<tr>
<td>Intravesical</td>
<td>Increases bladder capacity</td>
<td>Learn CISC or indwelling catheter</td>
</tr>
<tr>
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weekly, followed by a 12-week open-label, dose titration period. Doses of 2.6 and 3.9 mg oxybutynin TDS daily improved OAB symptoms and quality of life, and were well-tolerated. The most common adverse event was application site pruritus (oxybutynin TDS 10.8–16.8%, placebo 6.1%). Dry mouth incidence was similar in both groups (7.0 vs. 8.3%, p not significant). The oxybutynin TDS has also been compared with tolterodine ER and placebo (32). Oxybutynin TDS and tolterodine ER were found to be effective and comparable treatments for urge and mixed incontinence, when compared with placebo. Patients in the tolterodine ER and placebo groups applied placebo patches—application site reactions were most common in the oxybutynin TDS group (14 vs. 4.3% with placebo). However, 4.1% of patients taking oxybutynin TDS reported dry mouth (vs. 1.7% placebo, p not significant) compared with 7.3% of patients in the tolterodine ER group (p = 0.0379 when compared with placebo). Transdermal oxybutynin has the lowest reported incidence of adverse anticholinergic side effects from large multicenter trials (27).

Propiverine

Propiverine has been shown to combine anticholinergic and calcium channel-blocking actions (33) and is the most popular drug for detrusor overactivity in Germany, Austria, and Japan. Open studies in patients with detrusor overactivity have demonstrated a beneficial effect (34) and in a double-blind, placebo-controlled trial of its use in neurogenic detrusor overactivity it has been shown to significantly increase bladder capacity and compliance in comparison to placebo. Dry mouth was experienced by 37% in the treatment group as opposed to 8% in the placebo group with dropout rates being 7% and 4.5%, respectively (35).

Flavoxate

The basis of the effect of flavoxate on the bladder has not been fully elucidated. It has direct smooth muscle-relaxant properties through calcium antagonistic activity, local anesthetic properties, and an ability to inhibit phosphodiesterase. It has no anticholinergic action (36). There are no or mild anticholinergic effects. Investigators have failed to demonstrate any benefit over placebo (37). In a double-blind crossover study on women with detrusor overactivity comparing emepronium bromide and flavoxate hydrochloride administered at 200 mg TDS, improvement rates of 66% and 83% were reported (38). No beneficial effect was found at a dose of 100 to 200 mg three to four times a day (39). Few side effects have been reported with flavoxate but efficacy compared with placebo has not been established and its use cannot be recommended.

Dicyclomine Chloride

This drug has anticholinergic and direct smooth muscle effects. An oral dose of 20 mg TDS produced a cure or significant resolution of symptoms
in 24 of 27 patients with detrusor overactivity. Side effects are mainly anticholinergic (40). There are no controlled clinical trials on its efficacy and side effects, and more work needs to be done in this area before this drug can be recommended.

**Antimuscarinic Drugs**

**Atropine**

Atropine is rarely used in the treatment of detrusor overactivity because of its side effects. Some trials have shown that intravesical atropine may have benefit in women with neurogenic detrusor overactivity (41).

**Emepronium Carrageenate**

Emepronium carrageenate has anticholinergic activity at both peripheral and ganglionic levels. Unfortunately, only 6% of the administered dose of emepronium is absorbed through the gastrointestinal tract (42), which is unfortunate as parenteral administration significantly increases bladder capacity and abolishes detrusor contractions (43). Unlike emepronium bromide, which may cause esophageal ulceration, emepronium carrageenate does not have this problem because the active drug is only released when in contact with the acid of the stomach. In a double-blind, placebo-controlled, randomized crossover trial, the doses were titrated against response in 72 women. Five women withdrew while titrating the dose, 24 were treated with a low dose (1200 mg daily), and 43 women with a medium/high dose (1600/2000 mg), there were improvements in symptoms and objective parameters (44). Emepronium carrageenate is only available in certain countries.

**Propantheline**

Propantheline bromide (Probanthine) is quaternary amine drug acting on both muscarinic and nicotinic acetylcholine receptors, at the ganglionic level and the neuromuscular junction. It is nonselective for muscarinic receptor subtypes, and has a low, variable (5–10%), bioavailability. It is most effective when frequency of micturition is the major problem. The usual dose is 15 to 30 mg qds, but this is often ineffective, and may need to be increased as high as 90 mg qds for benefit to be obtained. It is usually well tolerated with fewer side effects than other agents, but is correspondingly less effective. It is not often used in clinical practice.

**Tolterodine**

Tolterodine is a competitive muscarinic receptor antagonist with relative functional selectivity for bladder muscarinic receptors (45) and whilst it shows no specificity for receptor subtypes it does appear to target the bladder
over the salivary glands (46). The drug is metabolized in the liver to the 5-hydroxymethyl derivative which is an active metabolite having a similar pharmacokinetic profile and is thought to significantly contribute to the therapeutic effect (47).

Several randomized, double-blind, placebo-controlled trials both on patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity have demonstrated a significant reduction in incontinent episodes and micturition frequency (48–50). Further studies have confirmed the safety of tolterodine and at the recommended daily dosage the incidence of adverse events was no different to that in patients taking placebo (51).

In addition, the safety and efficacy of tolterodine has also been compared to that of oxybutynin. A randomized, double-blind, placebo-controlled, parallel-group study of 293 patients reported that the clinical efficacy of the two drugs was comparable although oxybutynin was associated with higher withdrawal rates and a higher incidence of adverse events, notably dry mouth (52). A pooled analysis of the safety, efficacy, and acceptability of tolterodine in 1120 patients in four randomized, double-blind, parallel, multicenter trials found that both tolterodine and oxybutynin significantly decreased incontinent episodes although tolterodine was associated with fewer adverse events, dose reductions, and patients withdrawals than oxybutynin (53).

More recently, tolterodine has also been developed as an extended-release once daily preparation, Detrusitol XL. A recent double-blind multicenter trial of 1235 women has compared extended-release tolterodine to immediate-release tolterodine and placebo. Although both formulations were found to reduce the mean number of urge incontinence episodes per week, the extended-release preparation was found to be significantly more effective (54). In addition to increased efficacy, extended-release tolterodine has been shown to have better tolerability. In a double-blind, multicenter, randomized placebo-controlled trial of 1529 patients, extended-release tolterodine was found to be 18% more effective in the reduction of episodes of urge incontinence while having a 23% lower incidence of dry mouth (55).

Inevitably extended-release oxybutynin and extended-release tolterodine have also been compared. In the OAB: Performance of Extended-Release Agents (OPERA) study, which involved 71 centers in the United States, improvements in episodes of urge incontinence were similar for the two drugs although extended oxybutynin was significantly more effective than extended-release tolterodine in reducing frequency of micturition. Significantly more women taking oxybutynin were also completely dry (23 vs. 16.8%; \( p = 0.03 \)) although dry mouth was significantly more common in the oxybutynin group (56).

Trospium

Trospium chloride is a quaternary ammonium compound which is nonselective for muscarinic receptor subtypes and shows low biological availability.
In a recent placebo-controlled, randomized, double-blind, multicenter trial, trospium chloride produced significant improvements in maximum cystometric capacity and bladder volume at first unstable contraction. Clinical improvement was significantly greater in the group receiving trospium and the frequency of adverse events was similar in both groups (58). Trospium chloride has also been compared to oxybutynin in a randomized, double-blind, multicenter trial. With both agents there was a significant increase in bladder capacity, a decrease in maximum voiding detrusor pressure and a significant increase in compliance although there were no statistically significant differences between the two treatment groups. Those taking trospium had a lower incidence of dry mouth (4 vs. 23%) and were also less likely to withdraw (6 vs. 16%) when compared to the group receiving oxybutynin (59).

**Solifenacin**

Solifenacin succinate is a potent M3 receptor antagonist that has selectivity for the M3 receptors over M2 receptors and has much higher potency against M3 receptors in smooth muscle than it does against M3 receptors in salivary glands. Despite solifenacin expressing a higher potency than that of darifenacin in a model of inhibition of M3 receptor-mediated calcium ion mobilization in guinea pig colonic smooth muscle cells (60), it has been shown to be 40-fold less potent than oxybutynin and 79-fold less potent than tolterodine in its inhibition of salivary secretion (61) as well as being more selective for the M3 receptor.

In a four-week phase 2 placebo and active controlled study conducted in Europe, solifenacin was evaluated in 225 patients (62). Overall, 150 patients received 2.5, 5, 10, or 20 mg solifenacin once daily, 38 received placebo, and 37 received tolterodine (immediate-release) 2 mg twice daily. There was a statistically significant reduction in the frequency of micturition and a statistically significant increase in volume voided per micturition at the 5, 10, and 20 mg dosage when compared with placebo. In addition, these doses of solifenacin were also found to lead to a greater reduction in episodes of frequency of micturition than tolterodine. The most common adverse effects were dry mouth and constipation, with dry mouth and blurred vision being the most common reasons for withdrawal.

Solifenacin has also been directly compared to tolterodine 2 mg twice daily in a phase 3 randomized, double-blind, parallel-group, placebo and active controlled multicenter study in Europe and South Africa. The primary aim of the study was to assess the efficacy of solifenacin 5 and 10 mg, whereas the secondary aims were to compare the safety and efficacy with that of tolterodine (63).

In total, 1033 men and women were recruited. There was a statistically significant reduction of micturition frequency with both solifenacin 5 and 10 mg when compared with placebo, the former equating to a reduction of...
2.2 micturitions per 24 hours and the latter 2.6. Tolterodine showed a smaller reduction of 1.9 micturitions. In those patients who were incontinent, 37.3% of the placebo group was continent at the end of study compared to 51.1%, 50.6%, and 48.4% in the 5 mg, 10 mg, and tolterodine groups, respectively. When considering safety, the incidence of one or more adverse event was 45.3% in the placebo group compared to 48.4%, 51.9%, and 48.3% in the 5 mg, 10 mg, and tolterodine groups, respectively. Most adverse events were anticholinergic and mild or moderate in severity.

Darifenacin

Darifenacin is a highly selective M3 receptor antagonist, which has been found to have a fivefold higher affinity for the human M3 receptor relative to the M1 receptor (64). Darifenacin is equipotent with atropine in the ileum and bladder and six times less potent at inhibiting muscarinic receptors in the salivary gland. Salivary responses are inhibited at doses 6- to 10-fold higher than those required to inhibit bladder responses. Clearly, these findings are important when considering the treatment of detrusor overactivity, and a pilot study has demonstrated its ability to reduce the number, maximum amplitude, and duration of unstable bladder contractions (65).

The effects of darifenacin have recently been reported in a multicenter, double-blind, placebo-controlled parallel-group study of 561 patients (85% female), with symptoms of OAB for over six months (66). After a washout and 2-week placebo run-in, patients were randomized to once daily darifenacin (3.75, 7.5, and 15 mg) or placebo for 12 weeks. Darifenacin 7.5 and 15 mg had a rapid onset of effect with significant improvement over placebo by week 2 and this was sustained throughout. Incontinence episodes were reduced from baseline by 67.7% ($p = 0.01$) with darifenacin 7.5 mg and 72.8% ($p < 0.001$) with 15 mg compared with 55.9% with placebo. Both doses were significantly superior to placebo for improvement in micturition frequency, bladder capacity, and both frequency and severity of urgency. There was no effect on nocturia. The most common adverse events were mild-to-moderate dry mouth and constipation although no patients withdrew due to dry mouth.

Darifenacin has also been reported to prolong “warning time,” the time from the first sensation of urgency to micturition, in a randomized double-blind, placebo-controlled, parallel-group study of 72 subjects (67). Change in warning time was 4.3 minutes longer in the darifenacin group when compared to placebo, and although this only represents a small increase it is likely to be of clinical significance. In addition, the individuals who showed at least a 30% improvement was significantly higher in the darifenacin arm.

Most recently, the use of darifenacin has been investigated in a multicenter, double-blind, randomized, placebo-controlled study of 439 women with symptoms of OAB (68). After a two-week placebo run-in, patients
were randomized to either darifenacin 7.5 or 15 mg once daily. After 12 weeks, darifenacin was associated with a dose-related reduction from baseline in the number of incontinence episodes per week with a median percentage reduction of 68.7% and 76.5% with 7.5 and 15 mg, respectively. In addition, there was a significantly greater reduction in incontinence episodes and nighttime voids with darifenacin when compared to placebo at all doses. The overall incidence of adverse events, the majority being mild to moderate in severity, was 57.4, 68.2, and 49.5% with 7.5 mg, 15 mg, and placebo, respectively. The most common adverse effects were dry mouth and constipation.

Antidepressants

These drugs have three pharmacological actions: they act at central and peripheral sites; they stop the reuptake by presynaptic nerve endings of the amine neurotransmitters serotonin and noradrenaline; and they are sedatives possibly due to antihistaminic activity and they have systemic anticholinergic effects which are weak on detrusor muscle. They desensitize β₂ adrenoceptors and some β adrenoceptors. They have also been shown to block β and serotonin 1 receptors. Imipramine appears to have a strong inhibitory effect on detrusor, which is not anticholinergic or adrenergic. This may be through a local anesthetic effect on nerve terminals. Additionally, detrusor contractility may be reduced due to the effect on α adrenoceptors and increased outflow resistance by the action on α adrenoceptors in the bladder base and proximal urethral smooth muscles. These two effects may combine to achieve continence.

At therapeutic levels, tricyclic drugs used to treat depression can cause orthostatic hypotension and ventricular arrhythmias. Because children are particularly sensitive to the cardiotoxic action, care must be taken in their use. Allergic reactions such as rashes, hepatic dysfunction, obstructive jaundice, and agranulocytosis may also occur. Stopping drug treatment should be done gradually as side effects of nausea, abdominal discomfort, vomiting, headache, lethargy, and irritability have been reported on discontinuing medication after having taken high doses.

Imipramine

Imipramine has been shown to have systemic anticholinergic effects (69) and blocks the reuptake of serotonin. Some authorities have found a significant effect in the treatment of patients with detrusor overactivity (70) although others report little effect (71). In light of this evidence and the serious adverse effects associated with tricyclic antidepressants, their role in detrusor overactivity remains of uncertain benefit although they are often useful in patients complaining of nocturia or bladder pain.
Doxepin

Doxepin has been found to be more potent in its musculotropic relaxant and antimuscarinic activity than other tricyclic antidepressants. Women with detrusor overactivity were studied in a randomized, double-blind, placebo-controlled crossover trial using doxepin 50 mg at night or 25 mg twice daily. There was a significant decrease in nocturia and nighttime incontinence. Cystometrically, an increase in first sensation to void and maximum bladder capacity occurred (72).

Prostaglandin Synthetase Inhibitors

Bladder mucosa has been shown to have the ability to synthesize eicosanoids (73) although it is uncertain whether they contribute to the pathogenesis of unstable detrusor contractions. However, they may have a role in sensitizing sensory afferent nerves increasing the afferent input produced by a given bladder volume. A double-blind controlled study of flurbiprofen in women with detrusor overactivity was shown to have an effect although it was associated with a high incidence of adverse effects (43%) including nausea, vomiting, headache, and gastrointestinal symptoms (74). Indomethacin has also been reported to give symptomatic relief although the incidence of adverse effects was also high (59%) (75). At present, this evidence does not support their use in detrusor overactivity.

Antidiuretic Agents

Desmopressin

Desmopressin (1-desamino-8-d-arginine vasopressin; DDAVP) is a synthetic vasopressin analog. It has strong antidiuretic effects without altering blood pressure. The drug has been used primarily in the treatment of nocturnal enuresis in children (76). The use of desmopressin has also been investigated for the management of nocturia in adults in a double-blind, placebo-controlled study of 151 adults (77). In the desmopressin group, 34% of patients had fewer than half the number of nocturnal voids compared with 3% in the placebo arm. In addition, the mean duration of the first sleep period, considered to be the most important for rest, increased by 59% in the desmopressin group compared to 21% in the placebo arm. Although there is a theoretical risk of hyponatremia, there were no serious adverse effects reported; although 4% of subjects were found to have a serum sodium less than 130 mmol/l, this only occurred during dose titration.

More recently, nasal desmopressin has been reported as a “designer drug” for the treatment of daytime urinary leakage in a multicenter, multinational, randomized, double-blind, placebo-controlled, crossover exploratory study of women with severe urinary incontinence (78). There was a higher incidence of periods without leakage in the first four hours on desmo-
pressin (62 ± 35%) compared to placebo (48 ± 40%) and during the first eight hours (55 ± 37 vs. 40 ± 41%). Furthermore, there was a higher frequency of dry days on desmopressin as compared to placebo; 36% of patients had no leakage on virtually all treatment days for four hours after drug administration and there were no serious or severe adverse events reported. Overall, the evidence would suggest that desmopressin is safe for long-term use; however, the drug should be used with care in the elderly due to the risk of hyponatremia.

β Adrenoceptor Agonists

These drugs have been shown to effectively relax detrusor muscle in vitro. In vivo mainly open studies have been performed. Norlen et al. (79) found that bladder capacity was increased after treatment with the β adrenoceptor agonist terbutaline 5 mg TDS. In a double-blind, controlled trial using clenbuterol, 0.01 mg TDS was found to have a good therapeutic effect on 15 of 20 women (80). Four patients complained of trembling of fingers and three complained of nervousness. None had to stop treatment. Other investigators have been unable to confirm these results using other β adrenoceptor agonists such as salbutamol and isoprenaline. The efficacy of these agonists has not been established.

Capsaicin and Resiniferatoxin

Intravesical instillation of capsaicin, a neurotoxin extracted from red chilli peppers (81), has significant effect over placebo in the treatment of neurogenic DO. It exerts a biphasic effect on sensory nerves, with initial excitation being followed by a long-lasting blockade of C-fibers, which are rendered resistant to natural stimuli (82). Side effects of intravesical capsaicin include discomfort and a burning sensation at the pubic/urethral level during the installation. Prior administration of local anesthetic gel does not negate the effects of the capsaicin. There have been no reported malignant changes after repeated instillations even up to five years. Bladder afferent desensitization with capsaicin is promising in subjects with motor or sensory bladder dysfunction, although initial pungency might limit its use (83). It is not in clinical use for idiopathic detrusor overactivity.

Resiniferatoxin is an analog of capsaicin extracted from Euphorbia, a cactus-like plant. When given intravesically, it is 1000 times more potent than capsaicin in stimulating bladder activity. It has been shown to have fewer side effects than capsaicin with a demonstrable increase in bladder capacity (84) in up to 30% of subjects with detrusor overactivity. Other studies (85,86), however, show little effect.

Botulinum Toxin A

In 1817, an illness caused by Clostridium botulinum toxin was first recorded, when Kerner described a link between a sausage and a paralytic illness that
affected 230 people. Kerner (87) was a district health officer and made botulism (Latin “botulus” meaning sausage) a notifiable disease. In 1897, the microbiologist Emile-Pierre van Ermengen identified a gram-positive, spore-forming, anaerobic bacterium in a ham that caused 23 cases of botulism in a Belgian nightclub. He termed the bacterium *Bacillus botulinus*; it was later re-termed *Clostridium botulinum* (88). The discovery that Botulinum toxin (“Botox”) blocks neuromuscular transmission, and thereby causes weakness, laid the foundations for its therapeutic development. In 1981, Scott (89), an ophthalmologist, pioneered “Botox” therapy by using it to treat strabismus.

The bacterium produces its effect by production of a neurotoxin—different strains produce seven distinct serotypes designated A to G. All seven have a similar structure and molecular weight, consisting of a heavy (H) chain and a light (L) chain, joined by a disulfide bond (90). They interfere with neural transmission by blocking the calcium-dependent release of neurotransmitter, acetylcholine, causing the affected muscles to become weak and atrophic. The affected nerves do not degenerate, but as the blockage is irreversible, only the development of new nerve terminals and synaptic contacts allows recovery of function. This usually takes up to three months.

In urogynecology, “Botox” has been successfully used to overcome outflow obstruction in women with voiding difficulty (91) and to overcome detrusor-sphincter dyssynergia after spinal cord injury (92,93), despite the expense of repeated injections. It is currently the subject of research to assess its efficacy in the suppression of detrusor overactivity, although the long-term effects of repeated cystoscopic injections are not known.

**NEW DEVELOPMENTS**

**Calcium-Channel-Blocking Agents**

Contractile activity in the bladder smooth muscle is activated by the movement of extracellular calcium into the cell. Spontaneous and evoked contractile activity is mediated by membrane depolarization and the movement of calcium into the smooth muscle cell through L-type Ca$^{2+}$ channels (94). The inhibition of the entrance of Ca$^{2+}$ can prevent spontaneous and evoked contractile activity (95) with L-type Ca$^{2+}$-blocking agents, such as nifedipine, inhibiting the entry of extracellular calcium.

Nifedipine has been shown to reduce the frequency and amplitude of detrusor contractions (96) although these findings have not been confirmed in a further study, which showed no significant effect on detrusor contractions (97). Similar contradictory findings have been reported regarding the use of flunarizine (6,98). Diltiazem has also been shown to significantly increase bladder capacity, lower bladder pressure, and decrease the number of episodes of incontinence (99).
At present, there is insufficient evidence to suggest that calcium-channel-blocking agents are effective in the treatment of detrusor overactivity although the development of a selective calcium-channel-blocking agent which eliminates spontaneous contractions without affecting micturition may prove to be of use in the treatment of detrusor overactivity.

Potassium-Channel-Opening Agents

The opening of $K^+$ ion channels in the membrane of the detrusor muscle cells results in an increase in $K^+$ movement out of the cell resulting in membrane hyperpolarization (100). This reduces the opening probability of ion channels involved in membrane depolarization and hence excitability is reduced (9). Three types of potassium channels have been identified in the detrusor muscles: ATP-sensitive channels, calcium-dependent large conductance channels, and calcium-dependent large conductance channels (31). At present, the relationship between each of these types of channels and the myogenic, neurogenic, and micturition forms of detrusor contraction has not been determined. To date, cromakalim, nicorandil, and pinacidil have been investigated although newer agents are currently under development (101).

Potassium channel openers are thought to be active during the bladder-filling phase and, while abolishing spontaneous detrusor contractions, are not thought to affect normal bladder contractions. However, their clinical usefulness is limited by significant cardiovascular effects, with cromakalim and pinacidil being found to be up to 200 times more potent as inhibitors of vascular preparations than of detrusor muscle (102). In clinical trials assessing the use of these drugs in patients with detrusor overactivity, no bladder effects have been found at doses which already lower blood pressure (103).

Urodynamic Stress Incontinence

Stress incontinence may be a symptom or a sign and refers to the complaint of involuntary leakage on effort or exertion or with coughing or sneezing (1). Urodynamic stress incontinence is the term used to describe the objective diagnosis made after urodynamic testing. Overall, approximately half of all incontinent women complain of pure stress incontinence and between 30% and 40% of mixed symptoms of stress and urge incontinence (3). Women who complain of urodynamic stress incontinence are currently managed with pelvic floor reeducation and may ultimately require continence surgery.

Although various agents such as $\alpha_1$-adrenoceptor agonists, estrogens, and tricyclic antidepressants have all been used anecdotally in the past for the treatment of stress incontinence, duloxetine is the first drug to be specifically developed and licensed for this indication.

Duloxetine

Duloxetine is a potent and balanced serotonin (5-hydroxytryptamine) and noradrenaline reuptake inhibitor, which enhances urethral-striated sphincter
activity via a centrally mediated pathway (104). The efficacy and safety of duloxetine (20, 40, and 80 mg) has been evaluated in a double-blind, randomized, parallel-group, placebo-controlled phase II dose-finding study in 48 centers in the United States involving 553 women with stress incontinence (105). Duloxetine was associated with significant and dose-dependent decreases in incontinence episode frequency. Reductions were 41% for placebo and 54, 59, and 64% for the 20, 40, and 80 mg groups, respectively. Discontinuation rates were also dose-dependent; 5% for placebo and 9, 12, and 15% of 20, 40, and 80 mg, respectively, the most frequently reported adverse event being nausea.

A further global phase III study of 458 women has also recently been reported (106). There was a significant decrease in incontinence episode frequency and improvement in quality of life in those women taking duloxetine 40 mg od, when compared to placebo. Once again, nausea was the most frequently reported adverse event occurring in 25.1% of women receiving duloxetine compared to a rate of 3.9% in those taking placebo. However, 60% of nausea resolved by seven days and 86% by one month. These findings are supported by a further double-blind, placebo-controlled study of 109 women awaiting surgery for stress incontinence (107). Overall, there was a significant improvement in incontinence episode frequency and quality of life in those women taking duloxetine when compared to placebo. Furthermore, 20% of women who were awaiting continence surgery changed their mind while taking duloxetine.

OTHER DRUGS AFFECTING LOWER URINARY TRACT FUNCTION

Drugs indirectly affecting the bladder by their actions should be borne in mind. Diuretics make detrusor overactivity symptomatically more severe due to the increased rate of filling provoking the bladder. Caffeine and alcohol may also act in this way, although they are thought to have direct actions on the detrusor. Calcium channel blockers prescribed for hypertension and tricyclic antidepressants have been noted to ameliorate detrusor overactivity in the elderly (108). However, patients taking β blockers were found to have more severe urge incontinence. In addition, because the α adrenoreceptors are found in the urethral sphincter musculature those women taking α adrenoreceptors antagonists, such as doxasosin and prazosin, may notice deterioration in symptoms of stress incontinence (109).

Epidural analgesia is an increasingly common choice of pain relief in labor—spinal or epidural anesthesia is known to have a lower morbidity and mortality than general anesthesia (110) for cesarean section.

However, it is well known that postoperative voiding difficulties are common (111), and there is a risk of permanent bladder damage if not managed properly. Bladder neck position is lower and more posterior during
spinal anesthesia as compared with preoperative assessment, and the posterior urethro-vesical angle is increased significantly (112).

Catheterization is to be strongly advised until full bladder sensation has returned. This may take at least eight hours, and during this time as much as 1400 mL of urine may be passed (113).

**VOIDING DYSFUNCTION**

Voiding dysfunction may be the result of decreased bladder contractility, increased outlet resistance, or a combination of the two. Failure of bladder contractility may be caused by alteration in the neuromuscular mechanisms responsible for initiating and maintaining a normal detrusor contraction. In addition, inhibition of the voiding reflex may also be caused by painful stimuli or be psychogenic in nature. Nonneurogenic causes of voiding dysfunction include intrinsic impairment of detrusor smooth muscle function secondary to overdistention injury, severe infection, or fibrosis. Increased outlet obstruction, while normally secondary to anatomical obstruction, may also be due to failure of coordination of the smooth muscle of the bladder and striated muscle of the urethral sphincter during a bladder contraction.

Women complaining of voiding dysfunction may be managed pharmacologically by either increasing intravesical pressure, lowering outflow resistance, or by a combination of both mechanisms.

**Parasympathomimetic Drugs**

As a major portion of the final micturition pathway is mediated by the stimulation of parasympathetic postganglionic muscarinic receptor sites, parasympathomimetic agents, such as bethanecol, may be used to facilitate bladder emptying by increasing bladder contractility. Bethanecol is relatively selective for the bladder and gut with no nicotinic action and has been shown to facilitate contraction of smooth muscles from all areas of the bladder (114). Bethanecol has historically been used in the management of postoperative and postpartum voiding dysfunction as well as in the treatment of atonic or hypotonic bladder (115). The use of bethanecol has also been described in the management of patients with spinal cord lesions in order to facilitate bladder emptying (116). However, short-term studies have failed to demonstrate significant efficacy in terms of flow and residual volumes (117). Although the use of parasympathomimetic agents may improve mild voiding dysfunction in the clinic setting, it is not particularly useful and may be associated with troublesome gastrointestinal symptoms. Often this group of women are often best managed by clean intermittent catheterization.
**α Adrenergic Antagonists**

The smooth muscle of the bladder base and proximal urethra contains predominantly α adrenoceptors, and the observation that α antagonists may facilitate bladder emptying was first made over 30 years ago (118).

Prazosin hydrochloride is a potent selective α₁ antagonist and may be used to lower outlet resistance although its clinical usefulness is limited by side effects of α blockade including faintness, dizziness, palpitations, and syncope. More recently, terazosin and doxasosin have been developed as highly selective postsynaptic α₁ antagonists. Their use is predominantly in men with benign prostatic hyperplasia and concomitant voiding difficulties.

Although a trial of such agents may be worthwhile, in women with mild voiding dysfunction at present there is no evidence to suggest that they are clinically useful.

**LOWER URINARY TRACT INFECTION**

Acute UTI is very common, with an estimated 0.5 to 0.7 episodes per person-year (119) among women, who are disproportionately affected. It is usually accepted that a pure culture of $10^5$ organisms/mL urine, obtained from a mid-stream “clean catch” specimen of urine, is diagnostic of infection (120). Twenty-five percent of women who have an episode of acute UTI go on to have recurrent episodes (121). The occurrence of three or more confirmed UTIs in a one-year period constitutes recurrent UTI.

**Principles of Treatment**

Treatment should be aimed at relieving or removing the underlying cause of infection. Incomplete emptying should be investigated, and treated, to reduce or overcome outflow obstruction, surgically or by use of clean intermittent self-catheterization. Surgical repair of a cystocele may “unkink” the urethra, and aid voiding, or urethrotomy may release a urethral stricture may overcome the limitation to flow.

Women should be advised to maintain an adequate fluid intake of 1 to 1.5 L/day, which allows a reasonable urine production and output, without being excessive. Constipation and fecal impaction should be treated. Women should be advised to shower before intercourse, and void afterward. It is also appropriate to offer advice and review their method of contraception because the use of a contraceptive diaphragm is associated with an increased risk of UTI.

**Cranberry Juice**

Cranberry juice contains fructose, which could interfere with the adhesion of the fimbriae of uropathic bacteria to the bladder mucosa (122). A well-designed...
study has demonstrated a reduction in episodes of bacteruria and pyuria in a population of 153 elderly women (mean age, 78.5 years) drinking 300 mL of cranberry juice compared to placebo drink, per day (123). Subjects randomized to the cranberry beverage had a risk of bacteruria (defined as organisms numbering $\geq 10^5$ mL$^{-1}$) with pyuria that were only 42% of that in the control group ($p = 0.004$). Their chance of remaining bacteruric-pyuric, given that they were bacteruric-pyuric in the previous month, were only 27% of the chance in the control group ($p = 0.006$). Both cranberry tablets and cranberry juice have also been shown to reduce the risk of UTI in sexually active women (aged 21–72) experiencing at least one symptomatic UTI/year (to 20% and 18%, respectively) compared with placebo (to 32%) ($p < 0.05$) (124). Cost-effective ratios revealed cranberry tablets were twice as cost-effective as organic juice for prevention.

Bearing in mind the potential for side effects and the likelihood of resistant bacteria in patients receiving conventional antibiotic prophylaxis, the opportunity of giving a safe, naturally occurring substance, such as cranberry juice, deserves further consideration (125).

**Antimicrobials**

When treating UTIs, an antimicrobial should be selected which has the appropriate sensitivity and is also able to achieve a high concentration within the urinary tract. Drugs should be safe and effective, have a broad spectrum of activity, and few side effects. Ideally, the drugs should be rapidly absorbed and not induce bacterial resistance.

Compliance with therapy may be improved using shorter courses of antimicrobial therapy or ideally using a single-dose regimen. This also has the advantage of reducing the effect on fecal and vaginal flora and may help in reducing the emergence of resistant organisms. A large number of studies have assessed the use of single-dose therapy and found it to be effective although better results have been reported using a short-term (3 days) regimen. There is no evidence to show that protracted courses are more effective. At present, trimethoprim, co-trimoxazole, and the fluoroquinolones (ciprofloxacin and norfloxacin) are the preferred single-dose agents, whereas amoxycillin has been shown to be less effective.

Antimicrobial therapy should ideally be based upon culture and sensitivity results from a mid-stream specimen of urine, although often treatment needs to be initially on a “best guess” basis (Table 3). Community-acquired infections often have a different range of sensitivities to those found in the hospital setting (Tables 4 and 5).

Some antimicrobials are particularly useful when treating urinary infections. Nitrofurantoin is specific to the urinary tract and therefore has little effect on bowel and vaginal flora. It is bactericidal to most common uropathogens and is particularly useful as a prophylactic measure. It is
safe to use in pregnancy although contraindicated in cases of renal failure. Trimethoprim, although primarily bacteriostatic, is also useful in the treatment of UTI, and a recent survey has shown it to be the most commonly used agent in general practice (126) although is associated with an increased risk of candidiasis.

When considering acute, uncomplicated cystitis short-term (3-day course) therapy would appear to be preferable. Trimethoprim, norfloxacin, ciprofloxacin, and ofloxacin are appropriate.

Prophylaxis
Antimicrobials may be used as prophylaxis for recurrent UTIs. Short- and long-term low-dose prophylaxis as well as intermittent and postcoital therapy may be used depending on the clinical situation. The most effective drugs include norfloxacin, nitrofurantoin, and trimethoprim. In addition, cephalexin may be used as effective prophylaxis against recurrent infections in sexually active women. Overall, prophylactic therapy has been shown to reduce recurrence rates by up to 95% when compared to placebo with

Table 3 Common Antimicrobial Sensitivities

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<tr>
<td>Gram-negative bacilli</td>
<td>Norfloxacin</td>
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<td>Staphylococci</td>
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<td>Streptococci</td>
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<td>Sulfonamides</td>
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<td>Co-trimoxazole</td>
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<td>Trimethoprim</td>
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<td>Nitrofurantoin</td>
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<tr>
<td>Pseudomonas</td>
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<td>Ciprofloxacin</td>
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<td>Gentamycin</td>
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Table 4 Proportions of Uropathogens Fully Sensitive to Antimicrobials in General Practice

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<tr>
<td>Amoxycillin/ampicillin (%)</td>
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<tr>
<td>Cephaloradine (%)</td>
<td>86.9</td>
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<tr>
<td>Ciprofloxacin (%)</td>
<td>90.3</td>
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<td>Nalidixic acid (%)</td>
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<td>64.5</td>
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<tr>
<td>Tetracycline (%)</td>
<td>65.0</td>
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<tr>
<td>Trimethoprim (%)</td>
<td>74.0</td>
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reinfection rates being reduced from 2 to 3 per patient-year to 0.1 to 0.4 per patient-year (127).

LOWER UTIs IN PREGNANCY

Asymptomatic bacteriuria occurs in 4% to 7% of pregnancies. It is associated with the development of acute cystitis, pyelonephritis, preterm labor, and low-birthweight. If untreated up to 30% of women will develop acute cystitis although this can be reduced to 3% with effective treatment.

When treating lower UTIs in pregnancy, penicillins, and cephalosporins have been shown to be safe in the first and second trimesters. Trimethoprim, because it is a folate antagonist, should be avoided in the first trimester although may be used safely in late pregnancy. Conversely, nitrofuantoin and sulfonamides are safe in early pregnancy although should be avoided in the third trimester when the former may cause a hemolytic anemia and the latter hyperbilirubinemia and kernicterus in the fetus. Tetracyclines should be avoided because of their chelating action, which will lead to hypoplasia and staining of the teeth. Although, in general, erythromycin is considered safe, the estolate salt may be associated with cholestatic jaundice. Finally, fluoroquinolones may affect fetal cartilage formation and chloramphenicol may be associated with neonatal cardiovascular collapse.

ESTROGENS

Estrogens in the Management of Incontinence

Estrogen preparations have been used for many years in the treatment of urinary incontinence (128,129) although their precise role remains controversial. Many of the studies performed have been uncontrolled observational series examining the use of a wide range of different preparations, doses, and routes of administration. The inconsistent use of progestogens to
provide endometrial protection is a further confounding factor making interpretation of the results difficult.

In order to clarify the situation, a meta-analysis from the Hormones and Urogenital Therapy (HUT) Committee has been reported (130). Of 166 articles identified, which were published in English between 1969 and 1992, only six were controlled trials and 17 were uncontrolled series. Meta-analysis found an overall significant effect of estrogen therapy on subjective improvement in all subjects. Subjective improvement rates with estrogen therapy in randomized controlled trials ranged from 64% to 75% although placebo groups also reported an improvement of 10% to 56%. In uncontrolled series, subjective improvement rates were 8% to 89% with subjects with urodynamic stress incontinence showing improvement of 34% to 73%. However, when assessing objective fluid loss, there was no significant effect. Maximum urethral closure pressure was found to increase significantly with estrogen therapy, although this outcome was influenced by a single small study showing a large effect (131).

A further meta-analysis of randomized controlled trials performed in Italy has reviewed clinical trials, which assess on the efficacy of estrogen treatment in postmenopausal women with urinary incontinence (132). A search of the literature (1965–1996) revealed 72 articles of which only four were considered to meet the meta-analysis criteria. There was a statistically significant difference in subjective outcome between estrogen and placebo, although there was no such difference in objective or urodynamic outcome. The authors conclude that this difference could be relevant although the studies may have lacked objective sensitivity to detect this.

The role of estrogen replacement therapy in the prevention of ischemic heart disease has recently been assessed in a four-year randomized trial, the Heart and Estrogen/Progestin Replacement Study (133) involving 2763 postmenopausal women younger than 80 years with intact uteri and ischemic heart disease. In the study, 55% of women reported at least one episode of urinary incontinence each week, and were randomly assigned to oral conjugated estrogen plus medroxyprogesterone acetate or placebo daily. Incontinence improved in 26% of women assigned to placebo as compared to 21% receiving HRT, whereas 27% of the placebo group complained of worsening symptoms compared with 39% in the HRT group (p = 0.001). The incidence of incontinent episodes per week increased by an average of 0.7 in the HRT group and decreased by 0.1 in the placebo group (p < 0.001). Overall, combined hormone replacement therapy was associated with worsening stress and urge urinary incontinence although there was no significant difference in daytime frequency, nocturia, or number of UTIs.

More recently, the effects of oral estrogens and progestogens on the lower urinary tract have been assessed in 32 female nursing home residents (134) with an average age of 88 years. Subjects were randomized to oral estrogen and progesterone or placebo for six months. At follow-up, there was no
difference in severity of incontinence, prevalence of bacteriuria, or the results of vaginal cultures, although there was an improvement in atrophic vaginitis in the placebo group.

**Estrogens in the Management of Stress Incontinence**

In addition to the studies included in the HUT meta-analysis, several authors have also investigated the role of estrogen therapy in the management of urodynamic stress incontinence only. Oral estrogens have been reported to increase the maximum urethral pressures and lead to symptomatic improvement in 65% to 70% of women (135,136) although other work has not confirmed this (137,138). More recently, two placebo-controlled studies have been performed examining the use of oral estrogens in the treatment of urodynamic stress incontinence in postmenopausal women. Neither conjugated equine estrogens and medroxyprogesterone (139) nor unopposed estradiol valerate (140) showed a significant difference in either subjective or objective outcomes. Furthermore, a review of 8 controlled and 14 uncontrolled prospective trials concluded that estrogen therapy was not an efficacious treatment for stress incontinence but may be useful for symptoms of urgency and frequency (141).

A recently reported meta-analysis has helped to determine the role of estrogen replacement in women with stress incontinence (142). Of the papers reviewed, 14 were nonrandomized studies, six randomized trials (of which four were placebo-controlled), and two meta-analyses. Interestingly, there was only a symptomatic or clinical improvement noted in the nonrandomized studies, whereas there was no such effect noted in the randomized trials. The authors conclude that currently the evidence would not support the use of estrogen replacement alone in the management of stress incontinence.

From the available evidence, estrogen does not appear to be an effective treatment for stress incontinence although it may have a synergistic role in combination therapy. Two placebo-controlled studies have examined the use of oral and vaginal estrogens with the α adrenergic agonist, phenylpropanolamine, used separately and in combination. Both studies found that combination therapy was superior to either drug given alone; although there was subjective improvement in all groups (143), there was only objective improvement in the combination therapy group (144). This may offer an alternative conservative treatment for women who have mild urodynamic stress incontinence.

**Estrogens in the Management of Urge Incontinence**

Estrogens have been used in the treatment of urinary urgency and urge incontinence for many years although there have been few controlled trials to confirm their efficacy. A double-blind, placebo-controlled crossover study using oral estriol in 34 postmenopausal women produced subjective improvement in eight
women with mixed incontinence and 12 with urge incontinence (145). However, a double-blind multicenter study of the use of estriol (3 mg/day) in postmenopausal women complaining of urgency has failed to confirm these findings (146) showing both subjective and objective improvements but not significantly better than placebo. Estriol is a naturally occurring weak estrogen, which has little effect on the endometrium and does not prevent osteoporosis although it has been used in the treatment of urogenital atrophy. Consequently, it is possible that the dosage or route of administration in this study was not appropriate in the treatment of urinary symptoms and higher systemic levels may be required.

The use of sustained release of 17β-estradiol vaginal tablets (Vagifem®, Novo Nordisk) has also been examined in postmenopausal women with urgency and urge incontinence or a urodynamic diagnosis of sensory urgency or detrusor overactivity. These vaginal tablets have been shown to be well absorbed from the vagina and to induce maturation of the vaginal epithelium within 14 days (147). However, following a six-month course of treatment, the only significant difference between active and placebo groups was an improvement in the symptom of urgency in those women with a urodynamic diagnosis of sensory urgency (148). A further double-blind, randomized, placebo-controlled trial of vaginal 17β-estradiol vaginal tablets has shown lower urinary tract symptoms of frequency, urgency, urge, and stress incontinence to be significantly improved although there was no objective urodynamic assessment performed (149). In both these studies, the subjective improvement in symptoms may simply represent local estrogenic effects reversing urogenital atrophy rather than a direct effect on bladder function.

To try to clarify the role of estrogen therapy in the management of women with urge incontinence, a meta-analysis of the use of estrogen in women with symptoms of OAB has been reported by the HUT Committee (HUT Committee, 20001 unpublished). In a review of 10 randomized placebo-controlled trials, estrogen was found to be superior to placebo when considering symptoms of urge incontinence, frequency, and nocturia although vaginal estrogen administration was found to be superior for symptoms of urgency. In those taking estrogens, there was also a significant increase in first sensation and bladder capacity in urodynamic studies as compared to placebo.

**Estrogens in the Management of Recurrent UTI**

Estrogen therapy has been shown to increase vaginal pH and reverse the microbiological changes that occur in the vagina following the menopause (150). Initial small uncontrolled studies using oral or vaginal estrogens in the treatment of recurrent UTI appeared to give promising results (151,152), although unfortunately this has not been supported by larger randomized trials. Several studies have been performed examining the use of oral and vaginal estrogens although these have had mixed results.
Kjaergaard et al. (153) compared vaginal estriol tablets with placebo in 21 postmenopausal women over a five-month period and found no significant difference between the two groups. However, a subsequent randomized, double-blind, placebo-controlled study assessing the use of estriol vaginal cream in 93 postmenopausal women during an eight-month period did reveal a significant effect (154).

Kirkengen et al. (155) randomized 40 postmenopausal women to receive either placebo or oral estriol and found that although initially both groups had a significantly decreased incidence of recurrent infections, after 12 weeks estriol was shown to be significantly more effective. These findings, however, were not confirmed subsequently in a trial of 72 postmenopausal women with recurrent UTIs randomized to oral estriol or placebo. Following a six-month treatment period and a further six-month follow-up, estriol was found to be no more effective than placebo (156).

More recently, a randomized, open, parallel-group study assessing the use of an estradiol-releasing silicone vaginal ring (Estring; Pharmacia and Upjohn, Sweden) in postmenopausal women with recurrent infections has been performed which showed the cumulative likelihood of remaining infection-free was 45% in the active group and 20% in the placebo group (157). Estring was also shown to decrease the number of recurrences per year and to prolong the interval between infection episodes.

### Urogenital Atrophy

Symptoms of urogenital atrophy are a manifestation of estrogen withdrawal following the menopause, and symptoms may appear for the first time more than 10 years after the last menstrual period (158). The female genital and lower urinary tract share a common embryological origin from the urogenital sinus and both are sensitive to the effects of female sex steroid hormones. Estrogen is known to have an important role in the function of the lower urinary tract throughout adult life, and estrogen and progesterone receptors have been demonstrated in the vagina, urethra, bladder, and pelvic floor musculature (159–162). Estrogen deficiency occurring following the menopause is known to cause atrophic changes within the urogenital tract (163) and is associated with urinary symptoms such as frequency, urgency, nocturia, incontinence, and recurrent infection. These may coexist with symptoms of vaginal atrophy such as dyspareunia, itching, burning, and dryness.

Increasing life expectancy has led to an increasingly elderly population and it is now common for women to spend a third of their lives in the estrogen-deficient postmenopausal state (164). The average age of the menopause is 51 years although there is some cultural and geographical variation (165). Worldwide, in 1990, there were approximately 467 million women aged 50 years or over and this is expected to increase to 1200 million over the next 30 years (166). The role of estrogen replacement in the treatment of these
symptoms of urogenital atrophy has still not been clearly defined despite several randomized trials and widespread clinical use.

**Estrogens in the Management of Urogenital Atrophy**

Symptoms of urogenital atrophy do not occur until the levels of endogenous estrogen are lower than that required to promote endometrial proliferation (65). Consequently, it is possible to use a low-dose estrogen replacement therapy in order to alleviate urogenital symptoms while avoiding the risk of endometrial proliferation and removing the necessity of providing endometrial protection with progestogens (167). The dose of estradiol commonly used in systemic estrogen replacement is usually 25 to 100 μg although studies investigating the use of estrogens in the management of urogenital symptoms have shown that 8 to 10 μg of vaginal estradiol is effective (168). Thus, only 10% to 30% of the dose used to treat vasomotor symptoms may be effective in the management of urogenital symptoms. Because 10% to 25% of women receiving systemic hormone replacement therapy still experience the symptoms of urogenital atrophy (169), low-dose local preparations may have an additional beneficial effect.

A recent review of estrogen therapy in the management of urogenital atrophy has been performed by the HUT Committee (170). Ten randomized trials and 54 uncontrolled series were examined from 1969 to 1995 assessing 24 different treatment regimens. Meta-analysis of 10 placebo-controlled trials confirmed the significant effect of estrogens in the management of urogenital atrophy.

The route of administration was assessed, and oral, vaginal, and parenteral (transcutaneous patches and subcutaneous implants) were compared. Overall, the vaginal route of administration was found to correlate with better symptom relief, greater improvement in cytological findings, and lower serum estradiol levels. With regard to the type of estrogen preparation, estradiol was found to be most effective in reducing patient symptoms although conjugated estrogens produced the most cytological change and the greatest increase in serum levels of estradiol and estrone.

Finally, the effect of different dosages was examined. Low-dose vaginal estradiol was found to be the most efficacious according to symptom relief although oral estriol was also effective. Estriol had no effect on the serum levels of estradiol or estrone, whereas vaginal estriol had minimal effect. Vaginal estradiol was found to have a small effect on serum estrogen although not as great as systemic preparations. In conclusion, it would appear that estrogen is efficacious in the treatment of urogenital atrophy and low-dose vaginal preparations are as effective as systemic therapy.

More recently, the use of a continuous low-dose estradiol-releasing silicone vaginal ring (Estring; Pharmacia and Upjohn, Sweden) releasing estradiol 5 to 10 μg/day has been investigated in postmenopausal women with
symptomatic urogenital atrophy (107). There was a significant effect on symptoms of vaginal dryness, pruritis vulvae, dyspareunia, and urinary urgency with improvement being reported in over 90% of women in an uncontrolled study. The maturation of vaginal epithelium was also significantly improved. The patient acceptability was high, and although the maturation of vaginal epithelium was significantly improved, there was no effect on endometrial proliferation.

These findings were supported by a one-year multicenter study of Estring in postmenopausal women with urogenital atrophy which found subjective and objective improvements in 90% of patients up to one year. However, there was a 20% withdrawal rate with 7% of women reporting vaginal irritation, two having vaginal ulceration, and three complaining of vaginal bleeding although there were no cases of endometrial proliferation (171). Long-term safety has been confirmed by a 10-year review of the use of the estradiol-ring-delivery system which has found its safety, efficacy, and acceptability to be comparable to other forms of vaginal administration (172). A comparative study of safety and efficacy of Estring with conjugated equine estrogen vaginal cream in 194 postmenopausal women complaining of urogenital atrophy found no significant difference in vaginal dryness, dyspareunia, and resolution of atrophic signs between the two treatment groups. Furthermore, there was a similar improvement in the vaginal mucosal maturation index and a reduction in pH in both groups with the vaginal ring being found to be preferable to the cream (173).

**Selective Estrogen Receptor Modulators**

A recent development in hormonal therapy has been the development of Selective Estrogen Receptor Modulators (SERMS). These drugs have estrogen-like actions in maintaining bone density and in lowering serum cholesterol but have antiestrogenic effects on the breast (174) and do not cause endometrial stimulation (175). In theory, partial estrogen antagonists may lead to a downregulation of estrogen receptors in the urogenital tract and consequently cause an increase in lower urinary tract symptoms and symptomatic urogenital atrophy. Early work would suggest that some SERMS in development, levormeloxifene and idoxifene, may increase the risk of urogenital prolapse (176) although there were some methodological problems noted in the study. However, in an analysis of three randomized, double-blind, placebo-controlled trials investigating raloxifene in 6926 postmenopausal women, there appeared to be a protective effect, with fewer treated women having surgery for urogenital prolapse: 1.5% versus 0.75% ($p < 0.005$) (177). At present, the long-term effect of SERMS on the urogenital tract remains to be determined and there is little data regarding effects on urinary incontinence and urogenital atrophy.
CONCLUSIONS

The management of women with pelvic floor dysfunction requires a multidisciplinary approach between urogynecologists, urologists, and colorectal surgeons. Likewise, the management of lower urinary tract pathology often requires an integrated approach using conservative therapies, drugs, and often surgical treatment modalities.

The first-line management of women with detrusor overactivity is predominantly a combined approach, which uses behavioral therapies such as bladder retraining and pelvic floor exercises and drug therapy. At present, antimuscarinic agents remain the most commonly used agents with the newer bladder-specific drugs offering improved efficacy and a reduction in adverse effects. Drugs with other mechanisms of action remain under development and may ultimately replace the currently available agents and thus avoiding the antimuscarinic side effects of dry mouth, constipation, and blurred vision.

When considering the management of women with stress urinary incontinence, pelvic floor exercises remain an important first-line therapy although the introduction of duloxetine may offer an alternative to continence surgery in those women who fail with a conservative approach.

Finally, for many years estrogens have been used in the management of women with symptoms of urogenital atrophy, recurrent UTIs, and urinary incontinence. Recent meta-analysis has now clarified many of the results of smaller studies and helped us understand the central role of estrogen replacement in many lower urinary tract conditions following the menopause.

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OVERVIEW

Background

Worldwide, there has been a huge increase in the incidence of sexually transmitted infections (STIs) and infection with human immunodeficiency virus (HIV). In the developed world, this is at least partially related to changing sexual attitudes and lifestyles: in resource-poor countries associated factors are poverty, armed conflict, civil unrest, migration, inadequate societal infrastructure, and poor access to education. Apart from the increasing prevalence of infection with HIV, there is a resurgence of syphilis and gonorrhea (1). There are high endemic levels of syphilis in pregnant and nonpregnant women in many North American cities, related to poverty, prostitution, and crack cocaine usage (2). The prevalence of chlamydial infection in sexually active young people in Northern Europe is around 10% (3). The chances are increasing, therefore, that specialists in gynecology and reproductive health will encounter STIs and other genital infections in daily practice. Many of these will compromise not only fertility but also satisfactory pregnancy outcome. There is an increasing body of evidence linking the transfer of HIV and progression of clinical HIV disease to the active inflammation associated with genital infections (4).

This chapter discusses the drug management of bacterial infections, both sexually transmitted (gonorrhea, chlamydial infection, and syphilis, in particular) and also nonsexually transmitted, including bacterial vaginosis.
and actinomycosis. The issues of pelvic inflammatory disease (PID) and drug therapy in pregnancy deserve special mention and also, because it continues to be a significant public health problem, tuberculosis (TB), although TB is more properly the subject of specialized texts.

General Properties of Antibiotics

It is only the bacterial cell wall that is significantly different from that of mammalian cells. Bacteriostatic antibiotics (tetracyclines, macrolides) affecting other parts of the organism (protein synthesis, nucleic acids) rely upon selective toxicity of the antimicrobials in bacteria which have a just sufficient cellular differentiation from mammalian cells for the agent to be clinically useful. Optimum usage not only takes into account likely and actual sensitivity of the causative organism, but also factors affecting the achievement of tissue levels, which exceed the mean inhibitory concentration (MIC) of the bacterium for the majority of the duration of treatment. These factors include absorption and route of administration, metabolism, distribution, and elimination and concentration at the site of action. Care must be taken in administration to subjects with hepatic or renal impairment, depending on whether the drug is eliminated predominantly by metabolism (ofloxacin, many macrolides, except clarithromycin), excretion in the urine (many tetracyclines; less with doxycycline), or both (ciprofloxacin).

For satisfactory oral administration, the drug should be strongly lipophilic and have a satisfactory relationship of its pKₐ to the pH of the surrounding medium, such that it passes out of the gut in the un-ionized state. The tetracyclines have a particular advantage here. Macrolides (erythromycin, azithromycin, clarithromycin) have variable water solubility and inactivation rates by stomach acid: erythromycin, in particular, has erratic bioavailability after oral administration but minor structural alterations to the erythromycin molecule have resulted in improved pharmacokinetic properties. The quinolones are completely heterogeneous in this respect, some (ciprofloxacin, ofloxacin) having a quite satisfactory absorption profile. Absorption particularly of the tetracyclines is adversely affected by the presence of food, milk, antacids, or divalent cations (especially calcium), although doxycycline and minocycline are best administered with food. They all show reduced serum concentrations in the presence of iron.

The plasma concentration curves for many antibiotics (tetracyclines, erythromycins, many oral penicillins) mean that multiple daily dosage is required to achieve plateau levels greater than many MICs. However, some agents are superior in this respect and may be administered once or twice daily. Doxycycline, minocycline, erythromycin stearate, and the quinolones show this advantage. The long elimination half-life of azithromycin permits once daily dosing. Some agents have the advantage of superior tissue penetration. These include doxy- and minocycline (compared with other
tetracyclines), some macrolides, and the quinolones. Metronidazole is rapidly and almost completely absorbed by mouth. Metabolized in the liver, peak plasma levels are dependent upon dosage. Tissue penetration is high: bactericidal concentrations have been found in pus from hepatic abscesses (5).

Duration of therapy depends upon the nature of the infection and the severity of the clinical presentation. As a general rule, treatment of acute, uncomplicated infections should be continued until the patient has been afebrile and clinically well for at least 72 hours; TB, genital, and pelvic infections require special consideration, and regimes have been developed after many years of clinical experience. The indiscriminate use of antimicrobial combinations should be avoided because of the risk of toxicity, pharmacological antagonism, and selection of resistant organisms. Therapy of TB, infective endocarditis, commonly mixed infections (such as PID), and septicemia in the immunocompromised are exceptions. The bacteriostatic agents should not be given with the bactericidal because one property of the latter is that they act upon actively dividing organisms.

**PRINCIPLES OF MANAGEMENT AND ANTIBIOTIC THERAPY OF GENITAL INFECTIONS**

**Sexually Transmitted Infections**

Drug therapy is but one member of the armamentarium for successful management and control of the STIs: the other strategies are summarized in Figure 1. At the very least, therapeutic success in the cure of the individual woman is marred by reinfection from an untreated sexual partner, either a regular partner or a new partner who may be a member of what is known as a “social network” or “core group” (6).

Most gynecologists are not in a position to engage in many of these activities themselves but should have access to specialized help for the management of individual and public health aspects of STIs. These are well developed in

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<td>Adequate drug therapy, utilizing pharmacokinetics to inform choice and engage better patient compliance</td>
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<td>Exclusion of concomitant STIs</td>
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<td>Tests of cure</td>
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<td>Contact tracing</td>
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<td>Educational interventions</td>
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**Figure 1** Strategies in case management of STIs. *Abbreviation:* STIs, sexually transmitted infections.
many countries but unfortunately the global situation is patchy (7). The response in some resource-poor situations has been to fashion strategies around ad hoc control and treatment programs, syndromic management, and presumptive mass treatment of STIs (8–10). These initiatives have had variable success (11,12).

In terms of the individual woman, there may be a paucity of clinical symptoms and signs yet, where present, common presenting symptoms may be shared with other gynecological disease (Fig. 2). Clinical practice validates survey research identifying sociodemographic factors alerting the clinician to the possibility of STI. Some of these are summarized in Figure 3.

There is no doubt that developments in more sensitive and specific diagnostic techniques (such as molecular methods) have enhanced not only our understanding of epidemiology of the STIs, but also the clinical management of women presenting with gynecologic symptoms (13). However, in office practice there is no substitute for the routine usage of sensitive and subtle questioning, in order to draw attention to the possibility of an STI, along the lines set out in Figure 4. It is important to establish timing of last coitus: whether barrier methods were used, whether the patient is in an established relationship, and whether there have been other concurrent partners who might have been implicated in a disease network. A frequent practice in the United Kingdom is to start sexual history by going back over the previous three months. The disclosure of orogenital or anal coitus should prompt the taking of tests from alternative sites. A history of previous STI and of recent antibiotic therapy is important.

As with any antimicrobial treatment, antibiotic therapy in the bacterial STIs will be dictated by efficacy, the likely and actual antibiotic sensitivity

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<td>Pruritus</td>
<td>Lower abdominal pain and tenderness, dyspareunia</td>
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<td>Dysuria and frequency of micturition</td>
<td>Increased vaginal discharge</td>
</tr>
<tr>
<td>Intermenstrual bleeding</td>
<td>Left upper quadrant pain (Fitz-Hugh Curtis)</td>
</tr>
<tr>
<td>Post-coital bleeding</td>
<td>Hypertrophic cervical ectopy</td>
</tr>
<tr>
<td>Delayed menstruation</td>
<td>More frequent menstruation</td>
</tr>
</tbody>
</table>

Figure 2  Clinical features present in many sexually transmitted infections.
pattern of the causative organism, for the clinical condition of the patient (disease severity, contraindications), tolerance, compliance, and cost. Adequate diagnosis before treatment is important and the clinician should be sensitive to not only the pattern of local antibiotic resistance, but also

<table>
<thead>
<tr>
<th>Recent sexual partner change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 15-24</td>
</tr>
<tr>
<td>Recent marital breakdown</td>
</tr>
<tr>
<td>Newly living away from parental home</td>
</tr>
<tr>
<td>Mobile occupation</td>
</tr>
<tr>
<td>Married below age 20 yrs</td>
</tr>
<tr>
<td>Multiparity below age 20 yrs</td>
</tr>
<tr>
<td>History previous STI</td>
</tr>
<tr>
<td>Previous unwanted pregnancy</td>
</tr>
<tr>
<td>Current usage of non-barrier contraceptive method</td>
</tr>
<tr>
<td>Current recreational drug usage</td>
</tr>
<tr>
<td>Prostitution</td>
</tr>
<tr>
<td>History of parasuicide</td>
</tr>
<tr>
<td>Tattooed^</td>
</tr>
<tr>
<td>Having been in local authority care</td>
</tr>
<tr>
<td>Convictions for felony</td>
</tr>
</tbody>
</table>

^Although nowadays it is apparently fashionable to have a discreet tattoo somewhere between the T12/L3 dermatomes!

**Figure 3** Factors suggesting the presence of an STI. *Abbreviation: STI, sexually transmitted infection.*

Ensure privacy & confidentiality
Act in a professional manner
Be open-minded & non-judgemental at all times
Recognize that many infections show great latency and may present a long time into a monogamous relationship
Try to recognize any non-verbal clues
Do not over-medicalize terms
Ask appropriate questions
Allow the patient to ask questions, to express fears and sometimes to vent anger
Engage in risk reduction promotion, recognizing that ‘thou shalt not’ strategies are not always effective

**Figure 4** Sexual history taking in a general setting. *Source: From Ref. 14.*
to the possible importation of resistant strains. Resistance in gonococcal infections has always been taxing in the day-to-day management of the disease (15), yet although in vitro studies are beginning to show that resistance in chlamydia is at the least a theoretical possibility (16). *Treponema pallidum* and *Chlamydia trachomatis* have to date been consistently sensitive to standard antimicrobials: choice of therapy in the clinical setting is centered mainly on factors related to clinical presentation. For example, neurosyphilis requires prolonged therapy with an antibiotic preparation known more readily to penetrate the blood–brain barrier. Or, in chlamydial disease, for example, the patient less likely to complete a week’s course of treatment might be more suitable for immediate or even directly observed therapy with azithromycin.

In the *syndromic approach* for managing STIs, simple clinical algorithms based on signs and symptoms determine antimicrobial treatment. The patient may be managed in a single visit in settings where access to laboratory facilities for microbial identification is limited. Advantages include access to rapid, effective therapy, and management appropriate to primary health care settings of simultaneously occurring multiple infections. Useful, as part of public health initiatives in countries where medical care is limited, syndromic management is not generally accepted as a satisfactory method in developed countries (Fig. 5). In resource-poor settings, careful watch has to be made on patterns of antimicrobial sensitivity and disease prevalence. All these considerations require a carefully planned epidemiological approach (17,18). The antimicrobial regimens are chosen to cover the major pathogens responsible for the syndromes in the specific geographical area, but the algorithms suffer in terms of sensitivity and specificity (e.g., vaginal discharge is not a good indicator of cervical infections with gonorrhea and chlamydia). In low-prevalence settings, the choice is whether to overtreat or not to treat at all. Recently suggested strategems for incorporating risk assessment has improved the sensitivity of the algorithms. Therapy of

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Treat for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower abdominal pain</td>
<td>Gonorrhea, chlamydia &amp; other bacteria</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>Cervicitis: gonorrhea &amp; chlamydia</td>
</tr>
<tr>
<td></td>
<td>Vaginitis: trichomoniasis &amp; candidiasis</td>
</tr>
<tr>
<td>Genital ulceration</td>
<td>Syphilis, chancroid &amp; genital herpes</td>
</tr>
</tbody>
</table>

**Figure 5** Treating STIs using the syndromic approach. *Abbreviation:* STIs, sexually transmitted infections.
specific infections is summarized in the appendices. All the bacterial infections may be complicated or uncomplicated. Some (*C. trachomatis*, *T. pallidum*, *Actinomycosis israelii*) demonstrate a relatively stable response to standard antibiotic therapy but others, *Neisseria gonorrhoeae*, in particular, show a progressive “resistance drift” due to evolutionary selection arising from unsatisfactory therapeutic practices (such as, e.g., the unsupervised over-the-counter sale of antibiotics in some parts of the world). A favorable response to treatment is encouraged by attention to local resistance patterns and to patient compliance: it should be remembered that published trials of antimicrobial drugs may reflect a historical snapshot of rapidly evolving organisms. In gonorrhea and TB, a knowledge of global endemic resistance patterns is helpful. With the STIs, single-dose therapy is often advantageous.

In some countries, the so-called “epidemiological” treatment of contacts without investigation is common. A better term, however, should perhaps be “empirical” because this approach is far from epidemiological. Justified in the case of the patient who refuses examination; in very late pregnancy, where time is of the essence; in patients who, because of emotional or social inadequacy, are unlikely to engage in repeated search for infection, this practice terminates the “chain of evidence” necessary for fruitful contact tracing. The exception to this rule is in resource-poor situations where in high prevalence areas mass treatment of presumptive infections might be one strategy to help in control.

**Gonorrhea**

Looked at in public health terms, chosen regimens for infection with *N. gonorrhoeae* should result in elimination of the organism in at least 95% local cases (19). It was recognized very soon after the introduction of penicillin therapy that resistance was common and often causally related to lack of adequate public health control methods. As well as absolute numbers of cases, indices of poor control include upward trends in antibiotic resistance, as well as prevalence of complications in family and specialist practice (20).

In gonorrhea, two types of resistance occur: plasmid mediated β-lactamase production (conferring complete resistance to penicillin-based antibiotics), and mutational resistance. This latter has historically given rise to partial penicillin resistance which gradually became associated in the same organisms with multiple antibacterial resistances, particularly against the tetracyclines. Laboratory sensitivity testing should be available to all who treat the infection and local treatment policies should be modified according to temporal trends. At the time of writing, the precontemporary

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*a* My own supporting laboratory currently routinely tests isolates against penicillin, ciprofloxacin, spectinomycin, and azithromycin.
U.K. treatment of oral ciprofloxacin 500 mg in a single dose has been under threat by the importation of resistant strains from other countries. The mean prevalence of ciprofloxacin-resistant strains in U.K. clinics outside London was 10% (19) but switching to third-generation cephalosporin therapy has been successful and, due to positive selection pressure, can even reverse the negative resistance drift to ciprofloxacin. The standard therapy for gonococcal infections in the United Kingdom is now with cefixime or ceftriaxone (Appendix 1). Public health efforts (particularly contact tracing) must be energetically engaged to identify source contacts of persons with resistant strains. This is facilitated by having a unified service for STI treatment and surveillance.

Complicated infections such as PID, peri-urethral abscess, and Bartholinitis should be treated with longer courses of therapy and there is evidence that pharyngeal infection requires multiple-dose treatment. Fortunately, disseminated gonococcal infection is usually caused by gonococcal auxotypes that are sensitive to penicillin—although Centers for Disease Control and Prevention (CDC) recommends alternative regimes with third-generation cephalosporins or quinolone antibiotics (21). Prolonged, parenteral treatment is recommended. Up to 40% women with gonorrhcea also harbor C. trachomatis. If coinfection is proven or suspected, consideration should be given to therapy that covers both organisms, particularly in those patients whose willingness to attend for follow-up is suspect (16). A single dose of azithromycin (1G, added to antigonococcal therapy) is helpful here (22).

Chlamydial Infection
The majority of clinical studies into the most effective therapy for chlamydia have suffered from design flaws: studies have been small and the duration of follow-up short (23). The latter is probably important because there is an increasing body of thought that latency, chlamydial persistence, and recurrences of infection are more important than previously appreciated (24). Thus, the optimum length of treatment duration has not been established, although 7 to 14 days is standard. Most would give a longer duration of treatment in complicated infection (23).

Syphilis
In gynecological practice, the clinician is likely to encounter syphilis in latency—having been picked up on routine antenatal testing for antitreponemal antibodies. However, in some areas, acute, infectious disease (within the first two years of infection) is encountered more frequently, either in the primary, secondary, or early latent stages. The practitioner should be on the lookout for the primary chancre (with associated regional lymphadenopathy), or the lesions of secondary infection—mucous patches, generalized pleomorphic rash, lymphadenopathy, condylomata lata, patchy alopecia, or
splenomegaly (Figs. 6 and 7). The primary lesion may occur at the site of inoculation anywhere on the body, including the oropharynx and anorectum. In the endocervical canal, the primary lesion may result in an edematous, beefy cervix. Strong consideration should be given to screening for associated STIs, including HIV. HIV coinfected patients with early syphilis are at risk of developing neurological manifestations, and treponemal serological reactivity may be delayed or be falsely negative.

Penicillin treatment of the pregnant mother will often prevent disease in the fetus, but careful surveillance of the neonate and appropriate serological testing are recommended. Maternal antibodies may be carried over to the infant and be detectable for the first three months of life: serological tests that detect rises in neonatal IgM antibodies may be helpful as is sequential testing over a period of time. Treatment and follow up of the mother should be appropriate for her stage of disease: if penicillin-sensitive, follow-up after

Figure 6  Primary syphilitic chancre.
erythromycin therapy should be assiduous, there is a place here for treating
the mother postpartum with doxycycline when breast feeding ceases. The place
of azithromycin and cephalosporins in pregnancy is not yet determined (21). In
true penicillin allergy, consideration may be given to hospitalization and desen-
sitization by prescribing regular and increasing increments of oral penicillin,
starting with tiny doses and increasing until therapeutic levels are achieved.

It should be remembered that those antibody tests that detect IgG
antibody subgroups to syphilis antigens (TPPA, TP EIA, TPHA)\(^b\) may

\(^b\) *Treponema pallidum* particle agglutination, *T. pallidum* enzyme immunoassay, *T. pallidum*
hemagglutination.

**Figure 7** Perianal condylomata lata of secondary syphilis in pregnancy (note the
scar at the fourchette of the primary lesion).
Bacterial Genital and Pelvic Infections

Persist even after curative therapy: insurance courses of antibiotics in subsequent pregnancies are no longer thought necessary (21). The so-called Jarisch-Herxheimer reaction (characterized by transient worsening of existing symptomatology after initialization of syphilis therapy) has been reported to cause premature labor sometimes with fetal distress. Hospitalization and fetal monitoring for the first 24 hours has been advocated.

Other Conditions: Actinomycosis, Bacterial Vaginosis, Tuberculosis

The diagnosis of pelvic actinomycosis remains fraught with difficulty. Fiorino (25) reviewed the clinical findings of 92 cases and was of the opinion that recognition of common features preoperatively often spares the patient from extensive surgery. Particularly, he found abdominal pain, weight loss, and vaginal discharge, often foul smelling. In other cases it presents as a bilateral ovarian tumor or retroperitoneal mass; fever and change in bowel habit or the menstrual cycle were not uncommon. Physical examination often elicited uterine tenderness and vaginal discharge. Anemia, leucocytosis, raised ESR and CRP were frequently found. He reported the condition to mimic pelvic or intra-abdominal malignancy, cervical carcinoma, inflammatory bowel disease, or diverticulitis.

Fortunately, the causative agents of pelvic actinomycosis (A. israelii and other implicated species—A. bovis, A. ericksonii, A. naeslundii, A. viscosus, and A. odelyticus) remain sensitive to penicillin. Classically manifest with unilateral lesions, clinical actinomycosis may present as a bilateral ovarian tumor or retroperitoneal mass (Fig. 8). The bedrock of treatment of clinically invasive disease is prolonged therapy for at least six weeks. Invasive pelvic disease in women is usually associated with the wearing of an intrauterine contraceptive device (IUCD), yet the simple carriage of actinomycetes in the genital tract is not predictive of the development of clinical disease even if associated with an IUCD (26–29).

The significance of finding actinomyces-like organisms (ALOs) in a Papanicolau-stained cervical cytology smear remains controversial. The conclusion of Gupta et al. in 1979 (30), that the observation of brown/black amorphous material surrounded by radial bacterial filaments is diagnostic of actinomycosis, should be viewed in the light of the similar appearance of other vaginal commensal organisms, such as fusobacteria and bacteroides. An emerging consensus is that the presence of ALOs on cytology neither necessitates IUCD change nor chemotherapy (31).

Bacterial vaginosis is the commonest cause of vaginal discharge in women of childbearing age. A clinical syndrome due to overgrowth of normal, vaginal commensal bacteria, not sexually transmitted and previously thought merely to be an inconvenience is now recognized to be with adverse pregnancy outcome and perhaps infective complications following termination of pregnancy (TOP) (32). There has been reported an increased
incidence of vaginal cuff cellulitis and abscess following transvaginal hysterectomy (33). Treatment of the symptomatic woman is generally accepted practice, but there may be a place in treating the asymptomatic in these two special circumstances.

Major issues are developing with respect to TB. Worldwide in 1995 there were about 9 million new cases of TB with 3 million deaths (34). Mycobacterium tuberculosis kills more people than any other single infectious agent: deaths from TB comprise 25% all avoidable deaths in developing countries. Ninety-five percent of TB cases and 98% TB deaths are in developing countries; 75% cases are in the economically productive age group (15–50 years).

In addition to the epidemic of TB seen in advanced HIV infection and the associated immune deficiency, there are problems around TB related to its endemicity in certain parts of the world, to international travel, to recreational drug usage, to compliance with therapy and to multidrug-resistant strains of M. tuberculosis. The latter poses particular difficulties for physicians dealing with large numbers of infected migrants or of chaotic drug users in whom the twin phenomena of poor communication and lack of compliance encourage the development and spread of multidrug resistance tuberculosis (MDRTB) (35). Many of such subjects have coinfection with hepatitis B and C and with HIV, raising issues of pharmacokinetics and drug–drug interaction resulting in overdose or inadequate therapeutic levels.
As in pulmonary disease, the extra-pulmonary disease seen by the gynecologist is best managed cooperatively with physician and nurse specialists in TB, and also sometimes HIV.

The abdomen is a frequent site of clinical disease in TB, particularly in persons from the Indian subcontinent (35). Usually disseminated by hematogenous spread, one-third of patients have simultaneous pulmonary infection. Patients with associated pulmonary TB who are actively excreting mycobacteria should be nursed in full respiratory isolation. Notification and contact tracing are imperative, and consideration should be given to chemoprophylaxis of contacts. A risk assessment for HIV coinfecion should be undertaken and appropriate antibody testing for HIV I and II performed with informed consent of the patient. A standard treatment regime is sufficient for most patients with abdominal disease (36,37).

To prevent the emergence of resistant strains, the standard of care is combination chemotherapy for up to six to nine months, with either first- or second-line antitubercular drugs. MDRTB, however, is become increasingly common and adherence to what is necessarily a longer, complicated treatment regime can be difficult. Second-line drugs have particular role here (Fig. 9). In some circumstances, directly observed therapy in a short course is recommended, as is pulsed or intermittent therapy (see later). Drug–drug interactions are common, particularly with some antiretroviral medications and care should be taken in subjects with coexistent hepatic impairment or renal disease. Corticosteroid therapy has often been advocated but efficacy is uncertain: there is a consensus that it should be given for pericardial, meningeal, and ureteric diseases (35). For all these reasons, care of abdominal TB is best undertaken jointly with an physician experienced in the management of TB and associated conditions (such as HIV and viral hepatitis).

Care must be taken with co-administration of antiretroviral and anti-TB therapies. Rifampicin is a first-line, bacteriocidal drug with excellent

<table>
<thead>
<tr>
<th>Drug</th>
<th>First line</th>
<th>Second line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>PAS</td>
<td>Ethionamide</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Ciprofloxacin</td>
<td>Capreomycin</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Kanamycin</td>
<td>Amikacin</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Cycloserine</td>
<td>Thiacetazon</td>
</tr>
<tr>
<td>Streptomycin</td>
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</tr>
</tbody>
</table>

Figure 9  First- and second-line antitubercular drugs.
antituberculous activity. Unfortunately, this and other rifamycins are potent inducers of hepatic enzymes and have the potential for many drug–drug interactions. Patients should be warned that rifampicin turns all bodily secretions, including urine and tears, orange. Isoniazid increases concentrations of some drugs (particularly some antiepileptic agents and the benzodiazeepines) to toxic levels.

In the treatment of TB, it is recommended that a six-month short course regimen with four chemotherapeutic agents is used for all forms except in meningitis (Table 1). The first two months with four drugs is the initiation phase: for the subsequent four months, treatment may be reduced to two agents only. In certain circumstances, the fourth drug (ethambutol) may be omitted. Treatment of all patients should be supervised by physicians with experience in the disease with access to nurse specialists and health visitors. In view of rising incidence of drug resistance, bacteriological confirmation and susceptibility testing is important. Particularly in MDRTB, patients should be managed in appropriate isolation units by physicians with special expertise and a close working relationship with mycobacterial reference laboratories. In HIV coinfection, rifabutin is a useful drug for patients receiving medications with significant interactions with rifampicin. In standard therapy, regular ophthalmological assessment is important and regular full blood counts and hepatic function tests are usual.

### Table 1  Standard Chemotherapeutic Regimens for Tuberculosis in Adults

<table>
<thead>
<tr>
<th>Drug [duration (mo)]</th>
<th>Daily dosage (dependent upon weight)</th>
<th>Intermittent dosage—weekly intervals (dependent upon weight)</th>
<th>Particular side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (6)</td>
<td>300 mg</td>
<td>15 mg/kg (3x)</td>
<td>Hepatitis, peripheral neuropathy</td>
</tr>
<tr>
<td>Rifampicin (6)</td>
<td>450–600 mg</td>
<td>600–900 mg (3x)</td>
<td>Hepatitis gastrointestinal intolerance, arthritis</td>
</tr>
<tr>
<td>Pyrazinamide (2)</td>
<td>1.5–2.0 g</td>
<td>2.0–2.5 g (3x), 3.0–3.5 g (2x)</td>
<td>Ocular toxicity</td>
</tr>
<tr>
<td>Ethambutol (2)</td>
<td>15 mg/kg</td>
<td>30 mg/kg (3x), 45 mg/kg (2x)</td>
<td></td>
</tr>
</tbody>
</table>

*For respiratory and nonrespiratory disease (except central nervous system disease), usual recommendation is for triple therapy (I, R, P) or quadruple therapy (± ethambutol) for the first 2 mo and then I, R for the subsequent 4 mo. In HIV coinfection, the rate of relapse in mycobacterial infection bring with them their own challenges.

*Source*: Adapted from Refs. 35,37,38.
Other Conditions: PID

PID is most often the result of infection ascending from the endocervix causing endometritis, salpingitis, parametritis, oophoritis, tuboovarian abscess, and pelvic peritonitis. Frequently the result of STI, the age-specific distribution mimics that of the distribution curves for STIs (Chart 1). Clinical diagnosis of PID is difficult because of the wide variation in symptoms and signs and the high rate of asymptomatic infection, particularly among adolescents. Considering the limitations of clinical evaluation, at the present time laparoscopy is the only tool that can provide definitive diagnosis (38). Unfortunately, this is an operative procedure and not a useful tool for routine diagnosis. The place of transvaginal ultrasound scanning and power Doppler imaging is not yet clear (39).

Although *Mycoplasma genitalium* has been implicated as a causative agent (independent of coinfection with *C. trachomatis*) (40), the association with *Ureaplasma urealyticum* is doubtful (41). Endogenous aerobic organisms (including nonhemolytic and group B hemolytic streptococci, *Escherichia coli*, and coagulase negative staphylococci) and anaerobic organisms have frequently been found in the upper genital tract of women.
with salpingitis (42). Seen most frequently in prolonged or recurrent infections, older patients, and wearers of an IUCD, superinfection with anaerobes is common (42) and most authorities recommend additional therapeutic cover with metronidazole.

In Canada and Sweden, there is evidence of a linear relationship between control of STIs and the incidence of both hospital admission with and office attendances for treatment of PID: incidence was falling in the early 1990s (Chart 2) (43–45). However, there are figures from many parts of the world to suggest that chlamydia rates in women are increasing again and a corresponding rise in PID incidence might be expected (although improved diagnostic methods for the \textit{Chlamydiales} and the initiation of screening programs might result in a spurious increase in chlamydial incidence rates).

Optimum management of PID relies not only upon an informed judgment of the likely causative organism(s), but also upon the clinical severity of the disease. Treatment guidelines stress the polymicrobial nature of the disease, the importance of \textit{C. trachomatis}, and of antibiotic resistant \textit{N. gonorrhoeae}. In severe acute infection, parenteral therapy is important, continued until 24 to 48 hours of clinical improvement and return of the temperature to normal. Regimens are summarized in Appendix 3. Indications for hospitalisation are summarised (Fig. 10).

\textbf{Other Conditions: Toxic Shock Syndrome and GBs}

Toxic shock syndrome, an acute, potentially life-threatening systemic disorder caused by exotoxin-producing \textit{Staphylococcus aureus} often demonstrates a fulminating downhill course. Characteristically, there is a febrile illness with maculopapular rash and hypotension, which may rapidly progress to multisystem involvement, typically with renal and hepatic compromise and cardiopulmonary distress (46). Therapy with a $\beta$-lactamase-resistant

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{tubovarianmass.png}
\caption{Indications for hospitalization in acute pelvic inflammatory disease.}
\end{figure}
antistaphylococcal antibiotic for 10 to 14 days is appropriate, but equally appropriate is careful observation. Severe cases are best managed in a critical care facility with facilities for hemodynamic, respiratory and coagulation support, and for renal dialysis. Corticosteroid therapy is no longer recommended but the use of vasopressor agents is a useful adjunct to treatment.

Although group B streptococcal disease (GBS) is the commonest cause of infection in newborn infants, only a small percentage of babies born to mothers carrying GBS will develop early-onset disease with septicemia. Screening the mother during pregnancy is problematic and generally not recommended: carriage is often intermittent or transitory, single swabs are inefficient, and the organism is only found in 10% cases (47). Strategies that have been discussed include universal screening, targeted screening, or targeted intrapartum prophylactic therapy in women with recognized risk factors. These include previous baby affected by GBS, preterm labor, GBS bacteriuria in current pregnancy, prolonged rupture of membranes, and fever in labor (47). Parenteral penicillin and clindamycin have been recommended in the United Kingdom.

Pregnancy

Specific bacterial infections in pregnancy bring their own considerations. Clinical syndromes are summarized in Figure 11. The issue of bacterial vaginosis in pregnancy deserves special mention. It is common in some populations undergoing TOP and has been associated with post-TOP pelvic inflammation (46). In pregnancy, it is associated with late miscarriage, preterm birth, preterm premature rupture of membranes, and postpartum endometritis (46). Metronidazole remains the treatment of choice in pregnancy: there is no evidence-base for topical therapy in the condition and there have been reports of adverse pregnancy outcome linked particularly with the use of topical clindamycin cream (48,49).

Antibiotic Prophylaxis in Surgery

There is plentiful literature supporting the employment of antibiotic prophylaxis to prevent infectious complications after gynecological surgery. The hypoxic tissue and fluid collections which may occur after abdominal approaches result in a milieu conducive to bacterial colonization (staphylococci, streptococci, coliforms. and Bacteroides spp.), and, in particular, vaginal hysterectomy may introduce vaginal flora to the pelvic cavity, with resultant cellulitis. In other procedures, such as reconstructive tubal surgery, the risk of infection is low but its occurrence may significantly jeopardize results (50).

Unfortunately, methodological differences between published studies compromise the choice of one antimicrobial agent over another but there has been recent emphasis on extremely short durations of therapy: there seems to be no advantage in continuation of therapy beyond the immediate
perioperative period. Such short durations mitigate the side effects of longer courses of treatment such as Clostridium difficile superinfection. Certainly, factors such as length of surgery, obesity, low socioeconomic status, and the nature of the operation are important considerations. Popular choices of appropriate agent include first- or second-generation cephalosporins (Fig. 12), of which the timing of administration should take into account the pharmacokinetics of the drug (including peak serum concentration and half-life). For example, cephalothin has a peak serum concentration 15 to 20 minutes after parenteral administration, but with cefotaxime such levels are not reached until 20 to 50 minutes. If given, antibiotics should be given to achieve peak plasma levels at the time of highest bacteremia, except at cesarean section when they should be given after clamping of the umbilical cord (50).
Cost-effective as are such measures, in terms of the morbidity of infectious complications and length of hospital stay, routine prophylactic antibiotics should be used prudently and judiciously. Indiscriminate and widespread usage always entertains the risk of selection of resistant bacteria.

Appendix 1

Recommended therapy of specific infections—gonorrhea and chlamydial infection (effectiveness evidence meta-review from Centres for Disease Control & Infection guidelines, Clinical Evidence, and BASHH guidelines)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Drug (oral, intravenous, intramuscular)</th>
<th>Comments</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gonorrhea</strong></td>
<td>Cefixime (O) 400 mg stat</td>
<td>Uncomplicated urethral, cervical, rectal infections</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone (I/M) 250 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin 500 mg (O) stat</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ofloxacin 400 mg (O) stat</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ampicillin (O) 2G + probenecid 1G (O) stat</td>
<td></td>
<td>Medium</td>
</tr>
<tr>
<td>Spectinomycin (I/M) 2G</td>
<td></td>
<td>Resistant infections</td>
<td>High</td>
</tr>
<tr>
<td>Ceftriaxone (I/M) 250 mg</td>
<td></td>
<td>Pharyngeal infections</td>
<td>Medium</td>
</tr>
<tr>
<td>Ofloxacin 400 mg (O) stat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin 500 mg (O) stat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime (I/V) 1G 8 hr or</td>
<td>Disseminated infection I/V until 24-48 hr after clinical improvement, then 1/52 oral Rx</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin (I/V) 8 hr, then</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefixime (O) 400 mg BD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chlamydial infections</strong></td>
<td>Doxycycline (O) 100 mg BD × 1/52</td>
<td>Uncomplicated infection</td>
<td>High</td>
</tr>
</tbody>
</table>

*Abbreviations*: I/M, intramuscular; I/V, intravenous; O, oral.  
*Source*: From Refs. 21,56–57.
### Appendix 2

Recommended therapy of specific infections—syphilis (effectiveness evidence meta-review from Centres for Disease Control & Infection guidelines, Clinical Evidence, and BASHH guidelines.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Drug (oral, intravenous, intramuscular)</th>
<th>Comments</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis (tertiary disease, particularly neurosyphilis; specialist consult; coexistent HIV, some recommend longer durations—specialist consult)</td>
<td>Benzathine penicillin G (I/M) 2.4 million units stat × 2 or 3</td>
<td>Primary, secondary, and early latent infection</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Procaine penicillin G (I/M) 900,000 units daily for 10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxycycline (O) 100 g BD × 2/52</td>
<td>Penicillin allergy (erythromycin in pregnancy—see caveats in text)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Erythromycin (O) 500 mg QID × 2/52</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benzathine penicillin G (I/M) 2.4 million units weekly × 3/52</td>
<td>Late latent syphilis</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Abbreviations: I/M, intramuscular; I/V, intravenous; O, oral.*

*Source: From Refs. 21,56,57.*
Appendix 3

Recommended therapy of specific infections—pelvic inflammatory disease, bacterial vaginosis (effectiveness evidence meta-review from Centres for Disease Control & Infection guidelines, Clinical Evidence, and BASHH guidelines.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Drug (oral, intravenous, intramuscular)</th>
<th>Comments</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PID</td>
<td>Cefoxitin (I/V) 2G 6qh PLUS</td>
<td>Severe acute PID, continue for 24 hr after clinical improvement then switch to oral therapy</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Doxycycline (O) 100 mg 12qh OR ofloxacin (I/V) 400 mg 12qh plus metronidazole (I/V) 8qh</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Clindamycin (I/V) 900 mg 8qh plus gentamycin, standard loading, and maintenance doses per kg body weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ofloxacin (O) 400 mg BD plus metronidazole (O) 400 mg BD × 2/52</td>
<td>Ambulatory therapy</td>
<td>Medium</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>Metronidazole (O) 400 mg BD × 1/52</td>
<td>Evidence of cure rates at 4/52</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Metronidazole (O) 2G stat</td>
<td>Evidence of cure rates at 4/52</td>
<td>Medium—high</td>
</tr>
<tr>
<td></td>
<td>Clindamycin 2% cream (intravaginally) daily × 1/52</td>
<td>Not in pregnancy</td>
<td>Medium—high</td>
</tr>
</tbody>
</table>

Abbreviations: PID, pelvic inflammatory disease; I/V, intravenous; I/M, intramuscular; O, oral.

Source: From Refs. 21, 56, 57.
REFERENCES

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Viral Sexually Transmitted Infections

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GENERAL OVERVIEW
In the United Kingdom, the number of patients presenting with viral sexually transmitted infections (STIs) has rapidly increased during the past 25 years (1). Women are more susceptible than men to their acquisition. They are often present subclinically and can be transmissible both vertically and to sexual partners over many years. They can cause serious acute and long-term complications and, unlike for the bacterial STIs, drug treatment is rarely curative. Thus, their management can pose complex clinical challenges (2,3) (Table 1).

GENITAL WARTS
Epidemiological and Clinical Features
Genital warts are the commonest viral STI and are caused by human papilloma virus (HPV) infections. There are several HPV types that can cause genital warts: most clinically overt lesions are caused by HPV 6 and 11; other oncogenic viral types, notably HPV 16, 18, and 33, are more often associated with subclinical lesions of the vulva and cervix (4).

The lifetime risk of acquiring a genital HPV infection is high. In the United States, over 50% of female college students were found to have become infected within two years of becoming sexually active. Genital warts
may occur in any age group, are most often acquired by young sexually active adults, but may persist in an overt or subclinical state for many years. Subclinical infection is common. Lesions may affect any of the mucoepithelial surfaces of the lower genital tract and external genitals. They are more common at the sites associated with trauma, especially at the vaginal introitus. They will often proliferate if there are associated dermatological conditions causing epithelial damage, such as vulva eczema, or excessive moisture caused by the increased vaginal discharge associated with candidiasis, bacterial vaginosis, or other bacterial STIs. They are also prone to become more extensive in pregnancy.

Their presence outside the anogenital lesion is extremely uncommon in otherwise health individuals. In immunocompromised individuals, lesions can be seen in a variety of extragenital sites including the face, the mouth, and the nail folds.

Management

Most often the diagnosis of genital warts is obvious clinically, but biopsy should be considered with lesions with atypical or pigmented appearances,

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Common Viral Sexually Transmitted Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human papillomavirus infections</td>
<td></td>
</tr>
<tr>
<td>Genital herpes</td>
<td></td>
</tr>
<tr>
<td>Viral hepatitis B</td>
<td></td>
</tr>
<tr>
<td>Viral hepatitis C</td>
<td></td>
</tr>
<tr>
<td>Molluscum contagiosum</td>
<td></td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Treatment Options for Genital Warts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Clinician applied</td>
<td></td>
</tr>
<tr>
<td>Podophyllin</td>
<td></td>
</tr>
<tr>
<td>Trichloracetic acid</td>
<td></td>
</tr>
<tr>
<td>Intralesional interferon</td>
<td></td>
</tr>
<tr>
<td>Self-applied</td>
<td></td>
</tr>
<tr>
<td>Podophyllotoxin</td>
<td></td>
</tr>
<tr>
<td>Imiquimod</td>
<td></td>
</tr>
<tr>
<td>Ablative</td>
<td></td>
</tr>
<tr>
<td>Scissor excision</td>
<td></td>
</tr>
<tr>
<td>Curettage</td>
<td></td>
</tr>
<tr>
<td>Cryotherapy</td>
<td></td>
</tr>
<tr>
<td>Loop electrosurgical excision</td>
<td></td>
</tr>
<tr>
<td>CO₂ laser ablation</td>
<td></td>
</tr>
</tbody>
</table>
especially in older patients and where there has been resistance to treatment. In these cases, it is important to exclude vulval intraepithelial neoplasia.

Because STIs often coexist, and because bacterial, chlamydial, and yeast infections that cause increased vaginal discharge produce a milieu that favors wart proliferation, screening for other conditions should be undertaken (5,6).

Condyloma acuminata cause considerable psychological distress because of their unsightly appearances but are rarely the cause of serious physical sequelae. Currently, it is generally believed that total viral eradication is not possible. Warts may regress spontaneously, especially if the local environmental conditions favoring their presence, such as poor genital hygiene, skin disease, and excessive vaginal discharge, are treated. However, most patients are unwilling to wait for months without treatment. Treatment aims to reduce the cosmetic burden and any associated local discomfort (7). Warts commonly recur whatever treatment modality is employed. However, the viral load and risk of transmission is reduced if visible lesions are treated. The subsequent risk of wart recurrence and of transmission to partners appears to decline the longer the patient has been lesion-free.

It is likely that both partners in monogamous partnerships have been infected with the HPV by the time of clinical presentation, although only one may have visible lesions. Although the use of condoms is always advisable with new sexual partners, their use in stable relationships is probably unnecessary. It is believed that recurrent lesions are usually results from persistent subclinical infection rather than reinfection from the partner.

**Drug Treatment**

**Topical Podophyllin and Podophyllotoxin**

Podophyllin resin is an extract of variable potency that is derived from the rhizome of the mayapple plant and has been the first-line treatment until recently (8). It is physician applied to lesions, usually in an alcoholic solution, with advice to wash off within four hours. It can cause severe local reactions to the surrounding skin with associated discomfort. Treatment applications are made a weekly or biweekly interval.

It is most effective on multiple small filiform external warts that are not well keratinized. It is not suitable to treat vaginal or cervical warts.

More recently, the active agent, podophyllotoxin, has become available in purified form with standard potency. Podophyllotoxin and its derivatives, etoposide and teniposide, are all cytostatic (antimitotic) glucosides. It is prescribed either as a 0.5% solution or a 0.15% cream to be self-administered after patient instruction at home. It need not be washed off. Weekly treatment cycles consist of application to the lesions on three consecutive days,
either once or twice daily, followed by four treatment-free days. Side effects are similar to those of podophyllin but milder. Home-based treatment reduces patient inconvenience and review clinic visits can be reduced to monthly. Patient success rates are 50% with recurrence rates of up to 65%.

Injudicious use of podophyllin can lead to systemic absorption and has produced side effects similar to those found when podophyllotoxin was being investigated as a chemotherapeutic agent. Adverse events included nausea, vomiting, diarrhea, mouth ulcers, and fever. It is also neurotoxic and nephrotoxic. Podophyllin use is contraindicated in pregnancy. Although there is no research evidence of harm to the children of pregnant or nursing mothers from the topical use of podophyllotoxin, its use in these women should also be avoided.

Trichloroacetic Acid

Trichloroacetic acid, usually used as 80% to 90% solution, is a caustic agent that causes necrosis of lesions to which it is applied. It has to be applied with extreme care to avoid damage to normal skin around warts. Its depth of penetration can be difficult to control. Local pain, ulceration, and subsequent scarring can occur. It is more suitable where there are relatively few lesions on external keratinized anogenital skin. It may be used in pregnancy. The response and recurrence rates are similar to those of podophyllin.

Topical Fluorouracil Cream

This cytotoxic agent is rarely used in U.K. practice but has been employed to treat vaginal warts in women and to prevent recurrence of vaginal and vulvar warts postablation. It has a high rate of complications including pain, watery discharge, and denuding of vaginal epithelium. It is contraindicated during pregnancy.

Intralesional Alpha-Interferon

The use of intralesional treatment overcomes the problem of absorption though heavily keratinized warts. The treatment dose for interferon is one million units per wart, two to three times weekly for up to eight weeks. Use is associated with response rates of around 50% with recurrence rates of 25%. Systemic reactions consisting of flu-like symptoms lasting six hours after treatment may occur, as may reversible leucopenia and elevated hepatic transaminases. This treatment is no longer widely used.

Imiquimod

Imiquimod is a new topical treatment licensed for use in the treatment of external genital and perianal warts, and also used to treat other skin conditions such as actinic keratoses and basal cell carcinomas of the skin (9–11). The drug is an immune response modifier and increases the local production of alpha-interferon and other cytokines, which mediate an immune response to HPV.
The drug is supplied as a 5% cream in single-use sachets and is applied three times per week to the cleaned wart area, prior to sleeping, and washed off after 6 to 10 hours. Treatment should continue until there is clearance of visible genital or perianal warts or for a maximum of 16 weeks per episode of warts. Sexual contact should be avoided when the cream is on the skin and the compound may weaken condoms and diaphragms.

In clinical trials, rates of complete clearance with imiquimod 5% cream were higher in female patients compared with male patients; median times to complete clearance with imiquimod 5% cream ranged from seven to nine weeks. Recurrence rates, within a 12-week follow-up period, occurred in 13% to 19% of patients who achieved complete clearance of baseline warts.

Imiquimod has not been directly compared to other currently available treatments. New warts may develop during treatment. The effect of imiquimod on the transmission of genital warts is unknown.

The most commonly noted adverse events are local skin reactions. These include erythema, erosion, excoriation, flaking, and edema. Less frequently reported skin reactions included induration, ulceration, scabbing, and vesicles. Application site pigmentation changes have also been reported. Most skin reactions were mild to moderate in severity and resolved within two weeks of treatment discontinuation.

Genital Warts in Pregnancy

The relative immune suppression of pregnancy may lead to accelerated growth of warts, but obstruction of the birth canal is rare. Transmission to the neonate appears to be rare although the appearance of juvenile laryngeal papillomata or of anogenital warts in early childhood is recognized complications after vaginal delivery. The role of cesarean delivery in preventing these rare complications is unclear.

Chemical treatment, other than with trichloroacetic acid, is contraindicated. Ablative treatments with outpatient cryotherapy are usually employed, but inpatient surgical excision may be required. In the postpartum period, any residual warts will often spontaneously regress (Table 2).

GENITAL HERPES

Epidemiology and Clinical Features

Genital herpes is the commonest infective cause of genital ulceration worldwide, and has an important role in facilitating the transmission of HIV (12,13).

In developing countries, acquisition of herpes simplex virus type-1 (HSV-1) infection, usually in an orolabial site, occurs in a majority of individuals during childhood. In contrast, in the United Kingdom and other industrialized countries, less than 25% females are infected before adolescence (14,15). The HSV-1 seroprevalence rates reach around 50% by the age of 30,
and 70% by the age of 50. Acquisition of HSV during the reproductive years is as likely to be in a genital site, usually from orogenital contact, as it is in the orolabial region. Thus, HSV-1 is now the more common cause of newly acquired genital herpes but has a lower recurrence frequency than HSV-2 (16,17). Recurrence rates with HSV-2 decline over time in most individuals, although this pattern is variable.

Acquisition of infection may be symptomatic or asymptomatic. Prior HSV-1 ameliorates the clinical manifestations of newly acquired HSV-2 infection. Typically, true primary infections with either viral type are similar with painful ulceration, dysuria, and vaginal discharge. There are often systemic symptoms with fever and myalgia. There is an accompanying extensive vesicular eruption and painful ulcers affecting both labia, the vaginal introtitus, perineum, and cervix. Bilateral tender inguinal lymphadenopathy is common. Complications such as aseptic meningitis, sacral neuralgia, and autonomic neuropathy, resulting in constipation and urinary retention, are commoner in women than in men.

Atypical presentations and misdiagnosis are common, especially when based upon the patient history alone without examination at the onset of the illness. Untreated, the first episodes may last for three to four weeks (Table 3).

Following primary infection, the virus becomes latent in local sensory ganglia, periodically reactivating to cause symptomatic lesions, or asymptomatic, but infectious, viral shedding.

Recurrent episodes have favored sites within the individual but may occur anywhere in the anogenital area, the buttocks, or natal cleft. Each episode is usually unilateral and may have local or systemic prodromal symptoms for 24 to 48 hours before lesions appear. Lesions have a characteristic evolution and progress through stages of erythema, papule formation, papule formation, papule formation, papule formation, papule formation, papule formation, papule formation, papule formation, papule formation, papule formation.

### Table 3  Classification of Genital Herpes Episodes

<table>
<thead>
<tr>
<th>First episodes</th>
<th>Recurrent episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td><strong>Symptomatic</strong></td>
</tr>
<tr>
<td>Newly acquired, no prior infection with HSV-1 or HSV-2</td>
<td>First clinical episode with either HSV-1 or HSV-2, prior subclinical HSV-1 and/or HSV-2</td>
</tr>
<tr>
<td><strong>Nonprimary</strong></td>
<td><strong>Asymptomatic shedding</strong></td>
</tr>
<tr>
<td>Newly acquired HSV-2, previous infection by HSV-1</td>
<td></td>
</tr>
<tr>
<td><strong>First symptomatic recurrence</strong></td>
<td></td>
</tr>
<tr>
<td>First clinical episode with either HSV-1 or HSV-2</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviation: HSV, herpes simplex virus.*
vesiculation, ulceration, and crusting before healing. Total episode duration is typically 5 to 10 days.

Asymptomatic shedding is more common in those infected with HSV-2, occurs most frequently in the first year after acquisition of genital herpes, and is an important cause of transmission (18,19).

The diagnoses of genital herpes can definitively be made by the isolation of the causative virus in culture or positive polymerase chain reaction tests from the lesions. Type-specific immune responses can take 8 to 12 weeks to fully develop after primary infection. The use of type-specific serology can be helpful to determine the causation of symptomatic lesions where culture tests have been negative, and for determining the maternal risk of acquiring genital herpes in pregnancy where the partner only has a history of genital herpes (20). In many cases, the woman is found to have HSV antibodies from prior subclinical infection. In such circumstances, there is no risk of reinfection and the risk of vertical transmission is extremely low. There is no current evidence to support screening of all pregnant women for type-specific HSV antibodies.

Management

First Episodes

In first episodes, the maintenance of genital hygiene by frequent saline bathing, prescription of adequate systemic, and local analgesia, and support with counseling are of paramount importance (21).

Screening for other STIs is advisable but is usually delayed until lesions are resolving.

Antiviral Drugs: Oral antiviral drugs are indicated within five days of the start of the episode while new lesions are still forming. Intravenous therapy is only indicated when the patient cannot swallow or tolerate oral medication because of vomiting.

Nucleoside analog drugs such as aciclovir, valaciclovir, and famciclovir all reduce the severity and duration of episodes (Table 4) (22). Antiviral therapy does not alter the natural history of the disease (23). Topical antiviral agents are less effective than oral agents, and combined oral and topical treatment is of no benefit. Usual treatment courses are for five days, but may be continued longer if new lesions are still appearing.

Table 4  Recommended Regimens for First Episode Genital Herpes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>200 mg, five times daily</td>
</tr>
<tr>
<td>Valaciclovir</td>
<td>500 mg, twice daily</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>250 mg, thrice daily</td>
</tr>
</tbody>
</table>

*All for 5 days.*
Other than mild gastrointestinal symptoms, occasional rash, and headache, treatment with these drugs appears to have few side effects or adverse reactions. The development of antiviral resistance is extremely rare in immunocompetent individuals.

Hospitalization may be required for urinary retention, meningism, and severe constitutional symptoms. If urinary catheterization is required, the suprapubic approach is preferred to prevent theoretical risk of ascending infection, to reduce the pain associated with the procedure, and to allow normal micturition to be restored without multiple removals and recatheterizations.

In HIV-positive patients, newly acquired HSV infection is rare. Some clinicians advocate a 10-day course of treatment. Lesions unresponsive to therapy may be due to drug-resistant HSV and drug susceptibility testing of the virus isolate should be considered.

Recurrent Genital Herpes

Recurrences are self-limiting and generally cause minor symptoms. Treatment strategies include advice upon supportive therapy only, episodic antiviral treatments, and continuous suppressive antiviral therapy. Treatment should be tailored to the needs of the individual taking into account recurrence frequency, symptom severity, and relationship status.

Patient-initiated episodic treatment, preferably during the symptomatic prodrome, is preferred. Oral aciclovir, valaciclovir, and famciclovir reduce the duration (by median of one to two days) and severity of recurrent genital herpes (RGH) (Table 5) (24,25).

For patients having frequent recurrences, continuous oral antiviral treatment can effectively suppress recurrences. There is now around 15 years of safety and resistance data on patients on long-term therapy with aciclovir in North America (26). In the United Kingdom and Europe, most clinicians advocate treatment cessation after one year to allow the pattern of recurrences to be reassessed.

Recently, a large multinational, randomized, placebo-controlled trial in serodiscordant couples has shown that transmission of genital herpes can be reduced by continuous suppressive treatment with oral valaciclovir

<table>
<thead>
<tr>
<th><strong>Table 5</strong> Episodic Antiviral Treatment of Recurrent Genital Herpes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acyclovir</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Valacyclovir</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Famciclovir</strong></td>
</tr>
</tbody>
</table>
500 mg daily administered to the affected partner (Table 6) (27). The role of antiviral suppression of genital herpes upon the transmission of HIV infection is now being studied in several large international trials.

Counseling
The diagnosis of genital herpes often causes considerable distress. Most people with recurrences adjust over time but antiviral treatment can probably reduce anxiety, assist adjustment, and improve quality of life (28,29). Counseling should cover the natural history of the condition, the use of natural history, the use of antiviral drugs for symptom control, and the risk of transmission. Issues related to pregnancies are also important.

Management of Herpes in Pregnancy
The maternal risk of HSV acquisition in pregnancy varies geographically. In United Kingdom, the risk may be increasing with the rising incidence of STIs and the more frequent acquisition of HSV-1 infection during the reproductive years.

All women should be asked at their first antenatal visit if they or their partner have ever had genital herpes. Asymptomatic, HSV seronegative female partners of men with GH should be strongly advised not to have sex during recurrences. Conscientious use of condoms throughout pregnancy, especially the third trimester, may reduce the risk of acquisition, but this is unproven. Pregnant women should be advised of the risk of acquiring HSV-1 as a result of orogenital contact.

All women, not just those with a history of GH, should undergo careful vulval inspection at the onset of labor to look for clinical signs of herpes infection.

First Episodes
None of the oral antiviral agents are licensed for use in pregnancy or nursing mothers, however, there is substantial clinical experience supporting the safety of aciclovir.

The major vertical transmission risk occurs with first episode genital herpes occurring during the final trimester.

### Table 6  Suppressive Antiviral Treatment of Recurrent Genital Herpes

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>400 mg, twice daily</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>250 mg, twice daily (18)</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>500 mg–1 g, once daily</td>
</tr>
</tbody>
</table>

Viral Sexually Transmitted Infections
In first and second trimesters, management should be in line with the clinical condition with the use of either oral or intravenous aciclovir in standard doses. Vaginal delivery should be anticipated. The use of continuous aciclovir in the last four weeks of pregnancy reduces the risk of both clinical recurrence at term and of delivery by cesarean section (CS) (30,31).

With third trimester acquisition, particularly those developing symptoms after 34 weeks of gestation, there is a high risk of viral shedding in labor. If a true first episode is confirmed, CS should be considered for all women.

CS for the prevention of neonatal herpes has not been evaluated in randomized controlled trials and may not be completely protective against neonatal herpes. If vaginal delivery is unavoidable, aciclovir treatment of mother and baby may be indicated.

Recurrent Episodes
Recurrences during pregnancy are not regarded to pose a significant risk to the fetus. Symptomatic recurrences during the third trimester are likely to be brief and vaginal delivery is appropriate if no lesions are present at the onset of labor. The risk of intrapartum transmission is very low in the absence of lesions. Sequential cultures during late pregnancy do not predict viral shedding at term. The risks of vaginal delivery for the fetus are small and must be set against risks to the mother of CS.

If there are no genital lesions at delivery, vaginal delivery is normally undertaken.

If lesions are present at the onset of labor, current practice in the United Kingdom is for delivery by CS, despite lack of evidence for its effectiveness. Continuous aciclovir in the last four weeks of pregnancy may be cost-effective compared with no therapy or with CS (32).

MOLLUSCUM CONTAGIOSUM

Epidemiology and Clinical Features
This common condition is caused by a very large DNA pox virus which has two viral subtypes. The virus replicates in epithelial cells and causes intracytoplasmic inclusions and cell enlargement.

It may occur in all age groups and in tropical countries having a peak incidence in children younger than five years. In the United Kingdom, it is commonly seen as an STI in young adults. The incubation period is variable and ranges from two to eight weeks (33,34).

The characteristic lesions consist of smooth, firm, and umbilicated papules up to 6 mm in diameter commonly present in groups on skin of the lower abdomen, inner thighs, pubic region, and external genitalia. There may be associated itching and tenderness. The condition is often self-limiting with individual lesions resolving within two months. New crops of lesions may, however, appear over several months.
In immunocompromised patients, lesions can be seen on the face, eyelids, and conjunctiva and may be coalesce to give giant lesions.

**Treatment**

Sexually active patients may have other STIs, and so it is generally recommended that they and their partners are screened for other infections. The diagnosis is usually clinically based but can be confirmed by biopsy.

There have been no controlled trials of different treatment methods. A wide variety of topical caustic and chemotherapeutic preparations have been used including canthardin, tretinoin, podophyllin, trichloracetic acid, tincture of iodine, phenol, silver nitrate, cidofovir, and imiquimod (35). Most of these have not had their safety in pregnant women established. The most common treatment modality is cryotherapy with liquid nitrogen or other ablative therapy.

**VIRAL HEPATITIS C**

**Epidemiology and Clinical Features**

Hepatitis C is an RNA virus with at least six genotypes and more than 80 serotypes. It is easily transmitted via infected blood exposure but far less so through exposure to semen, saliva, or other body fluids. Intravenous drug users account for around half of all infected patients. Other risk factors for HCV infection include blood transfusion, organ transplantation, tattoos, needle accidents, and vertical transmission (36,37).

Acute hepatitis C usually causes no symptoms or only mild constitutional upset. Only about 25% of patients become jaundiced with fatigue, nausea, and anorexia. Chronic HCV infection may progress to hepatic cirrhosis in around 35% patients after 20 years, and hepatocellular carcinoma in up to 25% patients after 30 years.

Screening is by HCV antibody test and is indicative of prior or current infection. Subsequent serological testing to detect HCV RNA by polymerase chain reaction reflects disease activity and the risk of vertical transmission.

**Treatment**

**Alpha Interferon**

Alpha-interferon-2b, given by IM or SC injection three times weekly for 6 to 18 months, was the mainstay of treatment. It has frequent side effects including fever, joint pains and myalgia, headache, and fatigue. More recently, pegylated interferon has been available for the treatment of chronic hepatitis C. There are two preparations of peginterferon alpha that have been studied in patients with hepatitis C: peginterferon alpha-2b (Peg-Intron; Schering-Plough) and peginterferon alpha-2a (Pegasys; Hoffmann-La Roche). The
differences between these two preparations are subtle and most data suggest that they are equivalent with regards to efficacy and side-effect profile. Peginterferon alphas differ from the older, unmodified interferon alphas in that a polyethylene glycol molecule is attached to the interferon molecule. As a result, its elimination from the body is slowed and higher, more constant blood levels of interferon alpha are achieved with less frequent dosing. In contrast to unmodified interferon alpha, which must be injected three times a week to treat chronic hepatitis C, peginterferon alpha needs to be injected only once a week. With peginterferon alpha-2a alone, approximately 30% to 40% of patients achieve a sustained response to treatment for 24 to 48 weeks (38).

Interferon alpha is associated with many side effects. During treatment, patients must be monitored carefully for side effects including flu-like symptoms, depression, rashes, other unusual reactions, and abnormal blood counts. The viral clearance rates used as a single agent are 10% to 50%, but are increased by concomitant use of oral ribavirin.

Ribavirin

The addition of ribavirin to interferon alpha is superior to interferon alpha alone in the treatment of chronic hepatitis C. Ribavirin is a synthetic nucleoside that has activity against a broad spectrum of viruses. FDA approval of interferon alpha-2b plus ribavirin for the treatment of individuals with chronic hepatitis C was originally based on trials in patients who “relapsed” after previous interferon alpha monotherapy. Subsequent studies showed that the combination of interferon alpha-2b plus ribavirin is more effective in achieving a sustained response than interferon alpha-2b alone in the treatment of patients with chronic hepatitis C not previously treated with interferon. The sustained response rates are 31% to 50% for those receiving combination therapy for 24–48 weeks (39–42). Most recently, the FDA has approved the combination of peginterferon alpha plus ribavirin for the treatment of chronic hepatitis C. For eligible patients with chronic hepatitis C, a peginterferon alpha plus ribavirin is likely to be the best treatment option for the near future. Clinical trials have show that the sustained response rate is in over 50% of patients given this combination for 24 to 48 weeks.

A reversible hemolytic anemia, which is dose- and time-dependent, is the principal adverse effect associated with oral ribavirin, and cardiac and pulmonary events associated with anemia have been reported in about 10% of patients receiving ribavirin in conjunction with interferon-a2b, especially during oral or parenteral use of the drug in dosages of 1.2 g or higher daily (15–17 mg/kg/day) for more than 10 days. Additionally, insomnia, depression, and irritability have occurred in more than half of the treated patients. Most studies indicate that genotypes 1a and 1b are more resistant to treatment with any interferon alpha-based therapy than non-type 1 genotypes. For this reason, some doctors may prescribe longer durations of treatment for patients infected with viral genotypes 1a or 1b.
Pregnant and Nursing Mothers

Overall vertical transmission rates are 5%, but are much higher in HIV-coinfected mothers. Pregnancy does not appear to adversely affect the progression of hepatitis C nor is there any increased risk of obstetric complications. Sexual transmission rates are low (<1%) in the absence of blood-borne exposures and HIV infection, and other intrafamilial transmissions are also rare. HCV has been detected in breast milk, but at much lower levels than in the serum. Studies examining the risk of HCV by breast feeding have failed to demonstrate transmission via this route.

Passive transfer of maternal HCV antibody occurs and infants may remain positive for 15 months after delivery. Optimal screening for at-risk infants is by HCV RNA screening at 12 months and HCV antibody at 18 to 24 months.

Pregnant women with chronic hepatitis whose therapy can be delayed should not be treated with interferon due to a lack of controlled studies. There are several case reports of interferon monotherapy in patients with acute hepatitis C during pregnancy. Women exposed to interferon inadvertently during pregnancy may be encouraged to continue the pregnancy.

There are no studies of ribavirin in pregnant women; however, in pregnant animals receiving ribavirin in smaller doses than those given to humans there have been fetal birth defects and death. Women of childbearing potential should not begin therapy until a report of a negative pregnancy test has been obtained and not become pregnant during treatment. In addition, women who are receiving ribavirin therapy should wait at least six months after ribavirin is stopped before becoming pregnant. Although ribavirin may cause abnormalities in sperm, men taking ribavirin should avoid attempts to impregnate sexual partners and should wait six months after discontinuing the drug.

The risks of using interferons during breast feeding is not known. Because of the antiproliferative effects of interferons, there is concern about the potential for side effects in the infant, so breast feeding should be avoided by nursing mothers.

EPIDEMIOLOGY AND CLINICAL FEATURES

Hepatitis B virus (HBV) is a double-stranded DNA virus. The incubation period is six weeks to six months from time of exposure. The highest concentrations occur in the serum but other body fluids such as semen and vaginal secretions also harbor the virus. Sexual transmission accounts for around 25% cases in adults, and about 25% of regular sexual contacts of infected individuals will also become seropositive (43,44).

Acute HBV infections are symptomatic in around 50% adults and are manifest by loss of appetite, nausea, vomiting, fever, and jaundice. Progression to acute liver failure occurs in about 1% cases. Full recovery is the norm but around 5% individuals will become chronic carriers of the
virus, and represent a continuing risk of horizontal and vertical transmission. In the absence of immunoprophylaxis, 10% to 20% of hepatitis B surface antigen (HbsAg)-seropositive women will transmit the virus to their neonate; the risk is around 90% in women who are also e-antigen (HbeAg) -positive (45,46). The risk of vertical transmission with acute HBV infection is 10% with first trimester acquisition rising to 80% to 90% with third trimester infections. Chronic HBV infection occurs in 90% infected infants. There is a higher incidence of prematurity and low birth weight among infants born to mothers with acute infection during pregnancy.

The risk of developing liver cirrhosis and and/or hepatocellular carcinoma is 15% to 25% in chronic HBV infection.

PREVENTION OF HEPATITIS B

Pregnant women with hepatitis B should abstain from alcohol and avoid any potentially hepatotoxic drugs. Invasive methods of prenatal assessment represent a low risk of fetal HBV infection but should be avoided in HbeAg-positive mothers.

All neonates born to HBV-positive mothers should receive hepatitis B immunoglobulin at birth, and hepatitis B vaccine in three doses at birth, one month, and six months of age. So long as appropriate immunoprophylaxis is carried out at birth, CS delivery is not currently recommended nor does breast feeding poses any additional risk of transmission from HB carriers (47).

Management

The treatment of acute HBV infection is supportive.

Antiviral treatment for chronic HBV infection is available with alpha-interferon (48), lamivudine (49), and adefovir dipivoxil (50,51).

Interferon alpha-2b works best in people who have relatively low levels of HBV DNA. The older forms of interferon are given three or more times a week. Pegylated interferon has a longer duration of action and is given at weekly intervals. Interferon monotherapy gives viral clearance in about 40% in treated individuals.

Adefovir dipivoxil and lamivudine are oral antiviral agents that have been shown to have potent activity against HBV in vitro and in vivo. Both drugs have been used extensively in patients with HIV infection and more recently in controlled trials as monotherapy in patients with chronic hepatitis B. Lamivudine is currently approved as therapy of hepatitis B and has been evaluated extensively both as a one-year course of treatment as well as long-term continuous therapy. Lamivudine monotherapy induces a transient improvement in viral levels and liver histology, but viral resistance develops in a large proportion of patients with reappearance of HBV DNA in serum in high levels associated with mutations in the YMDD motif of the
HBV polymerase gene and worsening of the hepatitis. Adefovir monotherapy was recently approved by the FDA and in contrast, has not been shown to be associated with development of viral resistance even when given for up to two years. When given as monotherapy for one year, adefovir leads to improvement in histology of hepatitis B in approximately 50% of patients. At present, the long-term efficacy of adefovir has not been shown. Current trials are investigating lamivudine and adefovir combination therapy.

Lamivudine is generally well tolerated although cases of lactic acidosis, pancreatitis, and hepatotoxicity have been reported. Adefovir has been associated with gastrointestinal disturbances and rash, and is nephrotoxic in high dosage.

REFERENCES

INTRODUCTION

In westernized countries, the field of human immunodeficiency virus (HIV) medicine has been revolutionized by the widespread use of drugs that suppress viral replication such that the management of HIV infection can no longer be regarded as palliation of an inevitably terminal condition, as was the case at the advent of the epidemic in the 1980s, but rather involves the care of a chronic illness of currently indeterminate prognosis. The first agent to demonstrate antiretroviral activity, azidothymidine [(AZT), zidovudine], was licensed in 1987 after only 20 months in phase 3 trials; such was the demand for a therapeutic tool to combat this growing problem, and since that time, a wealth of research has been directed at expanding the armory, defining new therapeutic targets, and optimizing deployment of the agents currently available.

In addition to the management of infected individuals, antiretroviral agents play a vital role in the prevention of HIV transmission, as exemplified by the reduction in vertical mother-to-child transmission achievable with their use.

However, the success of antiretroviral agents is not without cost, both to individuals and to the public health. The use of anti-HIV medication can incur significant side effects, which may be life threatening, diminish efficacy
by reducing tolerability and therefore adherence to a prescribed regimen, and adversely affect quality of life. In financial terms, the cost of combination regimens using patented formulae effectively precludes their general usage in most resource-poor countries, which conversely bear the brunt of the global burden of HIV infection, and many of which are now using less expensive, locally produced, nonpatented generic products to improve access.

Alongside the antiretrovirals, which have a direct effect on viral replication, a variety of drugs are employed in HIV medicine to treat or prevent opportunistic conditions arising as a consequence of immunosuppression. A selection of these is considered here.

EPIDEMIOLOGY

Despite progress in the development and supply of specific drug therapy for HIV, the number of reported new cases has shown a significant rise in developed countries over the past five years, with a 120% increase in the United Kingdom (1). This reflects in part increased testing (e.g., routine antenatal screening) and increased population migration from areas of high seroprevalence (especially Africa), but there is also evidence of an increased incidence within the indigenous population (2), which may represent a reduction in safe sexual practices accompanying the perception of HIV as a treatable condition. The main route of transmission is by heterosexual contact in both developed and developing countries, and the increasing incidence coupled with improved longevity in existing cases renders it likely that HIV-infected individuals will increasingly be encountered in all health-care settings.

BASIC VIROLOGY

The HIV is an RNA-containing virus, first discovered in 1983. Two forms of HIV are currently recognized, HIV-1 and HIV-2. HIV-2 is largely confined to areas of western Africa, and tends to result in a more indolent, less easily transmissible infection, and thus the vast majority of infections globally are with HIV-1, accounting for an estimated 95.5% to 99.9% of all cases in the developed world (3).

HIV predominately targets cells expressing the CD4 receptor, with which it complexes in order to gain entry to the cell. This process involves fusion of the gp41 viral envelope proteins with the wall of the targeted cell such that the viral contents are extruded into the host cell cytoplasm. As a retrovirus, HIV possesses a DNA polymerase enzyme reverse transcriptase (RT), which facilitates the production of viral DNA from viral RNA within the host cell. This DNA can be incorporated into the host cell reproductive pathways, which are then utilized for viral replication (Fig. 1). The HIV genome codes for certain other enzymes, including an integrase and a protease, the latter being required for the maturation of virions into infective
The stages highlighted are the sites of action of the antiretroviral agents currently available.

The CD4 receptor is primarily expressed by a subgroup of T lymphocytes, derived from the thymus. The function of these “helper” cells is to stimulate immune responses by promoting B-cell, macrophage, and cytotoxic T-cell responses to foreign antigens. In this way, this cell population is integral to the body’s defence against invasion principally by viruses, yeasts, fungi, protozoa, and certain atypical bacteria, such as mycobacteria. The usual effects of HIV on this cell population over time is a reduction in function and in absolute numbers, rendering the host susceptible to infection by these organisms, which, if untreated, becomes overwhelming (the so-called acquired immunodeficiency syndrome or AIDS) and is ultimately fatal.

The host raises antibodies and cytotoxic T-cell responses to infection by HIV (the former being the basis for serological HIV detection), but these are insufficient to eliminate an established infection.

ANTIRETROVIRAL DRUGS

Mode of Action

Antiretroviral agents interfere with HIV replication. The two principal sites of action for these drugs are the viral RT enzyme and the protease enzyme.
More recently, an agent has been licensed that inhibits fusion of the virus with the host cell wall.

Reverse Transcriptase

RT is the enzyme that allows HIV to reverse the normal cellular pathways such that DNA is produced from the single strand of RNA. There are three main groups of drugs that target RT.

**Nucleoside RT Inhibitors:** These drugs are competitive analogs of the nucleic acid bases thymidine, cytosine, and inosine (e.g., AZT, dideoxyinosine, dideoxycytidine, didehydrodeoxythymidine, and fluoro-thio-cytosine). They are phosphorylated and incorporated into viral nucleic acid, thereby acting as chain terminators, blocking the action of the RT enzyme.

**Nonnucleoside RT Inhibitors:** These drugs bind to specific sites on the RT enzyme and directly block its action as a polymerase. They have little effect against HIV-2 (e.g., nevirapine, efavirenz, and delavirdine).

**Nucleotide RT Inhibitors:** These agents are nucleotide analogs, again competing with viral nucleotides and blocking the RT action (e.g., tenofovir).

Protease Inhibitors

Protease inhibitors (PIs) target the enzyme responsible for the posttranslational cleavage of polyproteins into the smaller units present in infective particles (e.g., nelfinavir, indinavir, saquinavir, lopinavir, ritonavir, atazanavir, amprenavir, and tipranavir).

Many of these preparations are available in both tablet and oral solution formulations, to date, only ziduvudine is available for intravenous administration.

Fusion Inhibitors

There is currently only one agent available in this group, enfuviritide (T-20), which binds to the gp41 HIV molecule, preventing extrusion of the viral contents into the host cell. This is at present licensed only as an adjunctive treatment for patients who have failed other more potent antiretroviral regimens, and requires twice daily subcutaneous administration.

Other Agents

In the absence of a curative treatment for HIV, new strategies are under development to increase the tolerability of existing drugs, to expand the therapeutic options available and to access novel viral targets. Therapeutic vaccines are under investigation to boost the body’s immune system, as an adjunctive treatment to a potent antiretroviral regimen. Interleukin-2 is a pro-inflammatory cytokine, which has a stimulatory effect on CD4 cell production, and can be used parenterally to effect an additive rise in CD4 cell
numbers when added to an antiretroviral combination. Hydroxyurea has been used previously to enhance the action of certain antiretroviral agents, but its use is no longer advocated. Inhibitors targeting the integrase enzyme and the CCR5 chemokine cellular receptor integral to HIV binding are also the subjects of ongoing research.

**Agents Available**

The coformulations combined within a single tablet are shown in Table 1. Highly active antiretroviral therapy refers to a minimum of triple therapy using a recommended potent drug combination (see below).

**Prescribing Principles**

Research to date indicates conclusively that a combination of at least three antiretroviral agents selected from at least two different classes of drug is the initial treatment of choice for controlling HIV infection (4). Commonly this involves the prescription of 2 nucleoside RT inhibitors (NRTIs) and 1 nonnucleoside RT inhibitor (NNRTI), or 2 NRTIs and 1 PI, the pharmacokinetic effects of which are boosted by the coprescription of a small dose of the PI ritonavir.

The choice of regimen depends upon the previous antiretroviral history of the virus (including a genetic resistance profile if appropriate), the likely efficacy and side-effect profile of the proposed combination, possible interactions with concomitant medications, comorbidities (e.g., hepatitis), and above all, the likelihood of the patient being able to adhere to the prescribed regimen.

The decision as to when to start an agreed combination depends primarily upon the level of immunodeficiency, as measured by the circulating CD4 count. Guidelines exist in the United States and United Kingdom as to when antiretrovirals should be commenced, both advocating therapy when the CD4 count falls to between 200 and 350 cells per mm$^3$. Commencing therapy at a count less than 200 cells per mm$^3$ incurs a less durable response.

### Table 1  Antiretroviral Agents and Commonly Associated Adverse Events

| **COMBIVIR** | Zidovudine + lamivudine | Dose: 1 tablet twice daily |
| **TRIZIVIR** | Zidovudine + lamivudine + abacavir | Dose: 1 tablet twice daily |
| **KALETRA** | Lopinavir + low-dose ritonavir | Dose: 3 capsules or 2 tablets twice daily |
| **KIVEXA** | Abacavir + lamivudine | Dose: 1 tablet daily |
| **TRUVADA** | Tenofovir + emtricitabine | Dose: 1 tablet daily |
Once indicated, combination therapy is currently recommended to be continued indefinitely, as viral rebound occurs rapidly on discontinuation, allowing the possibility of onward viral transmission or the occurrence of opportunistic conditions. Due to the varying half-lives of the different agents, failure to take a part of a regimen may result in the patient receiving what is in effect monotherapy, to which the virus is likely readily to develop resistance, thus compromising viral suppression and thereby promoting failure of that regimen and also possibly of other agents within the same class.

**Commonly Encountered Side Effects**

The occurrence of significant Grade 3/4 adverse events associated with antiretroviral agents now outnumbers the development of AIDS-defining illnesses. The long-term adverse event profiles of most drugs remain unknown. Predictable adverse events are pertinent to the choice of antiretroviral regimen employed, for example the use of nevirapine is of concern in patients with chronic viral hepatitis, and the use of efavirenz in patients with a history of psychiatric disorders may be inadvisable.

**Interactions**

The pharmacological characteristics of HIV medications have been documented, many being metabolized by the cytochrome P450 metabolic pathway within the liver. This may take the form of hepatic enzyme induction and/or inhibition, and will influence the duration of action and/or concentration of the drug in question and other coadministered substances sharing this route of elimination. This is particularly evident with the use of certain PIs, especially ritonavir.

It is essential that the possible drug interactions are considered before the coprescription of any medication with antiretroviral therapy. Further information can be obtained from www.hiv-interactions.org. Interactions with contraceptive agents are considered below.

**USE OF ANTIRETROVIRALS IN PREGNANCY**

Without intervention, the risk of transmission from an HIV-infected woman to her baby is in the order of 25% to 35%, dependent on viral burden in the mother and the use of breast-feeding. Thus, as the majority of transmission occurs peripartum, the priority is to reduce the exposure of the neonate to infected secretions, which may include the administration of antiretroviral agents to the mother and baby, performing elective Caesarian sections and the avoidance of breast-feeding, which reduces transmission to less than 2% (5). The benefits of using antiretrovirals to reduce maternal HIV viral load prior to delivery have been conclusively demonstrated in both comparative and placebo-controlled clinical studies using a variety of regimens (6–8), and is
recommended in women with higher CD4 counts who do not fulfil criteria for therapy in their own right.

It is often helpful to consider the following scenarios in pregnancy:

- Women established on antiretrovirals to control their own infection;
- Women who do not yet require antiretrovirals per se; and
- Women with HIV who present late in pregnancy or at delivery.

Further detailed information can be found in guidelines produced by the British HIV Association (9) available at www.bhiva.org, and by the American National Institutes of Health (10) available at www.aidsinfo.nih.gov.

**Women Established on Antiretrovirals to Control Their Own Infection**

**At Conception**

Women, planning to conceive, who require antiretroviral therapy, should preferably be commenced on a regimen not known to cause adverse effects in pregnancy. This currently involves avoidance of *efavirenz* (associated with possible teratogenicity and premature delivery) and the combination of *stavudine with didanosine* (reports of fatal lactic acidosis). Wherever possible, an established effective regimen containing these elements should be switched to an alternative combination preconception, and should be considered when pregnancy occurs.

**At Delivery**

The aim of therapy is to produce an undetectable maternal viremia. If an established regimen has not achieved this endpoint prior to delivery, an alternative combination may be considered to reduce the chance of transmission. Elective Caesarian section alone prior to rupture of membranes has been suggested to reduce transmission in untreated mothers by up to 50% (11), and is endorsed in many management guidelines. Antibiotics should be prescribed to reduce infective complications if a surgical delivery is performed. Many clinicians now advocate vaginal delivery if the maternal viral load is undetectable using antiretroviral agents. However, this strategy has not been universally accepted (12), particularly in view of concerns regarding possible discrepancies in the penetration of antiretrovirals into serum and genital compartments.

**Postpartum**

The mother should clearly continue with the most effective regimen after delivery. Guidelines recommend the use of postexposure prophylaxis to the infant for a period of four to six weeks, the choice of agent(s) dependent on the antiretroviral history of the maternal virus. Breast-feeding incurs an
overall 14% increase in transmission per se and should be avoided wherever possible (13).

**Women Who Do Not Yet Require Antiretrovirals**

**At Conception**

Antiretroviral therapy is not recommended for asymptomatic women with a CD4 count greater than 350 cells/mm³. In these women wishing to conceive, specific antiretroviral therapy is not currently advocated. However, a short course may be considered for invasive prenatal diagnostic procedures as prophylaxis, although this is of theoretical rather than proven benefit.

**At Delivery**

Following the studies from the 1990s, antiretrovirals are recommended to reduce a detectable viral load in pregnant women with higher CD4 counts in order to reduce neonatal transmission. Current recommendations suggest the use of therapy in the last trimester, and intravenously in early labor or four hours prior to Caesarian section, especially if the HIV is not undetectable serologically. Early studies used monotherapy during the last 4 to 12 weeks of pregnancy, with zidovudine or nevirapine. The continuing recommendation of monotherapy is controversial, in view of the demonstration of viral resistance even with single dose administration, which could compromise the future efficacy of certain classes of antiretrovirals in later stages of infection or in future pregnancies (14). The use of combination therapy must be balanced against possible toxicities, but is recommended in the absence of full viral suppression with monotherapy, or with a high pretreatment viremia.

**Postpartum**

The mother may discontinue therapy after delivery. However, if a combination regimen has been employed, discontinuation should take into account the differing half-lives of the agents used to prevent the development of resistance to those drugs with the longer half-lives, for example, nevirapine and efavirenz should be replaced by a PI for 7 to 10 days before the regimen is discontinued to allow time for complete elimination of the NNRTI. The neonate is commonly given prophylaxis with monotherapy (the choice of agent guided by the maternal regimen) although combination treatment is recommended in some circumstances, for example, unknown or detectable maternal viremia. Breast-feeding should be avoided.

**Women with HIV Who Present Late in Pregnancy or at Delivery**

If women known to have untreated HIV have not accessed antenatal care, or are diagnosed with HIV within the last four weeks of pregnancy, there may not be time to institute fully suppressive therapy. However, the use
of combination therapy at any time up to and intravenously during labor, and postpartum to the neonate may be particularly valuable in these circumstances, when the level of maternal viremia is unknown and a planned Caesarian section may not be possible. It would be sensible to continue therapy in the mother until her immunological status has been ascertained.

In the United Kingdom and United States, national recommendations have been established to include the offer of HIV testing in early pregnancy to all women attending for antenatal care, with targets set for uptake in order to reduce neonatal transmission by allowing access to the aforementioned preventative measures.

**USE OF ANTIRETROVIRALS IN PREGNANCY: SAFETY CONCERNS**

As with most medicines, wherever possible, the introduction of an antiretroviral regimen should be deferred until the second trimester (Table 2).

The only agent licensed for use in pregnancy at this time is **zidovudine**. However, several other agents are used and have not been shown to be associated with teratogenicity; these include **lamivudine, stavudine, nevirapine, nelfinavir, lopinavir**, and **abacavir**.

**Class-Specific Adverse Events**

**Nucleoside Reverse Transcriptase Inhibitors**

Nucleoside analogs may impair intracellular mitochondrial function by depleting mitochondrial DNA, resulting in increased anaerobic cellular respiration, manifestations including lactic acidosis, hepatic steatosis, peripheral neuropathy, myopathy, and pancreatitis. Initiation of these agents may induce self-limiting nausea and vomiting, myalgia, and weakness in the first six weeks of therapy, symptoms not uncommon in pregnancy.

**Nonnucleoside RT Inhibitors**

Nevirapine has been associated with hepatotoxicity, at times life threatening, and skin rashes, including rarely Stevens-Johnson syndrome. Both of these serious adverse events have been seen in pregnancy, and are more common in women with higher CD4 counts, greater than 250 cells per mm$^3$.

Efavirenz is associated with neuropsychiatric disturbance; as stated it should be avoided in pregnancy.

**Protease Inhibitors**

PIs increase insulin resistance and may exacerbate impaired glucose tolerance in pregnancy. It has been suggested that the use of PIs may be associated with premature delivery and very low birth weight, although this remains controversial (15). The pharmacokinetic profiles of certain PIs may be altered...
Table 2  Use of Currently Available Antiretroviral Agents in Pregnancy (May 2006)

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Generic name</th>
<th>Proprietary name</th>
<th>Use in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside reverse transcriptase inhibitors</td>
<td>Zidovudine (AZT)</td>
<td>Retrovir</td>
<td>Only licensed drug in pregnancy; may cause anaemia in mother or neonate; proven to reduce vertical transmission; available intravenously</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Epivir, Zeffix</td>
<td>Videx</td>
<td>No reported adverse events</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td></td>
<td></td>
<td>Should not be coadministered with stavudine, reports of potentially fatal lactic acidosis</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Zerit</td>
<td></td>
<td>Should not be coadministered with didanosine, reports of potentially fatal lactic acidosis</td>
</tr>
<tr>
<td>Zalticabine (ddC)</td>
<td>Hivid</td>
<td></td>
<td>Insufficient data; some toxicity with super-high dosages in animal studies; recently discontinued in the U.K.</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Ziagen</td>
<td></td>
<td>Insufficient data, no obvious adverse effects in humans; some toxicity with super-high dosages in animal studies; serious idiosyncratic hypersensitivity reactions occur in 4% population on commencing therapy, further use thereafter is contraindicated</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>Emtriva</td>
<td></td>
<td>Insufficient data; no obvious adverse effects to date in animal studies</td>
</tr>
<tr>
<td>Nucleotide reverse transcriptase inhibitor</td>
<td>Tenofovir</td>
<td>Viread</td>
<td>Insufficient data; some toxicity with super-high dosages in animal studies</td>
</tr>
</tbody>
</table>

(Continued)
Table 2 Use of Currently Available Antiretroviral Agents in Pregnancy (May 2006) (Continued)

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Generic name</th>
<th>Proprietary name</th>
<th>Use in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease inhibitors</td>
<td>Nelfinavir</td>
<td>Viracept</td>
<td>No specific contraindications</td>
</tr>
<tr>
<td>(PIs)</td>
<td>Lopinavir/r</td>
<td>Kaletra</td>
<td>Insufficient data; some toxicity with super-high dosages in animal studies</td>
</tr>
<tr>
<td></td>
<td>Indinavir</td>
<td>Crixivan</td>
<td>No specific contraindications; hyper-bilirubinaemia and renal nephrolithiasis may occur</td>
</tr>
<tr>
<td></td>
<td>Saquinavir</td>
<td>Fortovase, Invirase</td>
<td>No specific contraindications</td>
</tr>
<tr>
<td></td>
<td>Ritonavir</td>
<td>Norvir</td>
<td>No specific contraindications</td>
</tr>
<tr>
<td></td>
<td>Amprenavir</td>
<td>Agenerase</td>
<td>Insufficient data, possible adverse effects in animal studies; the oral solution containing propylene glycol is contraindicated in pregnancy and under four years of age</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir</td>
<td>Lexiva</td>
<td>Insufficient data, possible adverse effects in animal studies</td>
</tr>
<tr>
<td></td>
<td>Atazanavir</td>
<td>Reyataz</td>
<td>Insufficient data</td>
</tr>
<tr>
<td></td>
<td>Tipranavir</td>
<td>Aptivus</td>
<td>Nonpeptidic PI; insufficient data</td>
</tr>
<tr>
<td>Nonnucleoside reverse</td>
<td>Efavirenz</td>
<td>Sustiva</td>
<td>Associated with preterm delivery and possible teratogenicity; should be avoided in pregnancy</td>
</tr>
<tr>
<td>transcriptase inhibitors</td>
<td>Nevirapine</td>
<td>Viramune</td>
<td>No specific contraindications; proven to reduce MTC transmission</td>
</tr>
<tr>
<td></td>
<td>Delavirdine</td>
<td>Rescriptor</td>
<td>Insufficient data; some toxicity with super-high dosages in animal studies; unlicensed in the U.K.</td>
</tr>
<tr>
<td>Fusion inhibitor</td>
<td>Enfuvirtide (T20)</td>
<td>Fuzeon</td>
<td>Insufficient data; no obvious adverse effects to date in animal studies</td>
</tr>
</tbody>
</table>

Abbreviation: MTC, mother-to-child.
by pregnancy, leading to the possibility of subtherapeutic concentrations with nonritonavir-boosted regimens.

Agents to be avoided if possible, without compromising maternal viral suppression, include efavirenz, and the combination of stavudine with didanosine. Zidovudine may result in a temporary anemia in the neonate.

The majority of antiretroviral drugs have only been in regular usage for 10 years or less, and so the long-term toxicities cannot be fully known. National registries exist to record the cumulative experience of antiretrovirals in pregnancy and thus to document adverse event profiles in pregnancy and to facilitate the recognition of any potential long-term effects in the neonate. To date, none are as yet apparent following postpartum exposure alone (16).

ANTIRETROVIRALS AND FERTILITY

Although there is some evidence to suggest that untreated HIV infection is associated with impaired female fertility in late-stage infection (17), there is no adverse effect from infection per se, and HIV testing is recommended as a routine investigation for all couples seeking assisted conception. The evidence in male fertility is controversial, with small studies reporting conflicting results, although most suggest a correlation between sperm abnormality and CD4 depletion (18).

On the contrary, studies of antiretroviral agents have not indicated a detrimental effect on fertility. The appropriate use of antiretroviral agents may restore a degree of fertility by effecting immune reconstitution, and their use is not known to interfere with follicle stimulating agents.

ANTIRETROVIRALS AND SURGERY

Women undergoing therapy for HIV infection may present to gynecology services with conditions requiring surgery. Interactions with medications are considered above. Of note, the PIs are known to reduce the elimination of short-acting hypnotic agents commonly used in anesthesia, with some specific contraindications, e.g., midazolam.

It is important that an antiretroviral regimen should be maintained during nil-by-mouth periods prior to surgery, as the troughs in plasma concentrations following missed dosages of certain drugs has the potential to induce viral resistance. To date, only zidovudine and efuvirtide are administrable parenterally.

ANTIRETROVIRALS AND POSTEXPOSURE PROPHYLAXIS

Occupational Exposure

The nature of gynecological surgery and obstetrics/midwifery, wherein hands may be partially obscured at times within body cavities, carries a risk
of possible exposure of both patient and health-care worker to the other's blood following an accidental sharp injury. For this reason, occupational health guidelines restrict the practice of health-care workers in this field who know or suspect that they may be infected with HIV (19).

Most patients attending for gynecological surgery, and a minority of pregnant women in the United Kingdom, will be unaware of their HIV status.

Prior research has indicated that the risk of contracting HIV from an infected patient following a needlestick injury is in the order of 0.33%, dependent upon the degree of contamination of the needle and the amount of virus in the inoculant. The risk from a mucosal blood contact is estimated to be around 0.03%. The use of zidovudine in one study indicated an 81% reduction in HIV acquisition following occupational exposure from needlestick injury (20), and combination therapy (proven to be more effective at controlling HIV in established infection) is prescribed following a significant injury from an HIV infected individual, or someone deemed to be at high risk of being infected. Current U.K. guidelines recommend the use of zidovudine, lamivudine, and a PI for four weeks, to be commenced as soon as possible following the injury (21). This can clearly be discontinued if the index case is subsequently found to be uninfected and is not suspected of incubating the virus.

If the index patient is known to have received therapy for HIV, this regimen may be tailored following consideration of the treatment history of the virus in order to try and predict the most effective combination. The injured party should be advised regarding the possible side-effects of the medication, should be seen after two weeks for assessment of toxicity and adherence, and should be advised not to have unprotected sexual intercourse until three months following the incident, at which time serological HIV testing (in parallel with preincident serology) will indicate the presence or absence of seroconversion.

Collaboration with physicians experienced in HIV management will help to determine the need for postexposure prophylaxis and the choice of regimen.

**Sexual Exposure**

Women may be concerned about the risk of contracting HIV following sexual intercourse with a person known to be infected with HIV, or following an assault when the HIV status of the assailant is unknown. Postexposure prophylaxis (commenced as soon as possible after the episode but up to 72 hours afterwards) may be prescribed in cases involving a known HIV-infected partner, or someone considered to be at high risk of HIV, or if the patient remains extremely concerned regarding the possibility of infection following a risk assessment. The principles regarding the choice of
combination, and the recommended dosing and serological testing schedules, are similar to those following occupational exposure (see above) (22).

RESOURCE-POOR SETTINGS

The World Health Organization and Joint United Nations Programme on HIV/AIDS estimates that just under 40 million people are currently living with HIV worldwide, and 95% of these individuals live in developing countries in Africa, Asia, and South America, where competition for scarce resources usually precludes the universal availability of therapy where indicated. Antiretroviral coverage is estimated to be around 7% of the population in need, and in these settings, women are up to 2.5 times more likely to be infected than men (23). There has been some success in improving access to therapy in certain countries in recent years with increased funding by national programs or by donation from nongovernmental or charitable organizations, and the provision of cheaper locally produced generic antiretroviral preparations (for example, the coformulation of stavudine, lamivudine, and nevirapine). Developing countries, however, often lack the facilities to monitor efficacy or toxicity of prescribed regimens, and ingrained cultural beliefs or the fear of stigma can add to the challenges of trying to control HIV with medication in this setting. There are programs established (which include sponsorship from the pharmaceutical industry) to provide antiretrovirals free-of-charge to pregnant women to try and impact upon mother-to-child transmission, as at present their availability is limited to around 1% of affected women in areas of high seroprevalence, where up to 40% of the antenatal attendees are infected (24).

The benefits of breast-feeding in areas where the safe alternative of clean formula feeding may not be possible need to be weighed against the known risks of HIV transmission via this route.

In the absence of widespread antiretroviral availability, research is being directed toward preventative strategies, with the ongoing development of vaccines, currently in large multinational phase 2/3 trials, and topical vaginal microbicides aimed at local viral destruction at the portal of entry.

The World Health Organization has produced guidelines for antiretroviral usage in resource-constrained settings (25).

CONTRACEPTION

Certain antiretroviral agents, especially PIs and the NNRTIs, have the potential to reduce the contraceptive effect of combined pills by shared metabolic pathways (Table 3). In these circumstances it may be advisable to use an alternative method of contraception (e.g., progesterone-only pills, Depo-Provera, Implanon, intrauterine contraceptive device, and sterilization) (26).
**Table 3** Potential Interactions of Antiretroviral Agents with Oral Contraceptives

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Generic name</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside reverse transcriptase inhibitors</td>
<td>No anticipated interactions</td>
<td>Possible reduced efficacy of oral contraceptives</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Nelfinavir</td>
<td>Possible reduced efficacy of oral contraceptives</td>
</tr>
<tr>
<td></td>
<td>Lopinavir/r</td>
<td>Possible reduced efficacy of oral contraceptives</td>
</tr>
<tr>
<td></td>
<td>Indinavir</td>
<td>No reported adverse effect on hormone levels</td>
</tr>
<tr>
<td></td>
<td>Ritonavir</td>
<td>Contraceptive effect of combined oral contraceptives reduced</td>
</tr>
<tr>
<td></td>
<td>Tipranavir</td>
<td>50% reduction in ethinyl oestradiol levels; possible reduced efficacy of oral contraceptives</td>
</tr>
<tr>
<td>Nonnucleoside reverse transcriptase inhibitors</td>
<td>Efavirenz</td>
<td>Possible reduced efficacy of oral contraceptives</td>
</tr>
<tr>
<td></td>
<td>Nevirapine</td>
<td>Accelerated metabolism of oral and other hormonal contraceptives (reduced contraceptive effect)</td>
</tr>
</tbody>
</table>

HIV-infected women should be advised additionally to use condoms, demonstrated to be effective in the prevention of HIV sexual transmission (27).

**DRUGS USED IN THE PROPHYLAXIS AND TREATMENT OF OPPORTUNISTIC INFECTIONS IN HIV**

Patients whose CD4 count is less than 200 cells per mm³ are at risk of developing infection with or reactivation of certain organisms which will compromise health and survival, for example, *Pneumocystis jiroveci* (ex-carinii), *Toxoplasma gondii*. As the CD4 count falls, the spectrum of disease increases. Studies have shown that the use of prophylactic antimicrobials to prevent certain infections is associated with a better prognosis than delaying therapy until the apparent development of disease. Similarly, following treatment of an established infection, medication should be maintained to prevent recurrence unless the CD4 count recovers sufficiently with antiretroviral medication to negate the risk.

The use of certain commonly prescribed therapeutic/prophylactic drugs in pregnancy is considered below.
Cotrimoxazole

Cotrimoxazole (trimethoprim and sulfamethoxazole) is used for the treatment and prophylaxis of pneumocystis pneumonia (PCP), the commonest AIDS-defining illness in HIV infection in the developed world. It is prescribed for primary and secondary prophylaxis when the CD4 count is below 200 cells per mm$^3$. As a folate antagonist, its use in pregnancy should be restricted to women at significant risk of PCP when no alternative is available. Its use in early pregnancy has been reported to incur a greater risk of congenital abnormalities when used with antiretroviral agents than the combination regimen alone (28). Folic acid supplements should be coadministered.

Fluconazole

Fluconazole is the agent most commonly used for prophylaxis of cryptococcal infection, which generally causes disease at CD4 levels below 100 cells per mm$^3$. It is contra-indicated in pregnancy.

Aciclovir

Aciclovir is used for the prevention of recurrent herpes simplex infection, which occurs at CD4 counts less than 400 to 500 cells per mm$^3$. It remains unlicensed for use in pregnancy, but a wealth of clinical experience has not revealed any reproducible adverse effects in pregnancy.

Ganciclovir/Foscarnet

Ganciclovir and foscarnet are used for the treatment and prophylaxis of cytomegalovirus reactivation, which may occur in severely immunocompromised patients. Ganciclovir has a teratogenic potential and is contraindicated in pregnancy. Foscarnet should be avoided if possible, with the risks of disease reactivation weighed up against possible adverse events on a case-by-case basis.

Fansidar (Pyrimethamine and Sulfadiazine)

This antibiotic coformulation is used in the treatment and prophylaxis of toxoplasmosis. Pyrimethamine is a folate antagonist and may be teratogenic in the first trimester. Neonatal hemolysis and methemoglobinemia may result from its use in the third trimester.

Amphotericin

Amphotericin is commonly used in the treatment of cryptococcal meningitis, there are no known harmful effects in pregnancy, but as with nonpregnant
patients, electrolyte disturbances (especially hypokalemia and hypomagnesemia) should be anticipated.

**Antituberculous Therapy**

An estimated 11 million people are coinfected with tuberculosis and HIV, and isoniazid and rifabutin are agents that may be prescribed to prevent atypical mycobacterial infection in patients whose CD4 counts are less than 50 to 100 cells per mm$^3$. Most antituberculous drugs can be used in pregnancy, with the exception of streptomycin, which is ototoxic. Rifamycins have significant pharmacokinetic interactions with PI- and NNRTI-containing antiretroviral regimens.

**Pentamidine**

Pentamidine is a second line agent for the treatment and prevention of PCP. It may be administered via parenteral or nebulized routes, and should be avoided unless the clinical indications outweigh possible risks.

**KEY POINTS**

Pregnancy presents a unique window of opportunity for HIV prevention by allowing measures to be instituted to protect the neonate from infection, including the use of antiretroviral agents if indicated. Pregnant women should be encouraged to ascertain their HIV status prior to delivery in order to access this opportunity.

The prescription of antiretroviral regimens should, wherever possible, take into account the reproductive intentions of the individual concerned.

In this rapidly advancing area of medicine, attention should be paid to maintaining current awareness of best practice according to evolving evidence-based recommendations.

The opportunities to prevent vertical transmission may be hampered by late presentation, the refusal to accept intervention because of cultural or personal beliefs, or a lack of available resources.

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about the book...

The most comprehensive and current review available on the wide spectrum of pharmaceuticals used in gynecology and reproductive medicine, this manual provides all-encompassing chapters on specific drugs used in the management of gynecologic oncology and infection, pregnancy, menstrual dysfunction, menopause, and infertility—listing the licensed and commercial names of drugs alongside their mechanisms of action, utilization, benefits, side-effects, and limitations. Setting a gold-standard in the field, this guide is divided into nine top-specific segments for quick-access to material and will be repeatedly referenced by any practitioner caring for the female patient.

Collecting an abundance of expertly-written chapters describing the use of drugs in various gynecological contexts, this source reviews potential risks and side-effects associated with specific drugs...names drugs that may cause adverse effects to the developing fetus or terminate pregnancy...assists trainees in preparation for professional examinations such as the MRCOG...contains sections on drugs utilized in specialized areas of gynecology such as urogynecology, peripartum care, early pregnancy failure, and recurrent miscarriage...and leads professionals to appropriate treatment regimens for endometriosis, polycystic ovary syndrome, dysmenorrhea, and other conditions encountered in the OB/GYN setting.

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