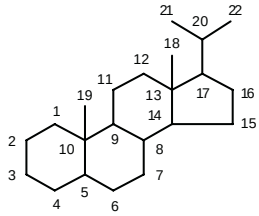
Sex Hormones and their Modulators

The male and female sex organs, the adrenal cortex, and the placenta produce steroidal hormones that influence the development and maintenance of structures directly and indirectly associated with reproduction. The secretion of these sex hormones is controlled by gonadotrophic hormones of the anterior lobe of the pituitary gland (and in pregnancy, from the placenta); the secretion of pituitary gonadotrophic hormones is in turn influenced by the hypothalamus and also by the concentration of circulating sex hormones. There are 3 groups of endogenous sex hormones, androgens, oestrogens, and progestogens, all of which are derived from the same steroidal precursors. The progestogenic hormone, progesterone, is formed from pregnenolone, and both of these compounds may be converted to androgen precursors such as androstenedione. Androstenedione is converted to the androgenic hormone testosterone by hydroxysteroid dehydrogenases. Oestrogenic hormones are synthesised from androstenedione (and also from testosterone) by the action of aromatase.



steroidal skeleton

Testosterone is the main androgenic hormone formed in the interstitial (Leydig) cells of the testes. A small proportion of circulating testosterone is also derived from the metabolism of less potent androgens secreted by the adrenal cortex and ovaries. In many target tissues testosterone is then converted to the more active dihydrotestosterone by 5α-reductase. Some testosterone also undergoes peripheral conversion to oestradiol.

Testosterone controls the development and maintenance of the male sex organs and the male secondary sex characteristics. It also produces systemic anabolic effects, such as increased retention of nitrogen, calcium, sodium, potassium, chloride, and phosphate. This leads to an increase in water retention and bone growth. The skin becomes more vascular and less fatty and erythropoiesis is increased.

Numerous derivatives of testosterone have been developed. Alkylation at the 17α position results in derivatives that are orally active, but associated with a risk of hepatotoxicity (see Table 1, below). Esterification of the 17β-hydroxyl group increases lipid solubility and is used to prepare long-acting intramuscular preparations (e.g. testosterone enantate). Removal of the 19-methyl group is reported to improve the anabolic to androgenic ratio (e.g. nandrolone). The derivatives also vary in their plasma protein binding affinity, and degree of conversion to dihydrotestosterone and aromatic conversion to oestrogen. Numerous other structural modifications have been made.

Oestradiol is the most active of the naturally occurring oestrogens formed from androgen precursors in the ovarian follicles of premenopausal women. In men and postmenopausal women (and to an insignificant extent in premenopausal women) oestrogens are also formed in adipose tissue from adrenal androgens.

Table 1. 17α-Alkylated testosterone derivatives

Danazol	Norethandrolone
Ethylestrenol	Oxandrolone
Fluoxymesterone	Oxymetholone
Methandienone	Stanozolol
Methyltestosterone	

Oestrogens control the development and maintenance of the female sex organs, secondary sex characteristics, and mammary glands as well as certain functions of the uterus and its accessory organs (particularly the proliferation of the endometrium, the development of the decidua, and the cyclic changes in the cervix and vagina). Large amounts of oestradiol are also formed in the placenta; in late pregnancy, this increases the spontaneous activity of the uterine muscle and its response to oxytocic drugs. The additional activity of progesterone is essential for the complete biological function of the female sex organs. Oestrogens also have some direct effects on metabolic processes, including those affecting bone mass, lipids, carbohydrates, and proteins.

A number of oestrogens are used therapeutically. Ethinyl substitution at the C17 position has led to the development of synthetic oestrogens such as ethinylestradiol and mestranol, which have greatly improved potency and oral activity. Oral activity of natural oestrogens is improved by esterification (e.g. estradiol valerate) or by conjugation (e.g. estrone sulfate). Esterification also increases solubility in lipid vehicles and is used to prepare long-acting intramuscular preparations.

A number of nonsteroidal oestrogens, including chlorotrianisene, dienestrol, and diethylstilbestrol, have also been used.

Progesterone is the main hormone secreted by the corpus luteum. It acts on the endometrium by converting the proliferative phase induced by oestrogen to a secretory phase thereby preparing the uterus to receive the fertilised ovum. Progesterone has a catabolic action and causes a slight rise in basal body temperature during the secretory phase of menstruation. During pregnancy the placenta produces large quantities of progesterone, which suppresses uterine motility and is responsible for the further development of the breasts.

Progestogens (gestagens, progestagens, progestins) are synthetic compounds with actions similar to those of progesterone. They are either progesterone derivatives or 19-nortestosterone analogues. The 19-nortestosterone analogues (such as norethisterone and norgestrel) possess some androgenic activity, but some newer norgestrel derivatives (desogestrel, gestodene, and norgestimate) have little androgenic activity. The progesterone derivatives dydrogesterone, hydroxyprogesterone, and medroxyprogesterone are less androgenic than the 19-nortestosterone analogues. The progesterone derivatives chlormadinone, and particularly cyproterone, have anti-androgenic activity.

The principal natural and synthetic sex hormones covered in this chapter are thus:

- **androgens and anabolic steroids**, typified by testosterone (p.2129)
- **oestrogens**, typified by estradiol (p.2097)
- **progestogens**, typified by progesterone (p.2125)

Other related substances also described in this chapter are:

- drugs with mainly **weak androgenic** properties such as danazol and gestrinone
- drugs that combine **oestrogenic and progestogenic** properties such as tibolone
- drugs with mainly **anti-androgenic** properties including the progesterone derivative cyproterone acetate. Those anti-androgens used principally in the hormonal treatment of prostate cancer are covered in the Antineoplastics chapter; they include the nonsteroidal drugs bicalutamide (p.686), flutamide (p.725), and nilutamide (p.756). The nonsteroidal 5α-reductase inhibitors finasteride (p.2188) and dutasteride (p.2188) and the plant extract saw palmetto (p.2192), used in the treatment of benign prostatic hyperplasia, are covered in the Urological Drugs chapter
- drugs with mainly **anti-oestrogenic** properties. These include the nonsteroidal anti-oestrogens clomifene, cyclofenil, and the more selective nonsteroidal anti-oestrogens ormeloxifene and raloxifene. Those anti-oestrogens used principally in the hormonal treatment of breast cancer are covered in the Antineoplastics chapter; they include the oestrogen receptor antagonists tamoxifen (p.772) and toremifene (p.781), and various aromatase inhibitors such as formestane (p.726) and anastrozole (p.681)
- **gonad-regulating hormones** (see below for more detail) include endogenous and recombinant forms of luteinising and follicle-stimulating hormones, and their releasing hormone gonadorelin and its analogues.

The therapeutic applications of sex hormones and related substances are broad and cover many circumstances where hormonal manipulation is desirable. Major applications are the use of oestrogens and progestogens for **contraception** (p.2070) and for the alleviation of **menopausal symptoms** (p.2077). A physiological application is the use of sex hormones or gonad-regulating hormones in the management of **delayed puberty** (p.2079) and **hypogonadism** (p.2079). Other clinical applications include the management of **benign prostatic hyperplasia** (p.2178), **endometriosis** (p.2091), **gynaecomastia** (p.2092), **hirsutism** (p.2089), **infertility** (p.2080), **mastalgia** (p.2092), **menorrhagia** (p.2126), and **premenstrual syndrome** (p.2099). Hormonal manipulation also has an important role in the treatment of **malignant neoplasms** of the breast (p.661), prostate (p.671), and endometrium (p.663).

Hormonal Contraceptives

Anticonceptivos hormonales; Contraceptifs Hormonaux; Hormonale Kontrazeptiva.

Гормональный Контрацептивы

Types of Contraceptive

Hormonal contraceptives are currently only available for women although preparations for men are being evaluated. Oral hormonal contraceptives for women are divided into 2 main types: 'combined' (containing an oestrogen and a progestogen) and 'progestogen-only'. Parenteral preparations have also been developed and include subcutaneous implants and depot intramuscular injections. Progestogen-releasing intra-uterine devices and a combined hormonal contraceptive vaginal ring are available. A combined hormonal transdermal patch has also been developed.

Parenteral progestogen-only contraceptives provide reliable suppression of ovulation by suppressing the necessary mid-cycle surge of luteinising hormone. However, the low doses in progestogen-only oral contraceptives do not suppress it reliably in all cycles. Contraceptive efficacy is instead achieved by thickening the cervical mucus so that it is not readily penetrated by sperm, and by preventing proliferation of the endometrium so that it remains unfavourable for implantation of any fertilised ova. Intra-uterine progestogen-only devices act similarly; the physical presence of the system in the uterus may also contribute to overall contraceptive efficacy.

Oestrogens inhibit ovulation by suppressing the mid-cycle release of follicle-stimulating hormone. They act synergistically with progestogens in combined oral contraceptives to provide regular and consistent suppression of ovulation.

Oral preparations are also available for *emergency contraception* after unprotected coitus; they prevent implantation of any fertilised ova.

Adverse Effects

Many reports have been published of adverse effects associated with the use of **combined oral contraceptives**. The data have mostly been gained retrospectively and often involve older preparations containing higher doses of oestrogen and progestogen than are used currently.

There may be gastrointestinal adverse effects such as nausea or vomiting, chloasma (melasma) and other skin or hair changes, headache, water retention, weight gain, breast tenderness, and changes in libido.

Menstrual irregularities such as spotting, breakthrough bleeding, or amenorrhoea can occur during treatment. These effects may result from the relative balance of oestrogenic and progestogenic effects of particular products and their incidence may be reduced by changing to a different product. For example, early or mid-cycle spotting or absence of withdrawal bleeding may require a preparation with a greater oestrogen to progestogen ratio or less progestogen as in multiphasic preparations.

Intolerance to contact lenses has been reported and vision may deteriorate in myopic patients. Some patients may experience depression and other mental changes. Preparations containing a progestogen with androgenic properties such as levonorgestrel or norgestrel may be associated with increased oiliness of the skin and acne. Conversely, acne may be improved with progestogens such as norgestimate or desogestrel.

There is an increased risk of cardiovascular disease and associated mortality related, at least in part, to the oestrogen content of combined oral contraceptives. The incidence of cardiovascular adverse effects is probably less with the newer lower-dose preparations than with the older higher-dose preparations. Increased mortality from myocardial infarction is much greater with increased age and in cigarette smokers, although some evidence suggests that healthy women aged over 35 years who do not smoke are not at increased risk. Other risk factors include a family history of arterial disease, diabetes mellitus, hypertension, obesity, and migraine. Thrombosis may be more common when factor V Leiden is present or in patients with blood groups A, B, or AB. Specific risk factors for venous thromboembolism include varicose veins, long-term immobilisation, obesity, and a family history of venous thromboembolism. Recent evidence has also indicated that the risk of venous thromboembolism varies according to the progestogen component of combined oral contraceptives; a higher incidence has been associated with desogestrel and gestodene than with levonorgestrel, norethisterone, and etynodiol. For further discussion see Venous Thromboembolism, below.

Combined oral contraceptives may cause hypertension and there may be reduced glucose tolerance and changes in lipid metabolism. Liver function can be impaired, although jaundice is rare. There appears to be a marked increase (though the incidence is still very low) in the relative risk of benign liver tumours. Malignant liver tumours have also been reported.

Combined oral contraceptives are reported to slightly increase the risk of cervical cancer (although other factors may be involved) and breast cancer, but to protect against ovarian cancer and endometrial cancer. For further discussion, see Carcinogenicity, below.

As with combined oral contraceptives, **progestogen-only contraceptives** may cause nausea, vomiting, headache, breast discomfort, depression, skin disorders, and weight gain. Menstrual irregularities such as amenorrhoea, breakthrough bleeding, spotting, and menorrhagia are more common with progestogen-only contraceptives, and are particularly common with parenteral preparations. Available progestogen-only contraceptives carry less risk of thromboembolic and cardiovascular disease than combined oral contraceptives.

Carcinogenicity. Concern has often been expressed as to whether the use of hormonal contraceptives by normally healthy women may either cause or increase the risk of developing malignant neoplasms. To investigate any possible link between such use and cancer, two main types of study have been used by epidemiologists, namely the prospective study and the case-control study. Many factors have made direct comparison of results difficult and such factors include the type and composition of oral contraceptive used (which has changed over the years), the age of the patient, the age at which use first began, and the sexual and obstetric history of the patient. Overall the evidence indicates that combined oral contraceptives in fact exert a protective effect against the development of endometrial and ovarian carcinoma. However, there is a small increase in risk of breast cancer during use and for 10 years after discontinuation. In addition, there does appear to be a slight risk of cervical cancer with the prolonged use of combined oral contraceptives and a negligible risk of liver cancer. For further details concerning the effects on individual organs, see the following sections. It should be noted that even where the relative risk has been shown to be substantially increased this will not translate into many new cases of a rare cancer, and this contributes to the difficulties of assessing clinical relevance.

In the long-term Oxford Family Planning Association contraceptive study, the beneficial effects of oral contraceptives on the uterus and ovary were calculated to outweigh the adverse effect on the cervix.[1] This large cohort study also found no increased risk of breast cancer although the data could not exclude a small increase in risk with current use that declined after stopping. Long-term follow-up of the prospective Royal College of General Practitioners' study has found no overall increased risk of cancer.[2] It is also worthy of note that two large prospective cohort studies (the Nurses' Health Study and the Royal College of General Practitioners' study) found no evidence of a difference in overall mortality between women who had used oral contraceptives and those who had not.[3,4] Some general reviews on hormonal contraceptives and cancer are cited below.[5-9]

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BREAST. Numerous epidemiological studies have been published on the potential link between hormonal contraceptives and breast cancer. Most of these data relate to **combined oral contraceptives**, which are the most widely used form. The breast cancer risk from use of these contraceptives will require monitoring for some time to come as the first users of oral contraceptives continue to age, and because of the changing patterns of use.

Early studies from the 1980s variously failed to show any significant increase in risk of breast cancer in women who had ever used hormonal contraceptives compared with those who had never done so,[1-4] or showed an increase in risk,[5] or identified a risk in specific sub-groups of users.[6-12] Potential identified risk factors, for which much of the evidence was conflicting, included current use,[10] duration of use,[7,11] age at first use,[6] duration of use before a first full-term pregnancy,[7,8] nulliparity,[9] high-dose preparations,[11] and family history of breast cancer.[12] It was also reported that use of oral contraceptives might lead to an accelerated presentation of breast cancer,[13] or an increased risk of invasive cancer.[4]

In response to these studies, the UK CSM,[14] the FDA in the USA,[15] and the International Committee for Research in Reproduction[16] issued advice that the available evidence did not require a change in prescribing practice. This advice has not been subsequently changed, although patients should be informed of the possible small increase in risk of breast cancer, which has to be weighed against established benefits of therapy.[17]

A Collaborative Group on Hormonal Factors in Breast Cancer was set up to re-analyse all the worldwide epidemiological evidence on breast cancer risk and hormonal contraceptives. The group identified individual data on 53 297 women with breast cancer, and 100 239 controls (women without breast cancer) from 54 studies, and published a summary of their findings,[18] and a further detailed review.[19] They reported that women currently using oral contraceptives have a slight increase in the relative risk of breast cancer (1.24; 95% confidence intervals 1.15 to 1.33), and that this risk decreases after stopping use, and is no longer significant after 10 or more years. There was a weak trend towards an increase in risk with increasing duration of use. Thus, it appears that the risk of breast cancer

- increases soon after first exposure
- does not increase with duration of exposure
- returns to normal 10 years after cessation of exposure.[18]

Reviews[20,21] of major studies published between 1990 and 2000, including that of the Collaborative Group, have also indicated that, in general, there is some excess breast cancer risk in current or recent users of oral contraceptives, but that excess risk does not persist in the long term after cessation of oral contraceptive use, regardless of duration of use.

The Collaborative Group found that cancers diagnosed in those who had ever used hormonal contraceptives were clinically less advanced than in those who had never done so.[18] Further information is required on whether this is related to earlier diagnosis or a biological effect of the hormones. In addition, data on breast cancer mortality are required.

When analysed by *age at first use*, the risk was largest in those women who started use as teenagers. Because of the trend towards earlier use, further review of long-term data is required.[18] The most important risk factor is, however, the *age at which women discontinue* the contraceptive; the greater the age at stopping, the more breast cancers are diagnosed.[17]

Data from the collaborative group suggested that there was no difference in risk with *parity* when comparing nulliparous women, parous women who began use of oral contraceptives before their first child, and parous women who began use of oral contraceptives after the birth of their first child.[18] However, a later meta-analysis[22] reported higher risks in parous women, particularly those who used oral contraceptives for 4 or more years before first full-term pregnancy.

Low-dose oral contraceptives were not associated with a decreased risk of breast cancer.[18] When preparations were grouped according to oestrogen dose (< 50 micrograms, 50 micrograms, and >50 micrograms), there was, if anything, a decrease in breast cancer risk with increasing dose among women who had stopped use 10 or more years before, largely due to a reduction in breast cancer risk in those who had used the highest dose preparations.

The Collaborative Group's analysis did not note any difference in risk according to *family history.*[18] However, a subsequent cohort study found an increased risk of breast cancer among women with a strong family history of the disease who used earlier formulations of oral contraceptives.[23] Another cohort study[24] provided support for the Collaborative Group's findings, reporting no statistical difference in the risk with oral contraceptive use in women with a family history of breast cancer; there was actually a trend towards a reduction in risk of breast cancer with long-term use. Women carrying mutations in the BRCA1 or BRCA2 genes are at increased risk of developing breast cancer; any additional risk from oral contraceptives is of particular concern because these women may be encouraged to take them to reduce their risk of ovarian cancer (see Ovary, below). However, results from studies in known carriers of these mutations have been mixed. A modest increase in the risk of breast cancer in BRCA1 carriers has been reported with ever use of oral contraceptives,[25] but another study[26] found a reduced risk in carriers who used current preparations containing lower oestrogen doses than those available before 1975. Further study is needed in these women.

There are far fewer data on risk of breast cancer with **progestogen-only contraceptives**, which are less frequently used than combined preparations.

A WHO study published in 1991 indicated that, overall, depot medroxyprogesterone acetate did not increase the risk of breast cancer (relative risk compared with never users 1.21; 95% confidence intervals 0.96 to 1.53) and that risk did not increase with duration of use.[27] However, there appeared to be a slight increase in risk within the first 4 years of use, especially in women under 35 years of age. These findings agreed with those of a smaller study[28] in which women who had used depot medroxyprogesterone acetate for 2 years or longer before the age of 25 had a relative risk of 4.6. Pooled analysis of these 2 studies indicated that current or recent use was the key factor.[29] The relative risk of breast cancer in women who had used medroxyprogesterone acetate in the last 5 years was 2.0, and there was no increased risk in women who had ceased use more than 5 years previously, regardless of their duration of use. Another small study[30] reported no increase in risk overall in women who had ever used medrox-

yprogesterone acetate; there was an increase for current use in the subgroup of women aged 35 to 44 (relative risk 2.3), but this was no longer the case 4 years after stopping.

The Collaborative Group on Hormonal Factors in Breast Cancer reported that there was some evidence of an increased risk of breast cancer for use of oral or injectable progestogens in the previous 5 years (relative risk 1.17), and no risk 10 or more years after stopping use.[18] These findings were broadly similar to those for combined preparations. As for combined preparations, the most important factor is the *age at discontinuation*. For women who stop by age 30 after 5 years use of a progestogen-only preparation there would be an estimated increase from 44 to 46 or 47 cases per 10 000 compared with those who have never used a hormonal contraceptive. For 5 years use stopping by age 40 there would be an estimated increase from 160 to 170 cases diagnosed in the following 10 years.[17]

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21. La Vecchia C, *et al.* Oral contraceptives and cancer: an update. *Drug Safety* 2001; **24:** 741–54.
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CERVIX. It is often considered difficult to carry out satisfactory epidemiological studies on the relationship between hormonal contraceptives and cervical cancer because of the many known variables that can influence the development of this type of neoplasm. For example, sexual activity *per se*, and multiple sexual partners (both of the woman and her partner) increase the risk, while the use of other non-hormonal barrier methods of contraception may offer some protection against cervical neoplasia. Nevertheless, there have been some suggestions that the use of oral contraceptives may be associated with an increased risk.

Two UK cohort studies from the 1980s revealed an increased risk of cervical cancer in women receiving oral contraceptives that was shown to increase with increasing duration of use.[1,2]

In 1992, WHO reviewed[3] these cohort data, and data from 18 case-controlled studies carried out up to 1990. They concluded that use of oral contraceptives for more than 5 years was associated with a modest increase in the relative risk of cervical squamous cell carcinoma (in the order of 1.3 to 1.8). Additional potential risk factors included recent or current use and high oestrogen dose. Of known risk factors for cervical cancer, women with multiple sexual partners, genital infection, or high parity had enhanced risks associated with oral contraceptives.[3] Later reviews came to similar conclusions.[4,5]

Most cervical cancers are squamous cell carcinomas, but it has been proposed that oral contraceptive use might be a particular risk factor for the rarer adenocarcinoma of the cervix, the incidence of which has risen in younger women. Reviewing studies up to 1990, WHO concluded that data were insufficient to draw firm conclusions on links between oral contraceptives and the risk of cervical adenocarcinoma.[3] A case-controlled study from 1994 found an increased risk of adenocarcinoma of the cervix in users of oral contraceptives.[6] Any use of oral contraceptives was associated with an approximate doubling of risk, and use for more than 12 years was associated with a relative risk 4.4 times greater than that in women who never used an oral contraceptive. In 1996, a WHO study reported that the strength of the observed relationship for cervical adenocarcinomas and adenosquamous carcinomas and oral contraceptives was about the same as that for invasive squamous cell cervical carcinomas.[7]

Human papillomavirus (HPV) has a role in the aetiology of cervical cancer; women who are HPV positive and using oral contraceptives may be at increased risk of cervical neoplasm.[8,9] A pooled analysis of 8 case-control studies in women who tested positive for HPV DNA suggested risk of invasive squamous cervical cancer or carcinoma *in situ* was increased about threefold in those who used oral contraceptives for 5 years or more.[10]

Data on the risk of cervical cancer with **progestogen-only contraceptives** are limited. WHO have investigated any possible link between the use of medroxyprogesterone acetate as a long-acting injectable contraceptive and cervical neoplasia. Analysis showed a small non-significant elevated risk (1.11; 95% confidence interval 0.9 to 1.29), and no clear association with duration of use.[11] A later case-control study[12] found no significant association between injectable progestogen contraceptives and invasive cervical cancer risk.

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3. WHO. Oral contraceptives and neoplasia: report of a WHO scientific group. *WHO Tech Rep Ser 817* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_817.pdf (accessed 14/01/08)
4. Moodley J. Combined oral contraceptives and cervical cancer. *Curr Opin Obstet Gynecol* 2004; **16:** 27–9.
5. Smith JS, *et al.* Cervical cancer and use of hormonal contraceptives: a systematic review. *Lancet* 2003; **361:** 1159–67.
6. Ursin G, *et al.* Oral contraceptive use and adenocarcinoma of cervix. *Lancet* 1994; **344:** 1390–4.
7. Thomas DB, Ray RM. Oral contraceptives and invasive adenocarcinomas and adenosquamous carcinomas of the uterine cervix. *Am J Epidemiol* 1996; **144:** 281–9.
8. La Vecchia C, *et al.* Oral contraceptives and cancer: a review of the evidence. *Drug Safety* 1996; **14:** 260–72.
9. La Vecchia C, *et al.* Oral contraceptives and cancer: an update. *Drug Safety* 2001; **24:** 741–54.
10. Moreno V, *et al.* Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. *Lancet* 2002; **359:** 1085–92.
11. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of invasive squamous cell cervical cancer. *Contraception* 1992; **45:** 299–312.
12. Shapiro S, *et al.* Risk of invasive cancer of the cervix in relation to the use of injectable progestogen contraceptives and combined estrogen/progestogen oral contraceptives (South Africa). *Cancer Causes Control* 2003; **14:** 485–95.

ENDOMETRIUM. It has been shown that **combined oral contraceptives** decrease the risk of endometrial cancer. WHO analysed data from case-control and cohort studies published up to 1990,[1] including data from the large Cancer and Steroid Hormone Study (CASH) in the USA,[2] and reported that there was a highly significant trend of decreasing risk of endometrial cancer with increasing duration of use of combined oral contraceptives. The reduction in risk was estimated to be 20% after 1 year and 50% after 4 years of use.[1] The protective effect was observed for endometrial cancer with and without squamous elements,[1,2] and was found to persist for at least 15 years after cessation of use.[2] More recent studies with longer term follow-up have indicated that the protection persists for at least 20 years.[3,4] Further follow-up is required to determine the true duration of protection; data from one study[5] suggested that the reduction in risk was more pronounced in women who had stopped contraceptive use more than 25 years before, but another study[4] suggested that any protective effect may no longer be present 30 years after stopping combined oral contraceptive use.

The results of the WHO Collaborative Study on Neoplasia and Steroid Contraceptives suggested that protection may be greater with preparations containing high-dose progestogen.[6] However, another study found that risk of endometrial cancer was unrelated to progestogen potency of the oral contraceptive, although this study also reported no protective effect for less than 5 years of use.[7] Further analysis of the CASH study data[8] found that although preparations containing high and low doses of progestogen had a similar protective effect overall, it was greatest for high-dose progestogen preparations in women with a higher BMI.

Unopposed menopausal oestrogen replacement therapy is known to increase the risk of endometrial cancer (see p.2072), and there is some evidence[3,7] that it reduces the protective effect of previous oral contraception.

There are limited data on the effect of **progestogen-only contraceptives** on the risk of endometrial cancer, although they would be expected to be protective. Results from the WHO Collaborative Study[9] suggest that depot medroxyprogesterone acetate reduced the risk of endometrial cancer; the estimated relative risk in users was 0.21. However, many of the women in this study received supplemental oestrogen to control menstrual irregularity, and were therefore technically taking a form of combined therapy.[10] There was some evidence that the protective effect of medroxyprogesterone acetate was greater in women who had not received oestrogen,[10] although this remains to be proven.

1. WHO. Oral contraceptives and neoplasia: report of a WHO scientific group. *WHO Tech Rep Ser 817* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_817.pdf (accessed 14/01/08)
2. The Cancer and Steroid Hormone Study of the CDC and the National Institute of Child Health and Human Development. Combination oral contraceptive use and the risk of endometrial cancer. *JAMA* 1987; **257:** 796–800.
3. Stanford JL, *et al.* Oral contraceptives and endometrial cancer: do other risk factors modify the association? *Int J Cancer* 1993; **54:** 243–8.
4. Weiderpass E, *et al.* Use of oral contraceptives and endometrial cancer risk (Sweden). *Cancer Causes Control* 1999; **10:** 277–84.
5. Tao MH, *et al.* Oral contraceptive and IUD use and endometrial cancer: a population-based case-control study in Shanghai, China. *Int J Cancer* 2006; **119:** 2142–7.
6. Rosenblatt KA, *et al.* Hormonal content of combined oral contraceptives in relation to the reduced risk of endometrial carcinoma. *Int J Cancer* 1991; **49:** 870–4.
7. Voigt LF, *et al.* Recency, duration, and progestin content of oral contraceptives in relation to the incidence of endometrial cancer. *Cancer Causes Control* 1994; **5:** 227–33.
8. Maxwell GL, *et al.* Progestin and estrogen potency of combination oral contraceptives and endometrial cancer risk. *Gynecol Oncol* 2006; **103:** 535–40.
9. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of endometrial cancer. *Int J Cancer* 1991; **49:** 186–90.
10. Szarewski A, Guillebaud J. Safety of DMPA. *Lancet* 1991; **338:** 1157–8.

GASTROINTESTINAL TRACT. A link between female sex hormones and the risk of colorectal cancer has been postulated. Epidemiological studies have variously shown a possible increased risk of rectal cancer,[1] a possible decreased risk of colorectal cancer[2] in women ever having used oral contraceptives, and no association between past oral contraceptive use and colorectal cancer.[3] A meta-analysis,[4] which included these 3 studies, found a reduction in the risk of colorectal cancer for women who had ever used oral contraceptives. Duration of use was not related to risk reduction, but the effect was apparently stronger for recent contraceptive use although this was based on limited data. Subsequent studies have produced similar results. A reduction in risk has been associated with ever use of oral contraceptives in one report,[5] while others have found no effect statistically but a trend towards protection with current or recent use.[6,7]. (See also under Hormone Replacement Therapy, p.2073.)

1. Kune GA, *et al.* Oral contraceptive use does not protect against large bowel cancer. *Contraception* 1990; **41:** 19–25.
2. Fernandez E, *et al.* Oral contraceptives, hormone replacement therapy and the risk of colorectal cancer. *Br J Cancer* 1996; **73:** 1431–5.
3. Troisi R, *et al.* Reproductive factors, oral contraceptive use, and risk of colorectal cancer. *Epidemiology* 1997; **8:** 75–9.
4. Fernandez E, *et al.* Oral contraceptives and colorectal cancer risk: a meta-analysis. *Br J Cancer* 2001; **84:** 722–7.
5. Lin J, *et al.* Oral contraceptives, reproductive factors, and risk of colorectal cancer among women in a prospective cohort study. *Am J Epidemiol* 2007; **165:** 794–801.
6. Hannaford P, Elliott A. Use of exogenous hormones by women and colorectal cancer: evidence from the Royal College of General Practitioners' Oral Contraception Study. *Contraception* 2005; **71:** 95–8.
7. Nichols HB, *et al.* Oral contraceptive use, reproductive factors, and colorectal cancer risk: findings from Wisconsin. *Cancer Epidemiol Biomarkers Prev* 2005; **14:** 1212–18.

LIVER. The use of **combined oral contraceptives** has been rarely associated with liver tumours, both benign (hepatic adenomas and focal nodular hyperplasia)[1] and malignant (hepatocellular carcinoma).[1,2]

Early studies of *hepatic adenoma* found that risk increased with the duration of use of oral contraceptives, and appeared to be higher in women who had used preparations with a high oestrogen content.[1] There are also case reports of adenoma that has regressed after stopping oral contraceptive use.[3] However, a study[4] in the 1990s found no increase in risk associated with contraceptive use, and the authors considered that lower doses of oestrogens might explain the different findings. The association between oral contraceptive use and *focal nodular hyperplasia* has also been studied. One case-control study[4] found a slight increase in risk associated with use for 10 years or more. Another study[5] that followed a series of patients for about 2 years after diagnosis found no correlation between oral contraceptive use and lesion size or number, and no increase in lesion size in those patients who continued to use hormonal contraception.

Hepatocellular carcinomas are associated with hepatitis B, and are relatively common in countries where this is endemic but rare elsewhere. Case-control studies in populations at high risk for hepatocellular carcinoma suggest that the use of oral contraceptives does not significantly affect the risk, although long-term data are scanty.[6,7] However, survival after curative treatment is better in women than men, and a retrospective study from Hong Kong has suggested that this may be associated with a history of oral contraceptive use.[8] In contrast, case-control studies in countries where the prevalence of hepatitis B is low have shown an increased risk of hepatocellular carcinoma among users of oral contraceptives, particularly after long-term use (reviewed by WHO[1] and La Vecchia[2,9]). However, because the malignancy is so rare, this increased risk may be negligible.[2] For example, there has been no increase in mortality from liver cancer in young women in the UK since the introduction and use of oral contraceptives.[10] Similar findings have been reported for the USA and Sweden.[11]

There are limited data specifically on **progestogen-only contraceptives**. Results from a WHO study[12] provided no evidence that use of medroxyprogesterone acetate as a long-acting injectable contraceptive altered the risk of developing liver cancer but the power of the study to detect small alterations in risk was low.

1. WHO. Oral contraceptives and neoplasia: report of a WHO scientific group. *WHO Tech Rep Ser 817* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_817.pdf (accessed 14/01/08)
2. La Vecchia C, *et al.* Oral contraceptives and cancer: a review of the evidence. *Drug Safety* 1996; **14:** 260–72.
3. Aseni P, *et al.* Rapid disappearance of hepatic adenoma after contraceptive withdrawal. *J Clin Gastroenterol* 2001; **33:** 234–6.
4. Heinemann LAJ, *et al.* Modern oral contraceptive use and benign liver tumors: the German benign liver tumor case—control study. *Eur J Contracept Reprod Health Care* 1998; **3:** 194–200.
5. Mathieu D, *et al.* Oral contraceptive use and focal nodular hyperplasia of the liver. *Gastroenterology* 2000; **118:** 560–4.
6. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Combined oral contraceptives and liver cancer. *Int J Cancer* 1989; **43:** 254–9.
7. Kew MC, *et al.* Contraceptive steroids as a risk factor for hepatocellular carcinoma: a case/control study in South African black women. *Hepatology* 1990; **11:** 298–302.
8. Lam CM, *et al.* Better survival in female patients with hepatocellular carcinoma: oral contraceptive pills related? *J Clin Gastroenterol* 2005; **39:** 533–9.
9. La Vecchia C, *et al.* Oral contraceptives and cancer: an update. *Drug Safety* 2001; **24:** 741–54.
10. Mant JWF, Vessey MP. Trends in mortality from primary liver cancer in England and Wales 1975-1992: influence of oral contraceptives. *Br J Cancer* 1995; **72:** 800–3.
11. Waetjen LE, Grimes DA. Oral contraceptives and primary liver cancer: temporal trends in three countries. *Obstet Gynecol* 1996; **88:** 945–9.
12. Anonymous. Depot-medroxyprogesterone acetate (DMPA) and cancer: memorandum from a WHO meeting. *Bull WHO* 1986; **64:** 375–82.

OVARY. There is convincing evidence that **combined oral contraceptives** reduce the risk of ovarian cancer,[1,2] possibly as a function of their inhibition of ovulation. Relative risks for ovarian cancer have variously been reported as 0.4 to 0.8 in those who have ever used oral contraceptives, and decrease with increasing duration of use. There is evidence that there may be a delay of several years before the protective effect becomes apparent,[3] but that it persists for as long as 20 or 30 years after cessation of use.[3-5] The protective effect has been noted for both malignant and borderline malignant tumours[6] and for each of the major histological subtypes of epithelial ovarian cancer, although there have been conflicting data for mucinous tumours.[5]

It has been suggested that newer lower-dose oestrogen preparations may be slightly less protective than higher-dose preparations.[7] The relative risk for use of high-dose preparations was 0.68, and for low-dose preparations was 0.81, but it was noted that this difference could have occurred by chance. A later study[4] reported that risk reduction was not affected by oral contraceptive formulation. In contrast, another study[8] found a greater risk reduction associated with low-dose contraceptives than older high-dose preparations (odds ratio of 0.24 versus 0.70). The authors speculated that the accompanying changes in progestogen content might have played a role. This was examined using the data from the Cancer and Steroid Hormone (CASH) study, which suggested that higher progestogen potency provided greater risk reduction than lower progestogen potency, regardless of oestrogen dose.[9] Androgenicity of the progestogen does not appear to influence the protective effect of combined oral contraceptives.[10]

The protective effect against ovarian cancer may have significant implications for public health. There have been substantial declines in ovarian cancer incidence and mortality in younger women in countries where oral contraceptives have become widely used; it is estimated that 3000 to 5000 cases (and consequently 2000 to 3000 deaths) are avoided each year in Europe; similar numbers are quoted in North America.[11]

There are few data on the effects of **progestogen-only contraceptives** on the risk of ovarian cancer. WHO have investigated the effect of depot medroxyprogesterone acetate on ovarian cancer, and found that it was not associated with either a decrease or increase in risk (relative risk 1.07; 95% confidence interval 0.6 to 1.8).[12] This is perhaps surprising since the preparation, like combined oral contraceptives, inhibits ovulation.

Women carrying mutations in either the BRCA1 or BRCA2 gene are at increased risk of ovarian cancer, and the effect of oral contraceptives in these women has been evaluated. Although there was no protective effect in one study,[13] others have found a risk reduction with contraceptive use similar to that reported for non-carriers.[14-17] It has been suggested that oral contraceptives might be used prophylactically to protect against ovarian cancer in women with these mutations, but this must be considered in the context of their increased risk of breast cancer (see Breast, above). Women with endometriosis may also be at increased risk of ovarian cancer, and an analysis[18] of the pooled data from 4 studies suggested that long-term use of oral contraceptives may also be protective in this group.

1. Whittemore AS, *et al.* Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies II: invasive epithelial ovarian cancers in white women. *Am J Epidemiol* 1992; **136:** 1184–1203.
2. Bosetti C, *et al.* Long-term effects of oral contraceptives on ovarian cancer risk. *Int J Cancer* 2002; **102:** 262–5.
3. Rosenberg L, *et al.* A case-control study of oral contraceptive use and invasive epithelial ovarian cancer. *Am J Epidemiol* 1994; **139:** 654–61.
4. Ness RB, *et al.* Risk of ovarian cancer in relation to estrogen and progestin dose and use characteristics of oral contraceptives. *Am J Epidemiol* 2000; **152:** 233–41.
5. Riman T, *et al.* Risk factors for invasive epithelial ovarian cancer: results from a Swedish case-control study. *Am J Epidemiol* 2002; **156:** 363–73.
6. Kumle M, *et al.* Risk for invasive and borderline epithelial ovarian neoplasias following use of hormonal contraceptives: the Norwegian-Swedish Women's Lifestyle and Health Cohort Study. *Br J Cancer* 2004; **90:** 1386–91.
7. Rosenblatt KA, *et al.* High-dose and low-dose combined oral contraceptives: protection against epithelial ovarian cancer and the length of the protective effect. *Eur J Cancer* 1992; **28A:** 1872–6.
8. Royar J, *et al.* Low-dose oral contraceptives: protective effect on ovarian cancer risk. *Int J Cancer* 2001; **95:** 370–4.
9. Schildkraut JM, *et al.* Impact of progestin and estrogen potency in oral contraceptives on ovarian cancer risk. *J Natl Cancer Inst* 2002; **94:** 32–8.
10. Greer JB, *et al.* Androgenic progestins in oral contraceptives and the risk of epithelial ovarian cancer. *Obstet Gynecol* 2005; **105:** 731–40.
11. La Vecchia C. Oral contraceptives and ovarian cancer: an update, 1998–2004. *Eur J Cancer Prev* 2006; **15:** 117–24.
12. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of epithelial ovarian cancer. *Int J Cancer* 1991; **49:** 191–5.
13. Modan B, *et al.* Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. *N Engl J Med* 2001; **345:** 235–40.
14. Narod SA, *et al.* Oral contraceptives and the risk of hereditary ovarian cancer. *N Engl J Med* 1998; **339:** 424–8.
15. McGuire V, *et al.* Relation of contraceptive and reproductive history to ovarian cancer risk in carriers and noncarriers of BRCA1 gene mutations. *Am J Epidemiol* 2004; **160:** 613–18.
16. Whittemore AS, *et al.* Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. *Br J Cancer* 2004; **91:** 1911–15.
17. McLaughlin JR, *et al.* Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. *Lancet Oncol* 2007; **8:** 26–34.
18. Modugno F, *et al.* Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. *Am J Obstet Gynecol* 2004; **191:** 733–40.

SKIN. Although there have been some suggestions of a possible association between the use of oral contraceptives and the development of malignant melanoma[1-4] most studies, including analyses of relatively large numbers of women suffering from malignant melanoma, found no such association with either current or prior use of oral contraceptive preparations.[5-12] A meta-analysis of 18 case-control studies confirmed the lack of association.[13]

1. Beral V, *et al.* Malignant melanoma and oral contraceptive use among women in California. *Br J Cancer* 1977; **36:** 804–9.
2. Lerner AB, *et al.* Effects of oral contraceptives and pregnancy on melanomas. *N Engl J Med* 1979; **301:** 47.
3. Beral V, *et al.* Oral contraceptive use and malignant melanoma in Australia. *Br J Cancer* 1984; **50:** 681–5.
4. Feskanich D, *et al.* Oral contraceptive use and risk of melanoma in premenopausal women. *Br J Cancer* 1999; **81:** 918–23.
5. Bain C, *et al.* Oral contraceptive use and malignant melanoma. *J Natl Cancer Inst* 1982; **68:** 537–9.
6. Helmrich SP, *et al.* Lack of an elevated risk of malignant melanoma in relation to oral contraceptive use. *J Natl Cancer Inst* 1984; **72:** 617–20.
7. Green A, Bain C. Hormonal factors and melanoma in women. *Med J Aust* 1985; **142:** 446–8.
8. Østerlind A, *et al.* The Danish case-control study of cutaneous malignant melanoma III: hormonal and reproductive factors in women. *Int J Cancer* 1988; **42:** 821–4.
9. Palmer JR, *et al.* Oral contraceptive use and risk of cutaneous malignant melanoma. *Cancer Causes Control* 1992; **3:** 547–54.
10. Holly EA, *et al.* Cutaneous melanoma in women III: reproductive factors and oral contraceptive use. *Am J Epidemiol* 1995; **141:** 943–50.
11. Smith MA, *et al.* Hormonal and reproductive influences and risk of melanoma in women. *Int J Epidemiol* 1998; **27:** 751–7.
12. Naldi L, *et al.* Cutaneous malignant melanoma in women. Phenotypic characteristics, sun exposure, and hormonal factors: a case-control study from Italy. *Ann Epidemiol* 2005; **15:** 545–50.
13. Gefeller O, *et al.* Cutaneous malignant melanoma in women and the role of oral contraceptives. *Br J Dermatol* 1998; **138:** 122–4.

Ectopic pregnancy. All methods of contraception effectively reduce the risk of ectopic pregnancy overall by reducing the rate of pregnancy. However, when contraception fails the proportion of pregnancies that are ectopic is higher for users of oral and intra-uterine **progestogen-only contraceptives** and levonorgestrel implants than in the general population.[1] There is no increase in the proportion of ectopic pregnancies for methods that inhibit ovulation more reliably, such as combined oral contraceptives[1] and medroxyprogesterone acetate depot injection.[2]

A small number of cases of ectopic pregnancy after failure of **emergency contraception**, with both the Yuzpe regimen (oestrogen plus progestogen)[3] and progestogen-only contraception,[4] have been reported. However, data from clinical studies[5] and postmarketing surveillance[6] have shown that when levonorgestrel emergency contraception does rarely fail, there is no increase in the chance of ectopic pregnancy occurring.

1. Furlong L-A. Ectopic pregnancy risk when contraception fails: a review. *J Reprod Med* 2002; **47:** 881–5.
2. Borgatta L, *et al.* Pregnancies diagnosed during Depo-Provera use. *Contraception* 2002; **66:** 169–72.
3. Nielsen CL, Miller L. Ectopic gestation following emergency contraceptive pill administration. *Contraception* 2000; **62:** 275–6.
4. Harrison-Woolrych M, Woolley J. Progestogen-only emergency contraception and ectopic pregnancy. *J Fam Plann Reprod Health Care* 2003; **29**(1): 5–6.
5. Trussell J, *et al.* Ectopic pregnancy following use of progestin-only ECPs. *J Fam Plann Reprod Health Care* 2003; **29:** 249.
6. Gainer E, *et al.* Progestogen-only emergency contraception. *J Fam Plann Reprod Health Care* 2003; **29**(2): 60. Correction. *ibid.*; 159.

Effects on body-weight. Weight gain has been reported as an adverse effect of combined oral contraceptives, but there is no strong evidence from clinical studies to confirm that they have a significant effect on weight.[1,2] However, there is some evidence that weight gain might be associated with medroxyprogesterone acetate when given as a long-acting injectable contraceptive. There have been reports of both weight gain[3] over 5 years, and no change in weight[4] over 10 years, in women using medroxyprogesterone compared with those using a copper IUD. Studies[5,6] in adolescents using medroxyprogesterone or an oral contraceptive for 12 or 18 months have reported more weight gain in those using medroxyprogesterone, and that significant weight gain was more likely in those who were overweight when contraception was started. The risk of weight gain, however, may be confounded by a number of factors including age, race, diet, exercise, and prior pregnancy.

For discussion of a possible association between obesity and oral contraceptive failure, see Obesity, under Precautions, below.

1. Gupta S. Weight gain on the combined pill—is it real? *Hum Reprod Update* 2000; **6:** 427–31.
2. Gallo MF, *et al.* Combination contraceptives: effects on weight. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 14/01/08).
3. Bahamondes L, *et al.* Comparison of weight increase in users of depot medroxyprogesterone acetate and copper IUD up to 5 years. *Contraception* 2001; **64:** 223–5.
4. Taneepanichskul S, *et al.* Effects of DMPA on weight and blood pressure in long term acceptors. *Contraception* 1999; **59:** 301–3.
5. Mangan SA, *et al.* Overweight teens at increased risk for weight gain while using depot medroxyprogesterone acetate. *J Pediatr Adolesc Gynecol* 2002; **15:** 79–82.
6. Bonny AE, *et al.* Weight gain in obese and nonobese adolescent girls initiating depot medroxyprogesterone, oral contraceptive pills, or no hormonal contraceptive method. *Arch Pediatr Adolesc Med* 2006; **160:** 40–5.

Effects on carbohydrate metabolism. The potential effects of oral contraceptives on carbohydrate metabolism are of concern because impaired glucose tolerance, hyperinsulinism, and insulin resistance contribute to atherogenesis and cardiovascular disease.[1] Early studies suggested that the prevalence of abnormal glucose tolerance in oral contraceptive users was increased from about 4 to 35%.[2] This decreased glucose tolerance was found to be related to oestrogen dose, particularly those greater than 75 micrograms daily, and to the type of progestogen. Marked hyperglycaemia has been associated with contraceptives containing high doses of oestrogen but is not seen with combined oral contraceptives used currently, which contain lower doses of oestrogen.[1] Progestogens have little effect on glucose tolerance, but are associated with hyperinsulinaemia. This effect is dose-dependent, and levonorgestrel has the most potent effect, with desogestrel, gestodene, and norethisterone reported to have less ef-

fect.[1] Combined oral contraceptives can also induce insulin resistance;[1] it is believed that the oestrogen is responsible and that the progestogen modifies this effect.[3]

Despite evidence of these effects, more recent studies of lower-dose preparations containing desogestrel, levonorgestrel, or norethisterone have found little or no effect on various measurements of carbohydrate metabolism;[4-6] this lack of effect has also been confirmed in a meta-analysis[7] of studies of hormonal contraceptive use in non-diabetic women although it was noted that no strong statement could be made since few studies compared the same types of contraceptives and some had large drop out rates. Also, data from the Nurses' Health Study indicate that oral contraceptive use does not appear to increase the risk of developing type 2 diabetes mellitus.[8,9] However, a study in the USA of breast-feeding women of Hispanic origin who had experienced recent gestational diabetes, suggested that the use of progestogen-only, but not combined, contraceptives was associated with an increased risk of developing type 2 diabetes mellitus in this group.[10]

Injectable progestogen-only contraceptives have been reported in epidemiological studies to be associated with an increase in the incidence of type 2 diabetes mellitus. However, metabolic studies in lean, non-diabetic women have generally found no effect on glucose concentrations, suggesting that obesity or weight gain associated with injectable progestogen-only contraceptive use may play a role.[11]

1. Crook D, Godsland I. Safety evaluation of modern oral contraceptives: effects on lipoprotein and carbohydrate metabolism. *Contraception* 1998; **57:** 189–201.
2. Hurel SJ, Taylor R. Drugs and glucose tolerance. *Adverse Drug React Bull* 1995; (Oct.): 659–62.
3. Godsland IF, *et al.* Insulin resistance, secretion, and metabolism in users of oral contraceptives. *J Clin Endocrinol Metab* 1992; **74:** 64–70.
4. Kim C, *et al.* Oral contraceptive use and association with glucose, insulin, and diabetes in young adult women: the CARDIA study. *Diabetes Care* 2002; **25:** 1027–32.
5. Troisi RJ, *et al.* Oral contraceptive use and glucose metabolism in a national sample of women in the United States. *Am J Obstet Gynecol* 2000; **183:** 389–95.
6. Knopp RH, *et al.* Comparison of the lipoprotein, carbohydrate, and hemostatic effects of phasic oral contraceptives containing desogestrel or levonorgestrel. *Contraception* 2001; **63:** 1–11.
7. Lopez LM, *et al.* Steroidal contraceptives: effect on carbohydrate metabolism in women without diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 14/01/08).
8. Rimm EB, *et al.* Oral contraceptive use and the risk of type 2 (non-insulin-dependent) diabetes mellitus in a large prospective study of women. *Diabetologia* 1992; **35:** 967–72.
9. Chasan-Taber L, *et al.* A prospective study of oral contraceptives and NIDDM among US women. *Diabetes Care* 1997; **20:** 330–5.
10. Kjos SL, *et al.* Contraception and the risk of type 2 diabetes mellitus in Latina women with prior gestational diabetes mellitus. *JAMA* 1998; **280:** 533–8.
11. Kahn HS, *et al.* Effects of injectable or implantable progestin-only contraceptives on insulin-glucose metabolism and diabetes risk. *Diabetes Care* 2003; **26:** 216–25.

Effects on the cardiovascular system. Soon after their introduction in the 1960s it became apparent that **combined oral contraceptives** were associated with an increased risk of cardiovascular effects including *hypertension, venous thromboembolism, myocardial infarction,* and *stroke*. Consequently, there are a number of contra-indications and precautions relating to their use in women with risk factors for cardiovascular disease (see under Precautions, below).

Changing patterns of use, and a progressive reduction in doses, have meant a continued need to evaluate the risks associated with oral contraceptives.

Current use of lower-dose combined oral contraceptives (less than 50 micrograms oestrogen) increases blood pressure in many women, and also results in a small but significant increased risk of venous thromboembolism. Any increased risk of myocardial infarction and stroke is low in women aged less than 35 years who do not smoke and who do not have pre-existing hypertension. Further details of these adverse effects are covered in the sections below.

The effect of progestogens on the cardiovascular risk profile of oral contraceptives has not been established. Some of the newer progestogens have been reported to have more favourable effects on plasma lipids (see Effects on Lipids, below) and there is some suggestion that they may have a lower risk of myocardial infarction, but there are insufficient data to confirm or refute this. However, it has been reported that desogestrel and gestodene are associated with a higher risk of venous thromboembolism than older progestogens.

The Nurses' Health Study found no association between ever having used oral contraceptives and death from cardiovascular disease.[1] The Royal College of General Practitioners' study reported an increase in death from cerebrovascular disease with current or recent (within 10 years) use of oral contraceptives, but not for past use (greater than 10 years).[2]

Some general reviews are cited below.[3-7]

1. Colditz GA, *et al.* Oral contraceptive use and mortality during 12 years of follow-up: the Nurses' Health Study. *Ann Intern Med* 1994; **120:** 821–6.
2. Beral V, *et al.* Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study. *BMJ* 1999; **318:** 96–100.
3. WHO. WHO Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraceptive: summary of conclusions. *Wkly Epidem Rec* 1997; **72:** 361–3.
4. Chasan-Taber L, Stampfer MJ. Epidemiology of oral contraceptives and cardiovascular disease. *Ann Intern Med* 1998; **128:** 467–77.
5. WHO. Cardiovascular disease and steroid hormone contraception. *WHO Tech Rep Ser 877* 1998. Also available at: http://libdoc.who.int/trs/WHO_TRS_877.pdf (accessed 14/01/08)
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HYPERTENSION. In a one-year prospective multicentre study[1] involving 704 women under the age of 35 using a **combined oral contraceptive** containing levonorgestrel 250 micrograms and ethinylestradiol 50 micrograms and 703 women using a non-hormonal intra-uterine contraceptive device, those using the oral contraceptive developed higher systolic and diastolic blood pressures (systolic pressures were 3.6 to 5.0 mmHg higher, diastolic pressures were 1.9 to 2.7 mmHg higher). Only 4 women receiving oral contraceptives developed hypertension. A similar increase in blood pressure was noted in a study[2] involving 222 users of combined oral contraceptives containing 30 micrograms ethinylestradiol. There was a greater increase in blood pressure for those preparations containing 250 micrograms levonorgestrel than those containing 150 micrograms levonorgestrel.

More recently, data from the Nurses' Health Study[3] showed an increased risk (relative risk 1.8) for the development of hypertension in women taking lower-dose combined oral contraceptives. Increasing doses of progestogen were positively associated with hypertension, and the lowest risk occurred in women receiving triphasic preparations, which have the lowest total dose of progestogen. A UK study[4] found a small increase in blood pressure of 2.3/1.6 mmHg associated with the use of combined oral contraceptives. In this study, oral **progestogen-only contraceptives** were not associated with an increase in blood pressure. A more recent review[5] also found no evidence that use of progestogen-only contraception for up to 2 to 3 years was associated with high blood pressure. Similarly, depot medroxyprogesterone acetate does not raise blood pressure.[6]

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MYOCARDIAL INFARCTION. Case-control studies from the 1970s and early 1980s revealed an increased risk of acute myocardial infarction in users of oral contraceptives (generally of the high-dose type) relative to those never having used them.[1,2] Several large cohort studies have provided similar findings.[3-6] Among current users the reported[1-3,5,6] relative risk of myocardial infarction has varied between about 1.8 and 6.4, whereas in women having used oral contraceptives in the past the reported[2-5] relative risk has varied between about 0.8 and 2.5. Women who *smoke* while using oral contraceptives are at a greatly increased risk,[1,5,7] those smoking more than 15 to 25 cigarettes daily having at least a twentyfold increased risk of myocardial infarction compared with non-smoking non-oral contraceptive users.[1,5]

These studies have principally been from the USA or the UK. The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception has reported the findings of an international multicentre case-control study.[8] The overall odds ratio for acute myocardial infarction in current users of combined oral contraceptives was 5.01 in Europe and 4.78 in Africa, Asia, and Latin America. This increase in risk reflected use in women who had coexistent risk factors such as smoking, and who had not had their blood pressure checked before use. Thus, when the background incidence of acute myocardial infarction is taken into account, use of combined oral contraceptives in non-smoking women aged less than 35 years is associated with an excess of 3 per million women-years, and this is likely to be lower in those women who have their blood pressure screened before and during use. However, in older women who smoke, the excess risk associated with the use of combined oral contraceptives is substantial (400 per million women-years). There was no increase in risk associated with past use of oral contraceptives irrespective of duration of use.

There has been interest in the effect of different progestogen components on the risk of myocardial infarction. Limited data from the WHO study[8] and from the USA[9] and the UK[10] suggested no difference in risk between desogestrel or gestodene compared with levonorgestrel. Analysis of European data[11] suggested a reduction in risk with gestodene- and desogestrel-containing products compared with other progestogens (0.28; 95% confidence intervals 0.09 to 0.86). A WHO Scientific Group meeting concluded that available data did not allow the conclusion that risk of myocardial infarction was related to progestogen type.[12]

More recently, data on combined oral contraceptives that have lower oestrogen doses have revealed at most small and non-significant increases in risk of acute myocardial infarction associated with oral contraceptive use,[10,13-15] although case-control studies have suggested that again, there may be a greatly increased risk in women who smoke more than 20 to 25 cigarettes daily.[10,16] However, subsequent meta-analyses including these and other studies have concluded that, overall, there was an increased risk of myocardial infarction with current use of low-dose combined oral contraceptives (oestrogen less than 50 micrograms). Subgroup analyses of progestogen type found that there was an increased risk in users of second generation contraceptives (generally containing levonorgestrel) compared with non-users; calculated odds ratios were 2.18 (1.62 to 2.94),[17] 2.17 (1.76 to 2.69),[18] and 1.85 (1.03 to 3.32).[19] However, the risk was not increased in users of third generation contraceptives (generally containing desogestrel or gestodene) compared with non-users.[17-19] Clinically, although the risk of myocardial infarction may be increased, the absolute risk is very low in healthy young women who do not smoke and do not have cardiovascular risk factors. Despite reassuring data for these newer progestogens regarding the risk of myocardial infarction, there is probably a small increased risk of venous thromboembolism associated with desogestrel or gestodene (see below).

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2. Slone D, *et al.* Risk of myocardial infarction in relation to current and discontinued use of oral contraceptives. *N Engl J Med* 1981; **305:** 420–4.
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11. Lewis MA, *et al.* The use of oral contraceptives and the occurrence of acute myocardial infarction in young women: results from the transnational study on oral contraceptives and the health of young women. *Contraception* 1997; **56:** 129–40.
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19. Baillargeon J-P, *et al.* Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. *J Clin Endocrinol Metab* 2005; **90:** 3863–70.

STROKE. Current use of **combined oral contraceptives** has been associated with an increased risk of stroke, with most data relating to older high-dose oestrogen preparations. In general this association has been strongest for ischaemic stroke, and relatively weak for haemorrhagic stroke.[1] A Danish study found that low-dose oral contraceptives (30 to 40 micrograms of oestrogen) were associated with a lower risk of cerebral thromboembolism than preparations containing 50 micrograms oestrogen.[2]

Data on 2198 cases of stroke (haemorrhagic, ischaemic, and unclassified) and 6086 controls have been reported from the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception.[3,4] For all strokes combined, odds ratios for the current use of lower-dose (less than 50 micrograms oestrogen) and higher-dose preparations were, respectively, 1.41 (95% confidence intervals 0.90 to 2.20) and 2.71 (1.70 to 4.32) in Europe, and 1.86 (1.49 to 2.33) and 1.92 (1.48 to 2.50) in Africa, Asia, and Latin America. In Europe, it was estimated that the

incidence rate of stroke in women aged 20 to 44 years was 4.8 per 100 000 women-years, and that this was increased to 6.7 per 100 000 in users of lower-dose preparations and 12.9 per 100 000 in users of higher-dose preparations.[3]

The risk of haemorrhagic stroke was significant only in women aged greater than 35 years, those who had a history of hypertension, and those who were current smokers.[3]

The overall odds ratio for ischaemic stroke was 2.99 (1.65 to 5.40) in Europe and 2.93 (2.15 to 4.00) in Africa, Asia, and Latin America.[4] Odds ratios were lower in women aged less than 35 years, those who did not smoke, those with no history of hypertension, and those who reported that their blood pressure had been checked before use. Duration of current use and past use were unrelated to risk.[4] A similar overall odds ratio of 2.3 (1.15 to 4.59) has been reported from the UK.[5] Similar findings have also been published from the USA.[6] Low-dose preparations (less than 50 micrograms oestrogen) were associated with a non-significant increase in ischaemic stroke; the odds ratio was 1.18 (0.54 to 2.59); a later meta-analysis considered the association between low-dose combined oral contraceptives and stroke to be tenuous at best, and possibly non-existent.[7]

A meta-analysis[8] of studies of ischaemic stroke found that there was an overall increased risk associated with the current use of oral contraceptives. However, the risk was less elevated with lower oestrogen doses, and in studies that controlled for smoking and hypertension.

As regards the effect of the type of progestogen on risk of stroke, one case-control study[9] reported that there was no significant difference in risk of ischaemic stroke between low-dose oral contraceptives containing second generation progestogens and those containing desogestrel, gestodene, or norgestimate. However, another study[10,11] found that levonorgestrel- or norgestimate-containing preparations were associated with a higher risk of cerebral thrombosis than preparations containing desogestrel or gestodene. A re-analysis of the WHO data led to the cautious conclusion that the risk for stroke between second and third generation progestogens was similar,[12] and this was also supported by analysis of the General Practice Research Database[13] and a Dutch case-control study.[14] Meta-analyses[8,15] also found no significant difference between progestogen generations in the risk of ischaemic stroke.

Data for **progestogen-only contraceptives** are limited. The Danish study reported no increase in cerebral thromboembolic attacks in users of oral progestogen-only contraceptives; the odds ratio was 0.9 (0.4 to 2.4).[2]

1. Vessey MP, *et al*. Oral contraceptives and stroke: findings in a large prospective study. *BMJ* 1984; **289:** 530–1.
2. Lidegaard Ø. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. *BMJ* 1993; **306:** 956–63.
3. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet* 1996; **348:** 505–10.
4. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet* 1996; **348:** 498–505.
5. Nightingale AL, Farmer RDT. Ischemic stroke in young women: a nested case-control study using the UK General Practice Research Database. *Stroke* 2004; **35:** 1574–8.
6. Petitti DB, *et al*. Stroke in users of low-dose oral contraceptives. *N Engl J Med* 1996; **335:** 8–15.
7. Chan W-S, *et al*. Risk of stroke in women exposed to low-dose oral contraceptives: a critical evaluation of the evidence. *Arch Intern Med* 2004; **164:** 741–7.
8. Gillum LA, *et al*. Ischemic stroke risk with oral contraceptives: a meta-analysis. *JAMA* 2000; **284:** 72–8.
9. Heinemann LAJ, *et al*. Case-control study of oral contraceptives and risk of thromboembolic stroke: results from international study on oral contraceptives and health of young women. *BMJ* 1997; **315:** 1502–4.
10. Lidegaard Ø, Kreiner S. Cerebral thrombosis and oral contraceptives: a case-control study. *Contraception* 1998; **57:** 303–14.
11. Lidegaard Ø, Kreiner S. Contraceptives and cerebral thrombosis: a five-year national case-control study. *Contraception* 2002; **65:** 197–205.
12. Poulter NR, *et al*. Effect on stroke of different progestagens in low oestrogen dose oral contraceptives. *Lancet* 1999; **354:** 301–2.
13. Jick SS, *et al*. Risk of idiopathic cerebral haemorrhage in women on oral contraceptives with differing progestagen components. *Lancet* 1999; **354:** 302–3.
14. Kemmeren JM, *et al*. Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. *Stroke* 2002; **33:** 1202–8.
15. Baillargeon J-P, *et al*. Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. *J Clin Endocrinol Metab* 2005; **90:** 3863–70.

VENOUS THROMBOEMBOLISM. Use of **combined oral contraceptives** has long been known to be associated with an increased risk of venous thromboembolic events, particularly deep-vein thrombosis and pulmonary embolism. This increased risk applies both to idiopathic events and events associated with surgery or trauma, is limited to current users and is probably highest in the first year of use. Most early data relate to high-dose combined preparations, and it has been suggested by some studies,[1] but not others,[2,3] that preparations containing lower doses of oestrogen may be associated with a lower risk. More recently, reports have identified an increased risk of cerebral-vein thrombosis with oral contraceptives.[4]

The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception reported data from over 10 times more cases than any previous study.[5] The increased risk of idiopathic deep-vein thrombosis and/or pulmonary embolism associated with current use of combined oral contraceptives was 4.15 (95% confidence intervals 3.09 to 5.57) in Europe and 3.25 (2.59 to 4.08) in Africa, Asia, and Latin America. The increased risk was apparent within 4 months of starting use, was unaffected by duration of use, and had disappeared within 3 months of stopping use. Risk was unaffected by age, hypertension, or smoking (in contrast to myocardial infarction, see above), but was increased in those with a body-mass index greater than 25 kg/m^2 and in those with a history of hypertension of pregnancy. Of preparations containing progestogens of the norethisterone or norgestrel type, risk was non-significantly less with lower-dose oestrogen than with high-dose oestrogen.

The progestogen component has generally been considered to be unrelated to thromboembolic events; therefore, it came as a surprise when WHO found a higher risk in combined oral contraceptives containing *desogestrel* or *gestodene* than in those containing older progestogens.[5] These risk data were the subject of a separate report,[6] and were subsequently confirmed by 3 further case-control studies.[7-9] The increased risk varied from 4.8 to 9.1 compared with non-users, and was found to be 1.5 to 2.6 times higher than for preparations containing levonorgestrel or other progestogens. The incidence of venous thromboembolic disease has been estimated to be 25 per 100 000 users per year for desogestrel- and gestodene-containing products and 15 per 100 000 users per year for products containing low-dose oestrogen with other progestogens, compared with 5 per 100 000 per year for non-users. The risk was especially high in women with the factor V Leiden mutation,[8] who are at increased risk of thrombosis, but screening to exclude these women from using oral contraceptives was not considered necessary.[10,11] Despite much debate about possible bias and confounding in these results,[12,13] and the ambiguous or contradictory results of subsequent studies,[14-16] many sources seem now to agree with the 1997 conclusion of a WHO scientific group meeting[17] that there is a modestly increased risk of venous thromboembolism associated with the use of products containing desogestrel or gestodene, compared with levonorgestrel. The extent of any risk associated with combined products containing *drospirenone* has also been questioned. Data from a prescription event monitoring study suggested that it was associated with a high incidence of deep-vein thrombosis and pulmonary embolism,[18] but the authors acknowledged potential bias that may have affected the result. Subsequent large cohort studies[19,20] reported that the risk of venous thromboembolism was similar to that for users of other combined oral contraceptives, including levonorgestrel-containing preparations. It is unclear to what extent products containing *cyproterone* are associated with increased risk (see Effects on the Cardiovascular System, under Cyproterone Acetate, p.2088).

Regulatory agencies have reacted in different ways to these data. The UK CSM has advised caution in prescribing of these products (see Cardiovascular Disease under Precautions, below), as have some other European authorities.

The mechanism behind differences in thrombotic potential is not known, but there is evidence that oral contraceptives may increase concentrations of prothrombin and factor VIII, and induce a resistance to the blood's natural anticoagulation system.[11] These effects may be greater with products containing desogestrel and gestodene compared with older progestogens.[11] Thrombophilias, including factor V Leiden, further increase the risk of thromboembolism from hormonal contraceptives.[21]

There has also been some concern about a possible increase in cardiovascular risk with a **transdermal patch** that releases ethinylestradiol and norelgestromin, because users are exposed to about 60% more total oestrogen than users of an oral contraceptive containing ethinylestradiol 35 micrograms (peak serum concentrations are lower but steady-state concentrations are higher). However, 2 studies comparing the patch with a combined oral contraceptive (ethinylestradiol plus norgestimate) came to different conclusions; one found the risk of venous thromboembolism to be similar,[22] while the other found a twofold increase in risk with the patch.[23] Further study is needed to explain this discrepancy, and to determine whether there is any effect on the risks of myocardial infarction and stroke.

1. Vessey M, *et al*. Oral contraceptives and venous thromboembolism: findings in a large prospective study. *BMJ* 1986; **292:** 526.
2. Kierkegaard A. Deep vein thrombosis and the oestrogen content in oral contraceptives—an epidemiological analysis. *Contraception* 1985; **31:** 29–41.
3. Helmrich SP, *et al*. Venous thromboembolism in relation to oral contraceptive use. *Obstet Gynecol* 1987; **69:** 91–5.
4. Dentali F, *et al*. Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a meta-analysis. *Blood* 2006; **107:** 2766–73.
5. WHO Collaborative Study Group. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet* 1995; **346:** 1575–82.
6. WHO Collaborative Study Group. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease. *Lancet* 1995; **346:** 1582–8.
7. Jick H, *et al*. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995; **346:** 1589–93.
8. Bloemenkamp KWM, *et al*. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. *Lancet* 1995; **346:** 1593–6.
9. Spitzer WO, *et al*. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. *BMJ* 1996; **312:** 83–8.
10. Vandenbroucke JP, *et al*. Factor V Leiden: should we screen oral contraceptive users and pregnant women? *BMJ* 1996; **313:** 1127–30.
11. Vandenbroucke JP, *et al*. Oral contraceptives and the risk of venous thrombosis. *N Engl J Med* 2001; **344:** 1527–35.
12. Lewis MA, *et al*. The increased risk of venous thromboembolism and the use of third generation progestagens: role of bias in observational research. *Contraception* 1996; **54:** 5–13.
13. Farley TMM, *et al*. Oral contraceptives and thrombotic diseases: impact of new epidemiologic studies. *Contraception* 1996; **54:** 193–5.
14. Farmer RDT, *et al*. Population-based study of risk of venous thromboembolism associated with various oral contraceptives. *Lancet* 1997; **349:** 83–8.
15. Farmer RDT, *et al*. Effect of 1995 pill scare on rates of venous thromboembolism among women taking combined oral contraceptives: analysis of General Practice Research Database. *BMJ* 2000; **321:** 477–9.
16. Jick H, *et al*. Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort and case-control analysis. *BMJ* 2000; **321:** 1190–5. Correction. *ibid*. 2001; **322:** 28.
17. WHO. WHO Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraceptives: summary of conclusions. *Wkly Epidem Rec* 1997; **72:** 361–3.
18. Pearce HM, *et al*. Deep vein thrombosis and pulmonary embolism reported in the Prescription Event Monitoring Study of Yasmin . *Br J Clin Pharmacol* 2005; **60:** 98–102.
19. Dinger JC, *et al*. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on Oral Contraceptives based on 142,475 women-years of observation. *Contraception* 2007; **75:** 344–54.
20. Seeger JD, *et al*. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol* 2007; **110:** 587–93.
21. Wu O, *et al*. Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. *Thromb Haemost* 2005; **94:** 17–25.
22. Jick SS, *et al*. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 µg of ethinyl estradiol. *Contraception* 2006; **73:** 223–8.
23. Cole JA, *et al*. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol* 2007; **109:** 339–46.

Effects on the ears. In the Royal College of General Practitioners' study of oral contraception in the UK,[1] by 1981 there had been 13 cases of newly occurring otosclerosis in each of the groups of oral contraceptive users (101 985 woman-years) and controls (146 534 woman-years); this showed a non-significant relative risk of 1.29. Although, by analogy with pregnancy, it may be prudent to suppose that oral contraceptives could exacerbate pre-existing otosclerosis, the data do not support the view that the condition is associated with their use. Similarly, the Oxford Family Planning Association contraceptive study[2] of 17 032 women followed for up to 26 years found no association between oral contraceptive use and the development of a range of ear diseases, including otosclerosis.

1. Kay CR, Wingrave SJ. Oral contraceptives and otosclerosis. *BMJ* 1984; **288:** 1164.
2. Vessey M, Painter R. Oral contraception and ear disease: findings in a large cohort study. *Contraception* 2001; **63:** 61–3.

Effects on the eyes. Analysis of data from 2 large UK cohort studies suggested that oral contraceptive use does not increase the risk of eye disease, with the possible exception of retinal vascular lesions.[1] Retinal vein thrombosis has also been reported after the use of emergency contraception.[2] The patient presented with a 10-day history of blurred vision that started the day after taking a regimen of ethinylestradiol with norgestrel; the condition resolved after 2 months of treatment with low-dose aspirin.

1. Vessey MP, *et al*. Oral contraception and eye disease: findings in two large cohort studies. *Br J Ophthalmol* 1998; **82:** 538–42.
2. Lake SR, Vernon SA. Emergency contraception and retinal vein thrombosis. *Br J Ophthalmol* 1999; **83:** 630–1.

Effects on fertility. After stopping hormonal contraceptives some patients may experience amenorrhoea, anovulation, and infertility. This infertility, however, has been shown by most studies to be only temporary.

Data from the Oxford Family Planning Association study[1] have indicated that impairment of fertility after oral contraceptives was only very slight and short-lived in women who had previously had a baby. In nulliparous women aged 25 to 29 years impairment of fertility was more pronounced but the effect had almost entirely disappeared after 48 months. In nulliparous women aged 30 to 34 years the duration of impairment was longer but, again, this was not permanent as by 72 months after stopping oral contraceptive use the numbers of women who had not conceived were similar to a group who had previously used non-hormonal methods of contraception. In contrast to women using intra-uter-

ine devices, in whom long-term use was associated with greater impairment of fertility than short-term (less than 42 months) use, there appears to be no association between fertility and duration of oral contraceptive use.[2] However, a later survey,[3] although concurring that the effects were transient, did find a relationship between duration of use of combined oral contraceptives and subsequent time to pregnancy.

Oral progestogen-only preparations do not appear to have a significant effect on fertility.[3] Smaller studies have also indicated that injectable progestogen-only contraceptives have no long-lasting effects on fertility;[3,4] but it has been suggested that a return to ovulation occurs significantly earlier in prior norethisterone enantate users than in medroxyprogesterone users.[5]

Infertility may also be related to the presence of pelvic inflammatory disease; for further details concerning the role of oral contraceptives in this disorder, see Pelvic Inflammatory Disease, below.

1. Anonymous. "Pill" use appears to impair fertility in a certain group of women. *Pharm J* 1986; **236:** 227.
2. Doll H, *et al.* Return of fertility in nulliparous women after discontinuation of the intrauterine device: comparison with women discontinuing other methods of contraception. *Br J Obstet Gynaecol* 2001; **108:** 304–14.
3. Hassan MAM, Killick SR. Is previous use of hormonal contraception associated with a detrimental effect on subsequent fecundity? *Hum Reprod* 2004; **19:** 344–51.
4. Fotherby K, *et al.* Return of ovulation and fertility in women using norethisterone enanthate. *Contraception* 1984; **29:** 447–55.
5. Garza-Flores J, *et al.* Return to ovulation following the use of long-acting injectable contraceptives: a comparative study. *Contraception* 1985; **31:** 361–6.

Effects on the gallbladder. Data from the Royal College of General Practitioners' (RCGP) oral contraception study accumulated up to December 1979 revealed no overall increased risk of gallbladder disease in the long-term, despite the indications of earlier data and other studies relating to short-term use.[1] Further studies[2,3] have identified an increased risk of gallbladder disease in oral contraceptive users under the age of 30 or 20, respectively. A systematic review[4] also found that oral contraceptives were associated with a slightly and transiently increased risk of gallbladder disease. However, the results of separate studies varied considerably and the reviewers highlighted a number of possible confounding factors and biases, nonetheless, it was concluded that newer low-dose contraceptives (less than 50 micrograms of oestrogen) were less likely to cause problems than older formulations. Later data from the RCGP study showed an increase in risk of mild hepatitis during the first 4 years of oral contraceptive use, possibly reflecting gallstone-associated cholestasis.[5] This risk then decreased to less than that seen in women who had never used oral contraceptives.

1. Wingrave SJ, Kay CR. Oral contraceptives and gallbladder disease: Royal College of General Practitioners' oral contraception study. *Lancet* 1982; **ii:** 957–9.
2. Scragg RKR, *et al.* Oral contraceptives, pregnancy, and endogenous oestrogen in gall stone disease—a case-control study. *BMJ* 1984; **288:** 1795–9.
3. Strom BL, *et al.* Oral contraceptives and other risk factors for gallbladder disease. *Clin Pharmacol Ther* 1986; **39:** 335–41.
4. Thijs C, Knipschild P. Oral contraceptives and the risk of gallbladder disease: a meta-analysis. *Am J Public Health* 1993; **83:** 1113–20.
5. Hannaford PC, *et al.* Combined oral contraceptives and liver disease. *Contraception* 1997; **55:** 145–51.

Effects on the gastrointestinal tract. Several studies,[1-3] epidemiological data,[4] and a meta-analysis,[5] have shown a weak association between oral contraceptive use and the onset of Crohn's disease or ulcerative colitis. However, the suggestion that oral contraceptives have an aetiological role in chronic inflammatory bowel disease cannot be regarded as established.

The rate of relapse of Crohn's disease in women taking oral contraceptives has also been studied. Although one study[6] reported an increased risk of relapse in women who had taken oral contraceptives in the past, both this study and another prospective cohort study[7] found no increase in risk in current users. These results may have been influenced by smoking, or changes in oestrogen dose and progestogen content.

Women with inflammatory bowel disease may be offered the same contraceptive choices as other women, although oral contraceptive absorption, and hence efficacy, may be reduced when there is small bowel involvement or malabsorption.[8]

1. Corrao G, *et al.* Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study. *Int J Epidemiol* 1998; **27:** 397–404.
2. Sicilia B, *et al.* Environmental risk factors and Crohn's disease: a population-based, case-control study in Spain. *Dig Liver Dis* 2001; **33:** 762–7.
3. García Rodríguez LA, *et al.* Risk factors for inflammatory bowel disease in the general population. *Aliment Pharmacol Ther* 2005; **22:** 309–15.
4. Alic M. Epidemiology supports oral contraceptives as a risk factor in Crohn's disease. *Gut* 2000; **46:** 140.
5. Godet PG, *et al.* Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease. *Gut* 1995; **37:** 668–73.
6. Timmer A, *et al.* Oral contraceptive use and smoking are risk factors for relapse in Crohn's disease. *Gastroenterology* 1998; **114:** 1143–50.
7. Cosnes J, *et al.* Oral contraceptive use and the clinical course of Crohn's disease: a prospective cohort study. *Gut* 1999; **45:** 218–22.
8. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC guidance (July 2003): contraceptive choices for women with inflammatory bowel disease. *J Fam Plann Reprod Health Care* 2003; **29:** 127–34. Also available at: http://www.ffprhc.org.uk/admin/uploads/IBD%20final%20pdf.pdf (accessed 15/01/08)

Effects on lipids. Combined oral contraceptives have been reported to be associated with an excess risk of various adverse cardiovascular events (see above). Because other epidemiological evidence suggests that the composition of blood lipids may be one of several factors involved in the aetiology of some of these disorders, many workers have investigated the biochemical profiles of women taking various formulations of oral contraceptives. Results have often been conflicting as the net effect is the result of opposing actions of the oestrogen and the progestogen components, and depends on the ratio between these. In general, the oestrogen component increases triglycerides, but decreases low-density lipoproteins, whereas the progestogen component tends to decrease high-density lipoproteins and increase low-density lipoproteins, particularly if it is androgenic (19-nortestosterone-derived progestogens). Newer non-androgenic progestogens such as desogestrel and gestodene appear to have a less detrimental effect on serum lipids. However, the contribution of these lipid changes to the incidence of cardiovascular disease in oral contraceptive users is uncertain. In particular, contrary to expectations, desogestrel and gestodene appear to be associated with a higher risk of venous thromboembolism than older progestogens (see above).

Some references to the effects of various oral contraceptives on serum lipid profiles are given below.[1-4]

For further details concerning the proposed role of the various serum lipids and subfractions in the aetiology of cardiovascular disease, see Hyperlipidaemias, p.1169.

For reports of pancreatitis secondary to hyperlipidaemia associated with the use of combined oral contraceptives, see below.

1. Crook D, Godsland I. Safety evaluation of modern oral contraceptives: effects on lipoprotein and carbohydrate metabolism. *Contraception* 1998; **57:** 189–201. Correction. *ibid.*: 420.
2. Knopp RH, *et al.* Comparison of the lipoprotein, carbohydrate, and hemostatic effects of phasic oral contraceptives containing desogestrel or levonorgestrel. *Contraception* 2001; **63:** 1–11.
3. Graff-Iversen S, Tonstad S. Use of progestogen-only contraceptives/medications and lipid parameters in women age 40 to 42 years: results of a population-based cross-sectional Norwegian Survey. *Contraception* 2002; **66:** 7–13.
4. Gaspard U, *et al.* A randomized study on the influence of oral contraceptives containing ethinylestradiol combined with drospirenone or desogestrel on lipid and lipoprotein metabolism over a period of 13 cycles. *Contraception* 2004; **69:** 271–8.

Effects on the liver. The use of combined oral contraceptives has been rarely associated with the benign liver tumours, hepatic adenoma and focal nodular hyperplasia (see under Carcinogenicity, above).

Hepatitis possibly associated with gallstones has also been reported (see Effects on the Gallbladder, above).

Effects on mental state. Changes in mood and affect have been reported with oral contraceptives, and the onset of depression is a common reason given for stopping use. Nonetheless, a review[1] concluded that most women taking oral contraceptives actually experienced beneficial effects, with less variability in affect across the menstrual cycle and less negative affect during the menstrual phase compared with non-users. However, there may be a subgroup of women predisposed to negative changes in mood and affect because of factors such as a history of depression, premenstrual mood symptoms before oral contraceptive use, a history of mood symptoms related to pregnancy, or a family history of mood complaints related to oral contraceptives. A lower ratio of progestogen to oestrogen was associated with more negative mood changes in women with a history of premenstrual emotional symptoms, while a higher ratio was associated with negative changes in women without such a history. In addition, monophasic regimens appeared to have a greater stabilising effect than triphasic preparations. A number of possible mechanisms have been suggested to explain how combined hormonal contraceptives might influence mood.[2]

Cohort studies of injectable[3] and implantable[4] progestogen-only contraceptives found no overall change in depressive symptom score. A small increase in depressive score noted at the 2-year follow-up of implant users was found to occur in women who also had a decrease in relationship satisfaction, which the authors concluded was independent of contraceptive use. Another study[5] found an association between injectable medroxyprogesterone acetate and depressive symptoms, but other factors that might have influenced this result were also identified and another explanation could not be ruled out.

1. Oinonen KA, Mazmanian D. To what extent do oral contraceptives influence mood and affect? *J Affect Disord* 2002; **70:** 229–40.
2. Kurshan N, Epperson CN. Oral contraceptives and mood in women with and without premenstrual dysphoria: a theoretical model. *Arch Womens Ment Health* 2006; **9:** 1–14.
3. Westhoff C, *et al.* Depressive symptoms and Depo-Provera . *Contraception* 1998; **57:** 237–40.
4. Westhoff C, *et al.* Depressive symptoms and Norplant contraceptive implants. *Contraception* 1998; **57:** 241–5.
5. Civic D, *et al.* Depressive symptoms in users and non-users of depot medroxyprogesterone acetate. *Contraception* 2000; **61:** 385–90.

Effects on the musculoskeletal system. ***BONE DENSITY.*** Combined oral contraceptives are generally considered not to have a detrimental effect on bone mineral density but study results have been inconsistent and any clinical significance unclear. However, overall, combined oral contraceptives appear not to affect bone mineral density or biochemical markers of bone turnover.[1]

Reviews of studies in different age groups have found that bone mineral density in healthy premenopausal women does not appear to be significantly affected.[2,3] However, there is limited evidence that adolescents and young women (less than 23 years of age) using oral combined contraceptives have a lower bone mineral density than non-users; it is unclear whether contraceptives might prevent young women from reaching their peak bone mass and put them at increased risk of osteoporosis later in life.[3] There is some evidence of a positive effect on bone mineral density in perimenopausal[2,3] and postmenopausal women[3] taking combined oral contraceptives, but past use in postmenopausal women appeared to have no effect. Although bone mineral density is used as an indicator of fracture risk, the true effects of combined oral contraceptives on this clinical outcome are unclear;[1] there is a particular lack of data in older women, in whom osteoporotic fractures are most common.[3]

There is stronger evidence that bone mineral density is reduced in current users of the depot progestogen-only contraceptive, medroxyprogesterone acetate. Recovery occurs after stopping treatment,[4,5] but it is still unclear whether adult women can regain baseline bone mineral density levels, and whether adolescents can reach peak bone mass.[4] There is also a lack of data on the clinical outcome of fracture in both current and former users of all ages.[1,4]

As adolescence is an age at which bone mineral density is normally increasing there is some concern about the possible long-term effects of medroxyprogesterone. The UK CSM has advised that in adolescents it should only be used if other methods of contraception are unsuitable or unacceptable, and that there should be a re-evaluation of risks and benefits for women of all ages who wish to continue use beyond 2 years.[6] The FDA has also advised[7] that, for all women, medroxyprogesterone should only be used as a long-term contraceptive, giving an example of more than 2 years, if other contraceptive methods are inadequate. In contrast, however, WHO[8] advises that there should be no restriction, including duration of use, on the use of medroxyprogesterone in women aged 18 to 45 who are otherwise eligible to use it; in adolescents and women over 45, the advantages generally outweigh the theoretical risks of fracture, but because of limited data on long-term use the overall risks and benefits should be reconsidered over time with the individual user. Others[9] offer similar recommendations in support, pointing out that further research is needed.

There is some evidence that oestrogen supplementation may reduce or prevent the reduction in bone mineral density caused by medroxyprogesterone acetate.[10,11] Although such supplementation could be considered in medroxyprogesterone users who have osteopenia or are at high risk, the optimal dose, route, and extent of benefit has not been established.[9]

1. Lopez LM, *et al.* Steroidal contraceptives: effect on bone fractures in women. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 14/01/08).
2. Liu SL, Lebrun CM. Effect of oral contraceptives and hormone replacement therapy on bone mineral density in premenopausal and perimenopausal women: a systematic review. *Br J Sports Med* 2006; **40:** 11–24.
3. Martins SL, *et al.* Combined hormonal contraception and bone health: a systematic review. *Contraception* 2006; **73:** 445–69.
4. Curtis KM, Martins SL. Progestogen-only contraception and bone mineral density: a systematic review. *Contraception* 2006; **73:** 470–87.
5. Kaunitz AM, *et al.* Bone mineral density in women aged 25-35 years receiving depot medroxyprogesterone acetate: recovery following discontinuation. *Contraception* 2006; **74:** 90–9.
6. MHRA. Updated prescribing advice on the effect of Depo-Provera contraception on bones. Message from Professor G Duff, Chairman of CSM (issued 16th November, 2004). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=con019478&RevisionSelectionMethod=Latest (accessed 14/01/08)
7. FDA. Black box warning added concerning long-term use of Depo-Provera contraceptive injection (issued November 17, 2004). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01325.html (accessed 14/01/08)
8. WHO. WHO statement on hormonal contraception and bone health (issued July 2005). Available at: http://www.who.int/reproductive-health/family_planning/docs/hormonal_contraception_bone_health.pdf (accessed 14/01/08)
9. Cromer BA, *et al.* Depot medroxyprogesterone acetate and bone mineral density in adolescents—the Black Box Warning: a Position Paper of the Society for Adolescent Medicine. *J Adolesc Health* 2006; **39:** 296–301.
10. Cundy T, *et al.* A randomized controlled trial of estrogen replacement therapy in long-term users of depot medroxyprogesterone acetate. *J Clin Endocrinol Metab* 2003; **88:** 78–81.
11. Cromer BA, *et al.* Double-blinded randomized controlled trial of estrogen supplementation in adolescent girls who receive depot medroxyprogesterone acetate for contraception. *Am J Obstet Gynecol* 2005; **192:** 42–7.

RHEUMATOID ARTHRITIS. There have been rare reports of arthritis or arthropathies attributed to oral contraceptives, and some large studies have investigated the incidence of rheumatoid arthritis in oral contraceptive users. A negative association between the use of oral contraceptives and the development of rheumatoid arthritis has been reported in some studies thus giving rise to the suggestion that oral contraceptive use may, in fact, have some sort of protective role. These findings were not, however, substantiated by a recent, large, long-term cohort study[1] which found no association, either beneficial or detrimental, between the use of oral contraceptives and the later development of rheumatoid arthritis. An earlier meta-analysis also found no conclusive evidence of a protective effect of oral contraceptives on rheumatoid arthritis risk.[2] There is limited information about the effect of oral contraceptives on pre-existing rheumatoid arthritis. One study[3] found that there was no significant influence on the progression of the disease, but there was a trend towards less radiographic joint damage and disability with long-term oral contraceptive use.

1. Karlson EW, *et al.* Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. *Arthritis Rheum* 2004; **50:** 3458–67.
2. Pladevall-Vila M, *et al.* Controversy of oral contraceptives and risk of rheumatoid arthritis: meta-analysis of conflicting studies and review of conflicting meta-analyses with special emphasis on analysis of heterogeneity. *Am J Epidemiol* 1996; **144:** 1–14.
3. Drossaers-Bakker KW, *et al.* Pregnancy and oral contraceptive use do not significantly influence outcome in long term rheumatoid arthritis. *Ann Rheum Dis* 2002; **61:** 405–8.

Effects on the nervous system. *Headache* is reported as a common adverse effect and frequent reason for stopping combined oral contraceptives. However, a systematic review[1] found that although study results could not be pooled, there was no strong evidence associating combined oral contraceptive use with headache. There may have been an increase in headache in the early cycles, but this tended to improve with continued use; for most women there was no effect on headache activity and some actually reported improvement. Headache also appeared to be associated with oestrogen withdrawal during the tablet-free week of the cycle, but there was no evidence that headache was improved by changing to a preparation with a lower dose of oestrogen. However, some women appeared to be at higher risk, such as those with a strong personal or family history of troublesome headaches, particularly migraine. Combined oral contraceptives are not contra-indicated in women with non-migrainous headache, but they should be used with caution or avoided in women with migraine because of the increased risk of stroke (see Migraine, under Precautions, below).

Chorea has been reported in women using combined oral contraceptives. Reviews of the literature have reported the onset of chorea to range from 1 week to 11 months,[2] with an average of 3 months,[3] and resolution of symptoms after stopping the contraceptive to occur after 1 week to 5 months[2] or an average of 5 weeks.[3] The mechanism of this effect is unclear. Some cases occurred in patients with no history of neurological disease,[2,3] but others had a history of rheumatic fever, often with Sydenham chorea, or chorea gravidarum, chorea secondary to other conditions, or congenital heart disease.[3] There is some evidence that chorea could be mediated by the production of antiphospholipid antibodies, as either a primary antiphospholipid syndrome or secondary to SLE.[4,5] It has been suggested that the production of these antibodies could be aggravated by the oestrogen component of combined oral contraceptives.[4] In another case report[6] it was suggested that the presence of anti-basal ganglia antibodies might have played a role in the development of chorea by making the basal ganglia more susceptible to the effects of the oestrogen component of an oral contraceptive.

It is generally advised that combined oral contraceptives should be used with caution or avoided in women with antiphospholipid antibodies because they are at increased risk of venous thromboembolism, see Cardiovascular Disease, under Precautions, below.

1. Loder EW, *et al.* Headache as a side effect of combination estrogen-progestin oral contraceptives: a systematic review. *Am J Obstet Gynecol* 2005; **193:** 636–49.
2. Wadlington WB, *et al.* Chorea associated with the use of oral contraceptives: report of a case and review of the literature. *Clin Pediatr (Phila)* 1981; **20:** 804–6.
3. Galimberti D. Chorea induced by the use of oral contraceptives: report of a case and review of the literature. *Ital J Neurol Sci* 1987; **8:** 383–6.
4. Omdal R, Roalsø S. Chorea gravidarum and chorea associated with oral contraceptives—diseases due to antiphospholipid antibodies? *Acta Neurol Scand* 1992; **86:** 219–20.
5. Cervera R, *et al.* Chorea in the antiphospholipid syndrome: clinical, radiologic, and immunologic characteristics of 50 patients from our clinics and the recent literature. *Medicine (Baltimore)* 1997; **76:** 203–12.
6. Miranda M, *et al.* Oral contraceptive induced chorea: another condition associated with anti-basal ganglia antibodies. *J Neurol Neurosurg Psychiatry* 2004; **75:** 327–8.

Effects on the pancreas. There have been reports of pancreatitis secondary to hyperlipidaemia associated with the use of combined oral contraceptives.[1,2]

1. Parker WA. Estrogen-induced pancreatitis. *Clin Pharm* 1983; **2:** 75–9.
2. Stuyt PMJ, *et al.* Pancreatitis induced by oestrogen in a patient with type I hyperlipoproteinaemia. *BMJ* 1986; **293:** 734.

Effects on the skin. Oral contraceptives may cause chloasma, and those containing androgenic progestogens may cause or aggravate acne and hirsutism. More rarely, oral contraceptives have been implicated in photosensitivity reactions[1] and photosensitivity associated with drug-induced lupus erythematosus.[2] A survey of people using UVA sunbeds at commercial premises in the UK revealed that the prevalence of pruritus, nausea, and skin rashes as adverse reactions to sunbed use was higher in women taking oral contraceptives than in women receiving no medication.[3] There has been a report of hidradenitis suppurativa, a condition resulting in the recurrence of boils at the axillary apocrine sweat glands, anogenital region, and breasts, occurring in 7 women using oral contraceptives.[4] Sweet's syndrome (acute febrile neutrophilic dermatosis) has been described very rarely with hormonal contraceptives. In one case,[5] the reaction started 10 days after beginning a combined oral contraceptive and resolved after stopping the contraceptive and treating with oral and topical corticosteroids. The woman reported that a similar reaction had occurred 6 months earlier with a different combined oral contraceptive. Sweet's syndrome has also occurred 1 month after insertion of a levonorgestrel IUD; the condition was controlled with corticosteroids, but only resolved completely after removal of the IUD.[6]

For mention of the refuted association between oral contraceptives and malignant melanoma, see Skin under Carcinogenicity above. Auto-immune progesterone dermatitis has been reported in women with a history of oral contraceptive use (see p.2125).

1. Cooper SM, George S. Photosensitivity reaction associated with use of the combined oral contraceptive. *Br J Dermatol* 2001; **144:** 641–2.
2. Smith AG. Drug-induced photosensitivity. *Adverse Drug React Bull* 1989; (Jun.): 508–11.
3. Diffey BL. Use of UV-A sunbeds for cosmetic tanning. *Br J Dermatol* 1986; **115:** 67–76.
4. Stellon AJ, Wakeling M. Hidradenitis suppurativa associated with use of oral contraceptives. *BMJ* 1989; **298:** 28–9.
5. Sáez M, *et al.* Sweet's syndrome induced by oral contraceptive. *Dermatology* 2002; **204:** 84.
6. Hamill M, *et al.* Sweet's syndrome and a Mirena intrauterine system. *J Fam Plann Reprod Health Care* 2004; **30:** 115–16.

Effects on the uterus. The Oxford Family Planning Association study found that the risk of developing uterine leiomyomas (uterine fibroids) was reduced by the use of oral contraceptives[1] by about 17% with each 5 years of oral contraceptive use. This was not thought to be due to selective prescribing.[2,3] The authors hypothesised that unopposed oestrogen may be a risk factor for uterine fibroids, and that the reduced risk with oral contraceptives might be analogous to the reduction in endometrial carcinoma seen with these drugs (see above).[1] Other studies[4,5] have also reported a reduced risk of uterine leiomyomas in current users of oral contraceptives, while past users have a risk similar to that in women who have never used oral contraceptives. However, one study[4] did suggest that in women who had first used oral contraceptives at an early age (13 to 16 years) there was a modestly elevated risk. Another case-control study involving 390 women with leiomyomas failed to find a protective (or detrimental) effect with oral contraceptive use.[6] A further cohort study[7] also found no association between oral contraceptive use and leiomyoma formation, but did report a reduced risk with current use of medroxyprogesterone acetate depot injection.

1. Ross RK, *et al.* Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *BMJ* 1986; **293:** 359–62.
2. Ratner H. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *BMJ* 1986; **293:** 1027.
3. Ross RK, *et al.* Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *BMJ* 1986; **293:** 1027.
4. Marshall LM, *et al.* A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. *Fertil Steril* 1998; **70:** 432–9.
5. Chiaffarino F, *et al.* Use of oral contraceptives and uterine fibroids: results from a case-control study. *Br J Obstet Gynaecol* 1999; **106:** 857–60.
6. Parazzini F, *et al.* Oral contraceptive use and risk of uterine fibroids. *Obstet Gynecol* 1992; **79:** 430–3.
7. Wise LA, *et al.* Reproductive factors, hormonal contraception, and risk of uterine leiomyomata in African-American women: a prospective study. *Am J Epidemiol* 2004; **159:** 113–23.

Pelvic inflammatory disease. It has been suggested that oral contraceptives protect against pelvic inflammatory disease. However, although oral contraceptives are thought to reduce the risk of developing acute pelvic inflammatory disease, higher rates of infection of the lower genital tract by *Chlamydia trachomatis*,[1] and, more tentatively, *Neisseria gonorrhoeae*,[2] have been reported. Other studies[3,4] have suggested that oral contraceptive use is associated with reduced symptom severity, but absence of symptoms is not the same as absence of disease: oral contraceptives might reduce the inflammatory reaction to infection, resulting in unrecognised disease and subsequent complications such as tubal infertility and ectopic pregnancy.[5] There is evidence that users of older oral contraceptives containing more than 50 micrograms of oestrogen may have been at increased risk of tubal infertility, particularly if first used before 20 years of age.[6] No increased risk, or an active decrease in risk (depending on age at first use) was reported for formulations containing 50 micrograms or less of oestrogen, which are now favoured.

The possible effects of depot medroxyprogesterone acetate have also been examined and one study[7] suggested that it was associated with an increase in cervical chlamydial and gonococcal infections. However, confounding factors in this study such as sexual practices, a history of infection, and the background pool of infectivity in sexual partners, have been highlighted[8,9] and cast doubt on a true causal relationship between medroxyprogesterone acetate and risk of infection.

1. Washington AE, *et al.* Oral contraceptives, Chlamydia trachomatis infection, and pelvic inflammatory disease: a word of caution about protection. *JAMA* 1985; **253:** 2246–50.
2. Louv WC, *et al.* Oral contraceptive use and the risk of chlamydial and gonococcal infections. *Am J Obstet Gynecol* 1989; **160:** 396–402.
3. Wølner-Hanssen P, *et al.* Decreased risk of symptomatic chlamydial pelvic inflammatory disease associated with oral contraceptive use. *JAMA* 1990; **263:** 54–9.
4. Ness RB, *et al.* Hormonal and barrier contraception and risk of upper genital tract disease in the PID Evaluation and Clinical Health (PEACH) study. *Am J Obstet Gynecol* 2001; **185:** 121–7.
5. Henry-Suchet J. Hormonal contraception and pelvic inflammatory disease. *Eur J Contracept Reprod Health Care* 1997; **2:** 263–7.
6. Cramer DW, *et al.* The relationship of tubal infertility to barrier method and oral contraceptive use. *JAMA* 1987; **257:** 2446–50.
7. Morrison CS, *et al.* Hormonal contraceptive use, cervical ectopy, and the acquisition of cervical infections. *Sex Transm Dis* 2004; **31:** 561–7.
8. Dayan L, Donovan B. Chlamydia, gonorrhoea, and injectable progesterone. *Lancet* 2004; **364:** 1387–8.
9. Warner P. Concerns regarding design, analysis, and interpretation of the Morrison study on hormonal contraceptive use and acquisition of cervical infections. *Sex Transm Dis* 2005; **32:** 644.

Precautions

Before hormonal contraceptives are given, the woman should undergo an appropriate medical examination and her medical history should be carefully evaluated. Regular examination is recommended during use. The contraceptive effectiveness of combined and progestogen-only preparations may be reduced during episodes of vomiting or diarrhoea and extra contraceptive measures may be necessary during and for 7 days after recovery. For precautions to be taken if a 'pill' is missed, see Uses and Administration, below.

Combined oral contraceptives are *contra-indicated* in women with markedly impaired liver function or cholestasis, the Dubin-Johnson or Rotor syndromes, hepatic adenoma, oestrogen-dependent neoplasms such as breast or endometrial cancer, cardiovascular disease (see also below) including previous or current thromboembolic disorders or high risk of them, and arterial disease or multiple risk factors for it, disorders of lipid metabolism, undiagnosed vaginal bleeding, possible pregnancy, or a history during pregnancy of pruritus or cholestatic jaundice, chorea, herpes gestationis, pemphigoid gestationis, or deteriorating otosclerosis. They are also contra-indicated in severe or focal migraine (or where there are other risk factors for cardiovascular disease) and should be used with caution in other forms of migraine (for further details, see below). They should be *given with caution* to women with a history of clinical depression, gallbladder disease, sickle-cell disease, or conditions influenced by fluid retention. Oral contraceptive absorption, and hence efficacy, may be reduced in women with inflammatory bowel disease when there is small bowel involvement or malabsorption. They should also be used with caution in those with varicose veins (and should be avoided where the restrictions outlined under Venous Thromboembolism apply, see Cardiovascular Disease, below). Where not actually contra-indicated, they should also be used with caution in those with a risk factor for cardiovascular disease such as diabetes mellitus, smoking, obesity, hypertension, or a family history of cardiovascular disorders (see also below). Current opinion is that low-dose combined oral contraceptives may be used in women over the age of 35 years provided they do not smoke and have no other risk factors for cardiovascular disease, but that they should be avoided over the age of 50 years. Use by those undergoing surgery or prolonged bed rest may increase the risk of thromboembolic episodes and it is generally recommended that combined oral contraceptives should be stopped 4 weeks before major elective surgery (but see also below). Combined oral contraceptives should not be used after recent evacuation of a hydatidiform mole until urine and plasma gonadotrophin concentrations have returned to normal. Contact lenses may irritate. The use of combined oral contraceptives may influence the results of certain laboratory tests including liv-

er, thyroid, adrenal, and renal-function tests, plasma concentrations of binding proteins and lipid/lipoprotein fractions, and fibrinolysis and coagulation parameters.

Combined oral contraceptives should be *stopped immediately*, and appropriate investigations and treatment carried out, if any of the following occur:

- sudden severe chest pain, sudden breathlessness, or severe pain/swelling in calf of one leg (possibly indicative of thromboembolic complications)
- unusual, severe, prolonged headache, sudden disturbances of vision or hearing or other perceptual disorders, collapse, marked numbness or weakness affecting one side of the body, or other signs or symptoms suggestive of cerebrovascular accident
- a first unexplained epileptic seizure
- hepatitis, jaundice, generalised itching, liver enlargement, severe upper abdominal pain
- significant rise in blood pressure (above 160 mmHg systolic or 100 mmHg diastolic)
- clear exacerbation of other conditions known to be capable of deteriorating during oral contraception or pregnancy.

Progestogen-only contraceptives, whether oral or injectable, may be used when oestrogen-containing preparations are contra-indicated but certain contra-indications and precautions must still be observed. They are contra-indicated in women with undiagnosed vaginal bleeding, possible pregnancy, severe arterial disease, hormone-dependent neoplasms, and severe liver disease such as hepatic adenoma.

Like combined oral contraceptives they should not be used after recent evacuation of a hydatidiform mole. Progestogen-only contraceptives should be used with caution in women with heart disease, malabsorption syndromes, liver dysfunction including recurrent cholestatic jaundice, or a history of jaundice in pregnancy. Oral progestogen-only contraceptives should also be used with caution in past ectopic pregnancy (see above) or functional ovarian cysts. Despite unsatisfactory evidence of hazard, other suggested cautions for progestogen-only contraceptives include diabetes mellitus, hypertension, migraine, and thromboembolic disorders.

Breast feeding. Progestogen-only contraceptives are the hormonal contraceptives of choice for breast-feeding women because they do not affect lactation,[1] but recommendations vary about when they can or should be started, and may not match licensed product information. Some guidelines[2] recommend that all progestogen-only methods can be started 6 weeks after birth. Others[3] suggest that oral preparations can be started any time in breast-feeding women, although they are not needed before 3 weeks postpartum; the *BNF* also warns that there is an increased risk of breakthrough bleeding if progestogen-only oral contraceptives are started before 3 weeks postpartum. Progestogen-only parenteral contraceptives, such as medroxyprogesterone acetate, are usually not given until 6 weeks postpartum;[1-3] troublesome bleeding can occur before this time.[3] The etonogestrel implant may be used 3 weeks postpartum and the levonorgestrel IUD may be inserted 4 weeks postpartum.[3]

Combined oral contraceptives can reduce the volume of breast milk and are therefore avoided in breast-feeding women for the first 6 weeks after birth.[1,3] In general, they are not recommended for 6 months or until weaning,[2,3] but some suggest[3] that they may be considered between 6 weeks and 6 months postpartum if breast feeding is established and other contraceptive methods are unacceptable.

Very small amounts of oestrogens and progestogens from hormonal contraceptives are distributed into breast milk, but there is no indication that this adversely affects development of the breast-fed infant.[3,4] The American Academy of Pediatrics[5] has also reviewed the use of hormonal contraceptives during lactation, commenting that early information was based on the use of high-dose contraceptives. It was noted that there might be a decrease in milk production, but that there was insufficient information to confirm that there was any alteration in the composition of breast milk, and that although there had been rare cases of gynaecomastia in breast-fed infants of mothers who received high-dose contraceptives, there was no consistent evidence of long-term adverse effects on the infant. A later study[6] of 48 children whose mothers had received high-dose combined oral contraceptives during breast feeding found no effect on these children compared with controls, up to 8 years of age. The Academy therefore considers[7] that combined oral contraceptives are usually compatible with breast feeding.

Breast feeding itself suppresses ovulation and can be used, if started immediately postpartum, as the lactational amenorrhoea method of contraception; for further details, see Contraception, p.2070.

1. Queenan JT. Contraception and breastfeeding. *Clin Obstet Gynecol* 2004; **47:** 734–9.
2. Hatcher RA, *et al. The essentials of contraceptive technology: a handbook for clinical staff*. Baltimore: John Hopkins Bloomberg School of Public Health, Population Information Program, 2003. Also available at: http://www.infoforhealth.org/pubs/ect/ (accessed 14/01/08)
3. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC guidance (July 2004): contraceptive choices for breastfeeding women. *J Fam Plann Reprod Health Care* 2004; **30:** 181–9. Also available at: http://www.ffprhc.org.uk/admin/uploads/breastfeeding.pdf (accessed 14/01/08)
4. Fraser IS. A review of the use of progestogen-only minipills for contraception during lactation. *Reprod Fertil Dev* 1991; **3:** 245–54.
5. American Academy of Pediatrics Committee on Drugs. Breastfeeding and contraception. *Pediatrics* 1981; **68:** 138–40. Also available at: http://pediatrics.aappublications.org/cgi/reprint/68/1/138.pdf (accessed 14/01/08)
6. Nilsson S, *et al.* Long-term follow-up of children breast-fed by mothers using oral contraceptives. *Contraception* 1986; **34:** 443–57.
7. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 14/01/08)

Cardiovascular disease. Combined oral contraceptives are associated with a number of arterial and venous risks. Progestogen-only contraceptives are associated with fewer risks, although they still need to be avoided when arterial disease is severe.

Arterial disease. In the UK the *BNF* has recommended that combined oral contraceptives may be used with **caution** if any **one** of the following factors are present, but should be **avoided** if **two or more** factors are present:

- *family history of arterial disease* in first-degree relative aged under 45 years (avoid if there is also an atherogenic lipid profile)
- *diabetes mellitus* (avoid if diabetic complications are present)
- *hypertension* (avoid if blood pressure is above 160/100 mmHg)
- *smoking* (avoid if 40 or more cigarettes are smoked daily)
- *age over 35 years* (avoid if over 50 years)
- *obesity*—body-mass index above 30 kg/m^2 (avoid if body-mass index exceeds 39 kg/m^2)
- *migraine*, see under Migraine, below.

Venous thromboembolism. Combined oral contraceptives increase the risk of venous thromboembolism and should not be used in women with a personal history of venous or arterial thrombosis. In addition they should be used with **caution** if any **one** of the following risk factors are present, but should be **avoided** if **two or more** factors are present:

- *family history of venous thromboembolism* in first-degree relative aged under 45 years (avoid if there is a known prothrombotic coagulation abnormality such as antiphospholipid antibodies, which may occur in patients with SLE, or factor V Leiden)
- *long-term immobilisation* such as wheelchair use (avoid if confined to bed or with a leg in plaster)
- *varicose veins* (avoid during sclerosing treatment)
- *obesity*—body-mass index above 30 kg/m^2 (avoid if body-mass index greater than 39 kg/m^2).

The *BNF* also advises that women taking combined oral contraceptives may be at an increased risk of deep-vein thrombosis during *travel* involving prolonged periods of immobility (over 5 hours). The risk may be reduced by appropriate exercise during the journey, and possibly by wearing graduated compression hosiery.

In the light of evidence indicating an increased risk of venous thromboembolism with combined oral contraceptives containing *desogestrel* or *gestodene* (see Venous Thromboembolism, under Effects on the Cardiovascular System, above), the UK CSM advised additional precautions for these products. As well as the usual precautions, it was initially advised they should not be used by obese women (body-mass index greater than 30 kg/m^2), those with varicose veins, or those with a history of thrombosis of any cause. Moreover, it was also recommended that they should be used only by women who were intolerant of other combined oral contraceptives and who were prepared to accept an increased risk of venous thromboembolism. Subsequently the CSM[1] modified its advice as follows: they recommended that these products should be avoided in women with known risk factors for venous thromboembolism. However, in women without contra-indications, the type of combined contraceptive was considered a matter of clinical judgement and personal choice, as long as the woman was fully informed of the small excess risk associated with desogestrel- and gestodene-containing products.

1. CSM/MCA. Combined oral contraceptives containing desogestrel or gestodene and the risk of venous thromboembolism. *Current Problems* 1999; **25:** 12. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023234&RevisionSelectionMethod=LatestReleased (accessed 14/01/08)

Lupus erythematosus. SLE is an auto-immune disease that is far more common in women than in men, and usually has a peak onset for women in their 20s and 30s. There is some evidence to suggest that oral contraceptive use may be associated with a slightly increased risk in the onset of SLE.[1-3] There are also reports and studies of the effect of contraceptives on disease exacerbation, although there has been an apparent reduction in reports which has coincided with the lowering of oestrogen content in contraceptive preparations.[2] More recently, controlled studies[4,5] have found that disease activity and flares over 12 months in women with stable SLE were similar whether they were given a combined oral contraceptive (containing ethinylestradiol 30 or 35 micrograms), a progestogen-only oral preparation, placebo, or copper IUD. However, patients with major disease, such as lupus nephritis, could be at greater risk of exacerbation. It is also generally advised that combined oral contraceptives should be avoided in women with antiphospholipid antibodies (which includes about a third of all patients with SLE) because they are at increased risk of venous thromboembolism.[1,2]

1. Petri M. Exogenous estrogen in systemic lupus erythematosus: oral contraceptives and hormone replacement therapy. *Lupus* 2001; **10:** 222–6.
2. Mok CC, *et al.* Use of exogenous estrogens in systemic lupus erythematosus. *Semin Arthritis Rheum* 2001; **30:** 426–35.
3. Costenbader KH, *et al.* Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis Rheum* 2007; **56:** 1251–62.
4. Sánchez-Guerrero J, *et al.* A trial of contraceptive methods in women with systemic lupus erythematosus. *N Engl J Med* 2005; **353:** 2539–49.
5. Petri M, *et al.* Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med* 2005; **353:** 2550–8.

Migraine. Both migraine and the use of combined oral contraceptives have been identified as risk factors for ischaemic stroke. A systematic review[1] concluded that in women with a history of migraine, users of combined oral contraceptives were 2 to 4 times more likely to have an ischaemic stroke than non-users. It was unclear, however, whether this increase in relative risk was due to independent effects of contraceptives and migraine, or whether contraceptive use had a greater effect in women with a history of migraine than in those without.

In the UK the *BNF* has recommended that combined oral contraceptives be **contra-indicated** in:

- migraine with typical focal aura
- severe migraine regularly lasting longer than 72 hours despite treatment
- migraine treated with an ergot derivative

It also recommends **caution** in migraine without focal aura and migraine controlled with a serotonin (5-HT$_1$) agonist. A woman receiving a combined oral contraceptive should report any increase in headache frequency or the onset of focal symptoms. If focal neurological symptoms not typical of aura persist for longer than one hour the combined oral contraceptive should be discontinued and the woman referred urgently to a neurologist.

Other risk factors for arterial disease should also be considered in women with a history of migraine (see Cardiovascular Disease, above).

1. Curtis KM, *et al.* Use of combined oral contraceptives among women with migraine and nonmigrainous headaches: a systematic review. *Contraception* 2006; **73:** 189–94.

Obesity. It has been suggested that higher body-weight or BMI might be associated with a greater risk of oral contraceptive failure. A number of cohort and case-control studies have evaluated this association, with mixed results that may have been confounded by recall bias, inaccuracy of reported body-weight, non-compliance, and change in oestrogen dose over time. Some studies have suggested that there is an increased risk of contraceptive failure,[1,2] while others have found no association.[3] In addition, some have found a weak association that was no longer statistically significant when results were adjusted for confounders such as education, income, and ethnicity.[4,5] It is therefore unclear whether an association exists, but obesity is a risk factor for cardiovascular disease and combined oral contraceptives should be used with caution, or avoided, in these women (see Cardiovascular Disease, above).

1. Holt VL, *et al.* Body weight and risk of oral contraceptive failure. *Obstet Gynecol* 2002; **99:** 820–7.
2. Holt VL, *et al.* Body mass index, weight, and oral contraceptive failure risk. *Obstet Gynecol* 2005; **105:** 46–52.
3. Vessey M, Painter R. Oral contraceptive failures and body weight: findings in a large cohort study. *J Fam Plann Reprod Health Care* 2001; **27:** 90–1.
4. Brunner LR, Hogue CJ. The role of body weight in oral contraceptive failure: results from the 1995 national survey of family growth. *Ann Epidemiol* 2005; **15:** 492–9.
5. Brunner Huber LR, *et al.* Body mass index and risk for oral contraceptive failure: a case-cohort study in South Carolina. *Ann Epidemiol* 2006; **16:** 637–43.

Porphyria. Oral contraceptives have been associated with acute attacks of porphyria and are considered unsafe in porphyric patients. The progestogen content is considered more hazardous than the oestrogen content. A progestogen-only contraceptive may be used with extreme caution if non-hormonal contraception is inappropriate and potential benefit outweighs the risk. The risk of an acute attack is greatest in women who have had a previous attack or are under 30 years of age. Long-acting progestogen preparations should never be used in those at risk.

Pregnancy. In contrast to the numerous cases of congenital malformations reported after the use of high doses of sex hormones for hormonal pregnancy tests, there have been only a few suggestions that continued use of oral contraceptives during early pregnancy may result in congenital limb reduction deformities,[1-3] and one case of neonatal choreoathetosis after prenatal exposure to oral contraceptives.[4]

Many studies, conversely, have shown no evidence that the use of oral contraceptives is associated with congenital malformations or teratogenic effects, whether past use (stopped before conception), use after the last menstrual period, or known use in early pregnancy. A meta-analysis[5] confirmed this; the relative risk for all malformations with use of oral contraceptives was estimated to be 0.99 (95% confidence intervals 0.83 to 1.19). The use of oral contraceptives in early pregnancy also appears unlikely to increase the risk of hypospadia in male fetuses[6,7] (see also under Precautions of Estradiol, p.2098).

Depot intramuscular medroxyprogesterone acetate is a highly effective contraceptive, but failures do occur rarely. A review[8] of such failures had limited data on birth outcome in 100 women who continued the pregnancy, but no abnormalities or fetal anomalies were reported.

In 25 pregnancies that were continued after the failure of levonorgestrel-based emergency contraception,[9] there was 1 case of gastro-oesophageal reflux requiring medical treatment and 1 case of nasolachrymal duct obstruction that was surgically drained, but compared with a control group and expected baseline risk there was no increased risk of congenital or genital abnormalities.

For a discussion of the ectopic pregnancy risk in users of hormonal contraceptives, see above.

1. Janerich DT, *et al.* Oral contraceptives and congenital limb reduction defects. *N Engl J Med* 1974; **291:** 697–700.
2. McCredie J, *et al.* Congenital limb defects and the pill. *Lancet* 1983; **ii:** 623.
3. Kricker A, *et al.* Congenital limb reduction deformities and use of oral contraceptives. *Am J Obstet Gynecol* 1986; **155:** 1072–8.
4. Profumo R, *et al.* Neonatal choreoathetosis following prenatal exposure to oral contraceptives. *Pediatrics* 1990; **86:** 648–9.
5. Bracken MB. Oral contraception and congenital malformations in offspring: a review and meta-analysis of the prospective studies. *Obstet Gynecol* 1990; **76:** 552–7.
6. Raman-Wilms L, *et al.* Fetal genital effects of first trimester sex hormone exposure: a meta-analysis. *Obstet Gynecol* 1995; **85:** 141–9.
7. Wogelius P, *et al.* Maternal use of oral contraceptives and risk of hypospadias—a population-based case-control study. *Eur J Epidemiol* 2006; **21:** 777–81.
8. Borgatta L, *et al.* Pregnancies diagnosed during Depo-Provera use. *Contraception* 2002; **66:** 169–72.
9. De Santis M, *et al.* Failure of the emergency contraceptive levonorgestrel and the risk of adverse effects in pregnancy and on fetal development: an observational cohort study. *Fertil Steril* 2005; **84:** 296–9.

Sickle-cell disease. *Sickle-cell disease* and oral contraceptive use are both associated with an increased risk of thrombosis but it is by no means certain that the two risks are additive. Study of a small number of women with sickle-cell disease found that combined and progestogen-only contraceptives had no effect on red cell deformability.[1] Licensed product information for some preparations has specifically warned against the use of combined oral contraceptives in sickle-cell disease. However, there is a lack of strong clinical evidence to support such a contra-indication,[2,3] and there is some suggestion that progestogen-only contraception may be associated with improvements in clinical symptoms and sickle-cell crises.[4] WHO considers[5] that in women with sickle-cell disease the benefits generally outweigh the risks for low-dose combined oral contraceptives (35 micrograms or less of ethinylestradiol) and other forms of combined hormonal contraceptives (injectable, transdermal patch, and vaginal ring), and that there is no restriction for the use of progestogen-only contraceptives (oral, depot injection, implant, and intra-uterine device).

For *sickle-cell trait* there is no increased risk of thrombosis and no contra-indication to the use of a combined or progestogen-only preparation. Many women with sickle-cell trait have, unnecessarily, been denied the use of oral contraceptives in the mistaken belief that advice for sickle-cell disease applies to the trait.[6]

1. Yoong WC, *et al.* Red cell deformability in oral contraceptive pill users with sickle cell anaemia. *Br J Haematol* 1999; **104:** 868–70.
2. Freie HMP. Sickle cell diseases and hormonal contraception. *Acta Obstet Gynecol Scand* 1983; **62:** 211–17.
3. Howard RJ, *et al.* Contraceptives, counselling, and pregnancy in women with sickle cell disease. *BMJ* 1993; **306:** 1735–7.
4. Legardy JK, Curtis KM. Progestogen-only contraceptive use among women with sickle cell anemia: a systematic review. *Contraception* 2006; **73:** 195–204.
5. WHO. *Medical eligibility criteria for contraceptive use.* Third ed. Geneva: WHO, 2004. Available at: http://www.who.int/reproductive-health/publications/mec/index.htm (accessed 14/01/08)
6. Evans DIK. Should patients who say that they have "sickle cells" be prescribed the contraceptive pill? *BMJ* 1984; **289:** 425.

Surgery. Case reports and epidemiological studies showing an increased risk of idiopathic deep-vein thrombosis and pulmonary embolism in young women taking **combined oral contraceptives** (see above) led to the widespread belief that oral contraceptives may predispose to deep-vein thrombosis postoperatively. In consequence, the advice commonly given in the UK has been that, if possible, combined oral contraceptives should be stopped 4 weeks before major elective surgery and all surgery of the legs, and that prophylactic heparin should be considered where this was not possible.[1] They can normally be started again at the first menses occurring at least 2 weeks after full mobilisation. However, estimates of the size of the risk are variable;[2-5] one report[2] found that the incidence of deep-vein thrombosis postoperatively in young women taking combined oral contraceptives was about twice that of women not taking contraceptives but the difference was not statistically significant. Some have considered[6] that the risk to young women of becoming pregnant after stopping oral contraceptives, or of developing adverse effects from heparin prophylaxis, may be greater than the risk of developing postoperative deep-vein thrombosis. This is in line with the views of the Thromboembolic Risk Factors (THRIFT) Consensus Group.[7] They suggested that unless there were other risk factors there was insufficient evidence to support a policy of routinely stopping combined oral contraceptives before major surgery. Additionally, there was insufficient evidence to support routine specific thromboembolic prophylaxis in women without additional risk factors. A review[8] has subsequently recommended that women for whom major elective surgery was planned should continue taking the combined oral contraceptive but should receive thromboprophylaxis in the perioperative period. It has also been pointed out[9,10] that for patients awaiting surgery who require contraception, a progestogen-only oral contraceptive or an injection of medroxyprogesterone acetate may be suitable since neither preparation increases the risk of thrombosis.

1. Guillebaud J. Surgery and the pill. *BMJ* 1985; **291:** 498–9.
2. Vessey M, *et al.* Oral contraceptives and venous thromboembolism: findings in a large prospective study. *BMJ* 1986; **292:** 526.
3. Tso SC, *et al.* Deep vein thrombosis and changes in coagulation and fibrinolysis after gynaecological operations in Chinese: the effect of oral contraceptives and malignant disease. *Br J Haematol* 1980; **46:** 603–12.
4. Gallus AS, *et al.* Oral contraceptives and surgery: reduced antithrombin and antifactor XA levels without postoperative venous thrombosis in low-risk patients. *Thromb Res* 1984; **35:** 513–26.
5. Sagar S, *et al.* Oral contraceptives, antithrombin III activity, and postoperative deep-vein thrombosis. *Lancet* 1976; **i:** 509–11.
6. Sue-Ling H, Hughes LE. Should the pill be stopped preoperatively? *BMJ* 1988; **296:** 447–8.
7. Thromboembolic Risk Factors (THRIFT) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *BMJ* 1992; **305:** 567–74.
8. Anonymous. Drugs in the peri-operative period: hormonal contraceptives and hormone replacement therapy. *Drug Ther Bull* 1999; **37:** 78–80.
9. Guillebaud J. Should the pill be stopped preoperatively? *BMJ* 1988; **296:** 786–7.
10. Guillebaud J, Robinson GE. Stopping the pill. *BMJ* 1991; **302:** 789.

Travel. For a warning that women taking oral contraceptives may be at increased risk of deep-vein thrombosis from travel involving prolonged immobility see Cardiovascular Disease, above.

Interactions

Enzyme-inducing drugs can cause combined oral contraceptives to fail by increasing their metabolism and clearance. This effect is well established for a number of *antiepileptics*, *griseofulvin*, and *rifamycin antibacterials*, and has also been suggested for some *antivirals* and for *modafinil*. Although less well documented, these interactions would also be expected to apply to progestogen-only contraceptives. The *BNF* has provided recommendations for contraception in women taking enzyme-inducing drugs.

- When a short course of an enzyme-inducing drug is taken, the dose of a combined oral contraceptive should be adjusted to provide ethinylestradiol 50 micrograms or more daily. Additional non-hormonal contraceptive methods should be used during the course and for 4 weeks after stopping it.
- For women requiring long-term treatment with an enzyme-inducing drug, an alternative method of contraception that is unaffected by the enzyme-inducing drug should be considered. However, if a combined oral contraceptive is used, a regimen that provides ethinylestradiol 50 micrograms or more daily should be used. 'Tricycling' has also been recommended where 3 or 4 cycles of monophasic tablets are taken without any breaks, followed by a short tablet-free interval of 4 days; the efficacy of this regimen is uncertain however. Enzyme activity may not return to normal for several weeks after stopping long-term treatment, and appropriate contraceptive measures should be continued for 4 to 8 weeks. These measures are not sufficient for long-term use of rifamycins, and an alternative method such as an IUD is always recommended.
- For women using a contraceptive transdermal patch, additional non-hormonal contraceptive methods should be used during a short-term course of an enzyme-inducing drug and for 4 weeks after stopping. If concomitant use runs beyond the 3 weeks of patch treatment, a new treatment cycle should be started immediately without a patch-free interval. For women taking an enzyme-inducing drug long-term, another form of contraception should be considered.
- Progestogen-only oral contraceptives and injectable preparations containing norethisterone or etonogestrel (but not medroxyprogesterone) may be affected by enzyme-inducing drugs, and an additional or alternative method of contraception is recommended during treatment and for at least 4 weeks after stopping. An alternative method of contraception should be considered if long-term treatment with an enzyme-inducing drug is required. Intra-uterine progestogen-only contraceptives are unlikely to be affected by enzyme-inducing drugs.
- An increased dose of postcoital (emergency) contraception, as a single oral dose of levonorgestrel 3 mg, has been suggested for women receiving enzyme-inducing drugs. Alternatively, a copper IUD may be used.

Rarely, *broad-spectrum antibacterials* have been associated with combined oral contraceptive failure, possibly by reducing enterohepatic recycling of the oestrogen component. As the doses of oestrogen and progestogen in oral contraceptives have decreased, reports of menstrual irregularities and unintended pregnancies attributed to these drug interactions have increased.

Further details of drugs affecting hormonal contraceptives are given below under specific headings.

Oral contraceptives may also *affect other drugs*. Compounds undergoing oxidative metabolism can have their plasma concentration raised by oral contraceptives through an inhibitory action. Conversely, oral contraceptives appear to induce glucuronidation of some drugs thus reducing their plasma concentration. Oral contraceptives can also antagonise the actions of a number of drugs. Drugs affected include:

- some analgesics (increased clearance of paracetamol and morphine)
- anticoagulants (increased and decreased effects reported; see p.1431)
- some antidepressants (reduced effectiveness, but also increased toxicity; see p.380)
- antidiabetics (antagonism of effect)
- the antiepileptic lamotrigine (decreased plasma concentrations; see p.486)
- antihypertensives (antagonism of effect)
- benzodiazepines (increased or decreased clearance; see p.991)
- ciclosporin (increased toxicity; see p.1828)
- clofibrate (increased clearance and antagonism of effect)
- corticosteroids (enhanced effect; see p.1495)
- levothyroxine (reduced free fraction due to increased binding globulin concentration; see p.2173)
- lidocaine (increased free fraction due to altered protein binding; see Protein Binding, under Pharmacokinetics, p.1864)
- selegiline (decreased clearance; see p.817)
- xanthines (decreased clearance; see p.1145)

◊ Reviews.

1. Back DJ, Orme ML'E. Pharmacokinetic drug interactions with oral contraceptives. *Clin Pharmacokinet* 1990; **18:** 472–84.
2. Shenfield GM. Oral contraceptives: are drug interactions of clinical significance? *Drug Safety* 1993; **9:** 21–37.

3. Quereux C, Bory JP. Interaction médicamenteuse et contraception orale. *Contracept Fertil Sex* 1998; **26:** 129–31.
4. Schwartz JB. Oral contraceptive therapy in women: drug interactions and unwanted outcomes. *J Gend Specif Med* 1999; **2:** 26–9.
5. Elliman A. Interactions with hormonal contraception. *Br J Fam Plann* 2000; **26:** 109–11. Correction. *ibid.*; 151.
6. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC guidance (April 2005): drug interactions with hormonal contraception. *J Fam Plann Reprod Health Care* 2005; **31:** 139–51. Also available at: http://www.ffprhc.org.uk/admin/uploads/DrugInteractionsFinal.pdf (accessed 14/01/08)

Antibacterials. An interaction between the *rifamycins (rifampicin* and *rifabutin)* and oral contraceptives is well established and alternative contraceptive measures are necessary (see Rifamycins, below).

A variety of *broad-spectrum antibacterials* have also been reported to decrease oral contraceptive efficacy. Some studies have pointed to interference with intestinal flora involved in enterohepatic circulation of oestrogens as being a likely mechanism for this interaction. Although up until 1985 there had been 32 reports[1] of unintended pregnancies in women receiving *penicillins* (25 of them with *ampicillin*) the ability of antibacterials to inhibit oral contraceptive efficacy remains unproven. The data are consistent, however, with the supposition that efficacy is occasionally impaired.[2] Several cases of unintended pregnancies have been reported after the use of *tetracyclines*. It is recommended that additional contraceptive precautions should be used while taking, and for 7 days after stopping, a short course of any broad-spectrum antibacterial. If these 7 days run into the last 7 days of the cycle, then the tablet-free interval (or the 7 inert tablets) should be omitted and the next cycle of tablets started immediately. If the course of antibacterial exceeds 3 weeks the intestinal flora develop resistance and additional precautions become unnecessary.

With regard to other antibacterials, in theory any one with significant effects on intestinal flora could affect contraceptive efficacy. Isolated cases of pregnancy have been reported following the use of *cephalosporins*, *chloramphenicol*, *dapsone*, *isoniazid*, *nitrofurantoin*, *sulfonamides*, and *co-trimoxazole* but it is impossible to determine which, if any, of these interactions is real.

1. Back DJ, *et al.* Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* 1988; **25:** 527–32.
2. Dickinson BD, *et al.* Drug interactions between oral contraceptives and antibiotics. *Obstet Gynecol* 2001; **98:** 853–60.

RIFAMYCINS. *Rifampicin* regularly results in menstrual irregularities and occasionally in unintended pregnancies in women receiving oral contraceptives. It is a potent enzyme inducer and considerably enhances the metabolism of oral contraceptives. For short courses of rifampicin, additional contraceptive precautions should be taken during the course and for 4 weeks after stopping. A non-hormonal method of contraception such as an IUD is recommended during, and for 4 to 8 weeks after stopping, long-term rifampicin therapy.

Similar precautions are recommended during *rifabutin* therapy.

Contraceptive failure, resulting in an ectopic pregnancy, has also been reported in a woman who started rifampicin therapy 3 months after placement of an etonogestrel implant.[1]

1. Patni S, *et al.* Ectopic pregnancy with Implanon . *J Fam Plann Reprod Health Care* 2006; **32:** 115.

TROLEANDOMYCIN. Severe pruritus and jaundice may occur if oral contraceptives and troleandomycin are given together.[1] It has been suggested that their hepatic effects may be additive or synergistic, and that concurrent use should be avoided.

1. Miguet J-P, *et al.* Jaundice from troleandomycin and oral contraceptives. *Ann Intern Med* 1980; **92:** 434.

Antidepressants. *St John's wort* may decrease blood concentrations of oral contraceptives by enzyme induction.[1-3] There have been reports of intermenstrual bleeding and altered menstrual bleeding in women on long-term oral contraceptives who started taking St John's wort.[4] Several pregnancies have also been reported.[5,6]

For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see above.

1. Hall SD, *et al.* The interaction between St John's wort and an oral contraceptive. *Clin Pharmacol Ther* 2003; **74:** 525–35.
2. Pfrunder A, *et al.* Interaction of St John's wort with low-dose oral contraceptive therapy: a randomized controlled trial. *Br J Clin Pharmacol* 2003; **56:** 683–90.
3. Murphy PA, *et al.* Interaction of St. John's Wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. *Contraception* 2005; **71:** 402–8.
4. Yue Q-Y, *et al.* Safety of St. John's wort (Hypericum perforatum). *Lancet* 2000; **355:** 576–7.
5. Läkemedelsverket (Medical Products Agency—Sweden). Minskad effekt av p-piller vid samtidig användning av johannesört har lett till oönskad graviditet (issued 4th February, 2002). Available at: http://www.lakemedelsverket.se/Tpl/NewsPage____580.aspx (accessed 14/01/08)
6. Schwarz UI, *et al.* Unwanted pregnancy on self-medication with St John's wort despite hormonal contraception. *Br J Clin Pharmacol* 2003; **55:** 112–13.

Antidiabetics. *Troglitazone* is an enzyme inducer and increases the clearance of oestrogens and progestogens. A high-dose oral contraceptive, or an alternative method of contraception should be considered in women receiving troglitazone and requiring contraception.[1] However, *rosiglitazone* is not an enzyme inducer and is not expected to affect the efficacy of oral contraceptives.[2]

For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see above.

1. Loi C-M, *et al.* Effect of troglitazone on the pharmacokinetics of an oral contraceptive agent. *J Clin Pharmacol* 1999; **39:** 410–17.
2. Inglis AML, *et al.* Lack of effect of rosiglitazone on the pharmacokinetics of oral contraceptives in healthy female volunteers. *J Clin Pharmacol* 2001; **41:** 683–90.

Antiepileptics. Oral contraceptive failure and breakthrough bleeding have been reported in numerous cases during antiepileptic therapy.[1,2] *Phenytoin*, barbiturates such as *phenobarbital* and *primidone*, and *carbamazepine* have been most frequently implicated, and *oxcarbazepine*, *felbamate*, and *topiramate* may interact similarly.[3] These drugs increase the clearance of both oestrogens and progestogens by enzyme induction, so diminishing their effects. Contraceptive methods that are not affected by enzyme induction include a copper or levonorgestrel IUD, or intramuscular depot medroxyprogesterone acetate.[4,5] If these are unsuitable, a combined oral contraceptive with an increased oestrogen content equivalent to ethinylestradiol 50 micrograms or more, and a corresponding increase in progestogen, is generally recommended. In addition, the use of a monophasic preparation given for 3 cycles without a break followed by a tablet-free interval of 4 days (tricycling) has also been suggested.[4] The importance of the progestogen in suppressing ovulation has also been discussed, with the suggestion that ethinylestradiol doses of less than 50 micrograms could be used provided the dose of progestogen is at least 1 mg of norethisterone, 150 micrograms of levonorgestrel, or 300 micrograms of norgestrel.[5] Biphasic, triphasic, and progestogen-only oral contraceptives are not recommended.[5]

Lamotrigine may also reduce contraceptive efficacy, and is markedly affected in turn by the contraceptive (see p.486).

For the effects of oral contraceptives on *valproate*, see p.511.

The efficacy of postcoital hormonal contraception (emergency contraception) is also reduced by enzyme-inducing antiepileptic drugs,[4] and an increased dose has been suggested (see above).

Antiepileptics that are reported not to interact with hormonal contraceptives include *ethosuximide*, *gabapentin*, *levetiracetam*, *tiagabine*, *valproate*, and *vigabatrin*.[4,5]

1. Mattson RH, Cramer JA. Epilepsy, sex hormones, and antiepileptic drugs. *Epilepsia* 1985; **26** (suppl 1): S40–S51.
2. Back DJ, *et al.* Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* 1988; **25:** 527–32.
3. Wilbur K, Ensom MHH. Pharmacokinetic drug interactions between oral contraceptives and second-generation anticonvulsants. *Clin Pharmacokinet* 2000; **38:** 355–65.
4. O'Brien MD, Guillebaud J. Contraception for women with epilepsy. *Epilepsia* 2006; **47:** 1419–22.
5. Thorneycroft I, *et al.* The impact of antiepileptic drug therapy on steroidal contraceptive efficacy. *Epilepsy Behav* 2006; **9:** 31–9.

Antifungals. Menstrual irregularities and pregnancies have been reported in women receiving oral contraceptives and *griseofulvin*,[1,2] which is known to be an inducer of hepatic enzymes and may increase the metabolism of hormonal contraceptives. Additional contraceptive measures should be considered during concomitant use and after stopping griseofulvin; for general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see above. There have also been anecdotal reports[3-5] of menstrual irregularities and contraceptive failure with *fluconazole*, *itraconazole*, and *ketoconazole*, and similar advice applies to these if pregnancy is to be avoided with certainty.

1. van Dijke CPH, Weber JCP. Interaction between oral contraceptives and griseofulvin. *BMJ* 1984; **288:** 1125–6.
2. Back DJ, *et al.* Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* 1988; **25:** 527–32.
3. Pillans PI, Sparrow MJ. Pregnancy associated with a combined oral contraceptive and itraconazole. *N Z Med J* 1993; **106:** 436.
4. Meyboom RHB, *et al.* Disturbance of withdrawal bleeding during concomitant use of itraconazole and oral contraceptives. *N Z Med J* 1997; **110:** 300.
5. van Puijenbroek EP, *et al.* Verstoring van de pilcyclus tijdens het gelijktijdig gebruik van itraconazol en orale anticonceptiva. *Ned Tijdschr Geneeskd* 1998; **142:** 146–9.

Antivirals. A number of antivirals are likely to accelerate the metabolism of oestrogens and progestogens; theoretically therefore, they may decrease the efficacy of hormonal contraceptives. This has been suggested for HIV-protease inhibitors such as *nelfinavir*,[1] *ritonavir*,[2] and ritonavir-boosted HIV-protease inhibitors, and for the NNRTI *nevirapine*.[3] An alternative form of contraception should be considered. For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see above.

Conversely, the area under the plasma-concentration-time curve for ethinylestradiol is reported to be increased by HIV-protease inhibitors such as *amprenavir*, *atazanavir*, and *indinavir*, and the NNRTIs *delavirdine* and *efavirenz*. Although the clinical implications are unknown, the licensed product information recommends alternative or additional contraception.

The *BNF* suggests that the use of condoms with a long-acting method, such as an injectable contraceptive, may be more suitable for patients with HIV infection or at risk of infection.

1. Clark RA, Theall K. Population-based study evaluating association between selected antiretroviral therapies and potential oral contraceptive failure. *J Acquir Immune Defic Syndr* 2004; **37:** 1219–20.
2. Ouellet D, *et al.* Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. *Br J Clin Pharmacol* 1998; **46:** 111–16.
3. Mildvan D, *et al.* Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when administered concurrently to HIV-infected women. *J Acquir Immune Defic Syndr* 2002; **29:** 471–7.

Endothelin receptor antagonists. In a pharmacokinetic study of healthy women[1] the area under the concentration-time curve (AUC) of both ethinylestradiol and norethisterone were reduced by *bosentan*, probably by enzyme induction. The possibility of contraceptive failure should be considered, and licensed product information for bosentan suggests that an additional or alternative method of contraception should be used during bosentan therapy. For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see above.

In contrast, *sitaxentan* is an inhibitor of some cytochrome P450 isoenzymes, and it has increased exposure to ethinylestradiol and norethisterone in women taking a combined oral contraceptive. An increase in oestrogen exposure may possibly increase the risk of thromboembolism.

1. van Giersbergen PLM, *et al.* Pharmacokinetic interaction between bosentan and the oral contraceptives norethisterone and ethinyl estradiol. *Int J Clin Pharmacol Ther* 2006; **44:** 113–18.

Retinoids. One woman taking an oral progestogen-only contraceptive (levonorgestrel 30 micrograms daily) showed a significant increase in plasma-progestogen while receiving *acitretin*, which indicated ovulation had occurred.[1] However, progestogen-only contraceptives do not suppress ovulation in all cycles, and this is not thought to be their primary mechanism of contraceptive efficacy (see Types of Contraceptive, p.2058). Nevertheless, because it is imperative that women receiving retinoids do not conceive, some have concluded that oral progestogen-only contraceptives are not suitable for use with retinoids.[2]

The anti-ovulatory efficacy of combined oral contraceptives was not affected by acitretin in 8 women in the study above,[1] or by *etretinate* in a study[3] in 12 women. Other studies have reported that *isotretinoin* did not significantly change plasma concentrations or adversely affect contraceptive efficacy of ethinylestradiol and levonorgestrel in 9 women,[4] or ethinylestradiol and norethisterone in 26 women.[5] It has been concluded that, unless otherwise contra-indicated, oral combined contraceptives are the contraceptive method of choice for women undergoing retinoid treatment.[2] Licensed product information for retinoids, including isotretinoin, reminds prescribers that two effective forms of contraception such as a combined oral contraceptive with a barrier method should be used during and after retinoid treatment (see also Pregnancy, under Isotretinoin, p.1601).

Both isotretinoin and combined oral contraceptives can have adverse effects on plasma lipids;[6] it has therefore been recommended that plasma lipids should be monitored during concurrent retinoid and oral contraceptive therapy, and that an oral contraceptive containing a non-androgenic progestogen is preferred,[2] since these have less detrimental effects on lipids (p.2064).

1. Berbis P, *et al.* Acitretin (RO10-1670) and oral contraceptives: interaction study. *Arch Dermatol Res* 1988; **280:** 388–9.
2. Lehucher Ceyrac D, *et al.* Retinoids and contraception. *Dermatology* 1992; **184:** 161–70.
3. Berbis P, *et al.* Study on the influence of etretinate on biologic activity of oral contraceptives. *J Am Acad Dermatol* 1987; **17:** 302–3.
4. Orme M, *et al.* Isotretinoin and contraception. *Lancet* 1984; **ii:** 752–3.
5. Hendrix CW, *et al.* The effect of isotretinoin on the pharmacokinetics and pharmacodynamics of ethinyl estradiol and norethindrone. *Clin Pharmacol Ther* 2004; **75:** 464–75.
6. Chen Y, *et al.* Elevation of serum triglyceride and cholesterol levels from isotretinoin therapy with concomitant oral contraceptives. *Pharmacoepidemiol Drug Safety* 1995; **4:** 91–6.

Stimulants. *Modafinil* induces hepatic enzymes and may reduce the efficacy of oral contraceptives.[1] Licensed product information for modafinil suggests that alternative or additional methods of contraception are needed; US information recommends that this is also continued for 1 month after stopping modafinil, but in the UK it is recommended for 2 months.

For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see Interactions, above.

1. Robertson P, *et al.* Effect of modafinil on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers. *Clin Pharmacol Ther* 2002; **71:** 46–56.

Vitamins. Large supplements of *vitamin C* have been reported to increase serum ethinylestradiol concentrations in women taking oral contraceptives,[1] but a further study showed no effect on either ethinylestradiol[2] or levonorgestrel.[3]

1. Back DJ, *et al.* Interaction of ethinyloestradiol with ascorbic acid in man. *BMJ* 1981; **282:** 1516.

2. Zamah NM, *et al.* Absence of an effect of high vitamin C dosage on the systemic availability of ethinyl estradiol in women using a combination oral contraceptive. *Contraception* 1993; **48:** 377–91.
3. Kuhnz W, *et al.* Influence of high doses of vitamin C on the bioavailability and the serum protein binding of levonorgestrel in women using a combination oral contraceptive. *Contraception* 1995; **51:** 111–16.

Pharmacokinetics

For a discussion of the pharmacokinetics of oestrogens and progestogens, see Estradiol, p.2098 and Progesterone, p.2126, respectively. The extent of binding of progestogens to serum sex-hormone binding globulin may be altered when they are given with an oestrogen. Oestrogens increase serum concentrations of sex-hormone binding globulin, and progestogens differ in their ability to suppress this effect.

◊ Reference to the effects of hormonal contraceptives on binding proteins.[1]

1. Fotherby K. Interactions of contraceptive steroids with binding proteins and the clinical implications. *Ann N Y Acad Sci* 1988; **538:** 313–20.

Uses and Administration

The main use of hormonal contraceptives is for contraception, but combined oral contraceptives are also commonly used in menstrual disorders such as dysmenorrhoea (p.6), premenstrual syndrome (p.2099), and menorrhagia (p.2126), particularly where contraception is also required. Combined oral contraceptives are also used in polycystic ovary syndrome (p.2080) and Turner's syndrome (p.2081), and may be used in endometriosis (p.2091); those containing non-androgenic progestogens may be used in acne (p.2070) and hirsutism (p.2089).

Combined oral contraceptives containing both an oestrogen and a progestogen are the most effective type of oral contraceptive for general use. The synthetic ethinyl derivatives ethinylestradiol and mestranol are the oestrogens typically used in such preparations. The progestogenic component is usually a 19-nortestosterone derivative such as desogestrel, etynodiol diacetate, gestodene, levonorgestrel, lynestrenol, norethisterone, norethisterone acetate, norgestimate, or norgestrel. Preparations may be *monophasic* (containing a fixed dose of oestrogen and progestogen), or *biphasic* or *triphasic* (when the dose of progestogen, or both the progestogen and oestrogen, are varied through the cycle). Phased preparations are designed to mimic more closely the pattern of endogenous hormone secretion and may provide better cycle control than monophasic preparations. More rarely, *sequential* preparations are used, which contain an oestrogen alone for part of the cycle. Most combined oral contraceptives are taken for 21 days followed by an interval of 7 days when menstrual bleeding will occur. Some preparations include 21 active tablets plus 7 inert tablets to remove the need for counting days ('every day' preparations). Variations on this 28-day cycle include 22 days of active tablets followed by a 6-day interval for bleeding, and 24 days of active tablets followed by a 4-day interval. Long- or extended-cycle preparations are also available: some preparations may be taken continuously for 84 days, followed by 7 days of inert tablets or a lower dose of oestrogen alone (such as ethinylestradiol 10 micrograms). More recently, a preparation containing active tablets to be taken every day without any tablet-free interval has been introduced. The oestrogen content of most preparations is currently ethinylestradiol 20 to 40 micrograms daily; in some preparations a lower dose of 15 micrograms is used and in others up to 50 micrograms is available (even higher doses were often formerly used). A formulation containing the lowest dose of oestrogen compatible with good cycle control should be chosen, considering the following:

- *low-strength* preparations (ethinylestradiol 20 micrograms) are most appropriate for women with risk factors for cardiovascular disease (see under Precautions, above), provided a combined oral contraceptive is considered otherwise suitable
- *standard-strength* preparations (ethinylestradiol 30 or 35 micrograms or mestranol 50 micrograms if monophasic, or ethinylestradiol 30 to 40 micrograms if phased) are appropriate for most other women
- *high-strength* preparations (ethinylestradiol 50 micrograms) are generally used only in circumstances where bioavailability of the oestrogen is reduced, such as concomitant use of some enzyme-inducing drugs (see Interactions, above)

When first **starting** combined oral contraceptives, if the first tablet is taken on the first day of the menstrual cycle (the first day of bleeding) additional contraceptive precautions are unnecessary. If the first tablet is taken on the fourth day of the cycle or later, additional contraceptive precautions should be undertaken for 7 days (or 14 days for 'every day' preparations in case the inert tablets are inadvertently taken first). If amenorrhoea is present and pregnancy has been excluded, combined oral contraceptives may be started on any day, but additional precautions should be used for the first 7 days. In the case of abortion or miscarriage combined oral contraceptives should be started on the same day. In women not breast feeding, they may be started 3 weeks postpartum, but additional contraceptive precautions should be taken for the first 7 days if the combined oral contraceptive is started later than 3 weeks postpartum; progestogen-only contraceptives are preferred in breast-feeding women (see under Precautions, above).

When **changing** to a combined preparation containing a different progestogen, the new preparation should be started on the day after the last active tablet of the old preparation. If a tablet-free interval is taken then extra contraceptive precautions are necessary for the first 7 days of the new preparation. In the case of 'every day' preparations, to allow for the fact that the inert tablets may inadvertently be taken first, extra contraceptive precautions are necessary during the first 14 days. Meticulous regularity of dosage is essential and contraceptive protection may be lost if a dose is not taken at the proper time or is missed, especially if the missed dose is at the beginning or end of a cycle.

If a tablet is **missed** the risk of pregnancy is greatest when this happens at the beginning or at the end of a cycle, which lengthens the tablet-free interval. Over time, advice for dealing with missed tablets has changed and varies between countries and preparations. In 2004, WHO issued recommendations based on how many combined oral contraceptive tablets have been missed and when.

- If 1 or 2 tablets containing 30 or 35 micrograms of ethinylestradiol (or 1 tablet of 20 micrograms) have been missed at any time, the most recent missed tablet should be taken as soon as possible, and the rest of the course should be taken as normal; no additional contraceptive protection or emergency contraception is needed. This advice also applies if a new course of tablets has been started 1 or 2 days late for 30- or 35-microgram tablets, or 1 day late for 20-microgram tablets.
- If 3 or more tablets containing 30 or 35 micrograms of ethinylestradiol (or 2 or more tablets of 20 micrograms) have been missed at any time, the most recent missed tablet should be taken as soon as possible, and the rest of the course should be taken as normal; the woman should also use condoms or abstain from intercourse until she has taken active tablets for 7 days in a row. This advice also applies if a new course of tablets has been started 3 or more days late for 30- or 35-microgram tablets, or 2 or more days late for 20-microgram tablets. In addition, emergency contraception should be considered if the tablets were missed in the first week of the course and she had unprotected intercourse during the tablet-free interval or in the first week. If the tablets were missed in the third week of the course, then the tablet-free interval (or the 7 inert tablets) should be omitted and the next course of tablets started immediately after the last.

If the woman has missed more than 1 tablet, she can take the first missed tablet and then either continue taking the rest of the missed tablets or discard them to stay on schedule. Depending on when she realises that she has missed a tablet, she may take 2 tablets on the same day or even at the same time.

For extended-cycle preparations, licensed product information gives similar advice regarding missed tablets (or starting a course late), in that the course should be resumed as soon as possible. If 1 tablet has been missed, additional contraception is not needed, but if 2 or more tablets have been missed, additional contraception should be used until 7 days of active tablets have been taken.

Similarly, extra contraceptive measures may be needed during, and after recovery from, vomiting or diarrhoea. WHO recommends that if the woman vomits within 2 hours after taking a tablet, she should take another tablet. If there is severe vomiting or diarrhoea for more than 24 hours she should continue taking the course if she can, and if it continues for 2 or more days she should follow the advice for missed tablets.

Progestogen-only oral contraceptives are suitable for women when an oestrogen component is contra-indicated. They are taken continuously, usually **starting** on day one of the menstrual cycle, with no interval during menstrual bleeding. They are associated with a higher failure rate than the combined preparations. Regularity in taking the doses is even more important with this type of preparation; contraceptive efficacy is reduced if a dose is delayed by more than 3 hours (a delay of up to 12 hours is acceptable for desogestrel). Commonly used progestogens include the 19-nortestosterone derivatives etynodiol diacetate, levonorgestrel or norgestrel, and norethisterone.

When **changing** from a combined oral contraceptive preparation to an oral progestogen-only contraceptive, the new tablets should be started immediately with no tablet-free interval (or, in the case of 'every day' preparations, omitting the inert tablets).

If a **missed tablet** is delayed by more than 3 hours (or 12 hours for desogestrel), it should be taken as soon as possible and the next tablet taken at the correct time. Although some UK licensed product information suggests that additional contraceptive methods should be used for the next 7 or 14 days, depending on the product, WHO suggests that extra contraception is only required for the next 2 days. Postcoital hormonal contraception (emergency contraception) should be considered if unprotected intercourse has occurred before 2 further tablets have been taken correctly. Additional contraceptive methods may also be needed during, and after recovery from, vomiting or diarrhoea, and WHO gives the same advice as that for combined oral contraceptives described above.

Progestogens are also used alone as **parenteral contraceptives** and provide a very high level of contraceptive efficacy. They are usually given within the first 5 days of the menstrual cycle. Injectable contraceptives are usually used to provide short-term protection for several months or are used in women unable to use other methods. Medroxyprogesterone acetate is given by intramuscular or subcutaneous injection as a long-acting depot preparation to provide contraception for at least 12 weeks. Norethisterone enantate is used similarly by intramuscular injection to provide protection for up to 8 weeks. Levonorgestrel is used in the form of a subcutaneous implant providing contraception for up to 5 years. A contraceptive implant containing etonogestrel, effective for 3 years, is also available. A combined parenteral contraceptive containing the oestrogen estradiol cipionate with medroxyprogesterone acetate, and given monthly by intramuscular injection, has been developed.

Hormonal **intra-uterine contraceptive devices** are also available. One such device releases progesterone to provide contraception for 1 year; another releases levonorgestrel for 5 years. These are usually inserted within 7 days of the onset of menstruation. A contraceptive **vaginal ring**, which releases ethinylestradiol and etonogestrel, is retained in the vagina for 3 weeks; it is then removed for a one-week interval after which a new ring is inserted.

A contraceptive **transdermal patch**, which releases ethinylestradiol and norelgestromin, has been developed. A new patch is applied each week for 3 weeks, followed by a one-week patch-free interval. If the patch becomes partly or completely detached, or there is a delay in its application, contraceptive efficacy can be reduced or lost.

- If the patch has been detached for less than 24 hours, it should be re-applied if it is still sufficiently adhesive, or replaced with a new patch; no additional contraceptive method is needed and the following patch should be applied on the usual day. If it has been detached for 24 hours or more, a new 4-week cycle should be started and a new patch applied; additional contraceptive precautions should be taken for the first 7 days.
- If application of the first patch of a new cycle is delayed after the patch-free interval, it should be applied as soon as remembered and this day used as the first day of the new cycle; additional contraceptive precautions should be used for 7 days, and if unprotected intercourse has occurred during the patch-free interval then the possibility of fertilisation should be considered.
- When the patch is changed in the middle of the cycle (week 2 and 3), if there is a delay of up to 48 hours the new patch should be applied immediately, with the next patch applied on the usual day; no additional contraceptive precaution is needed. If the delay is more than 48 hours, the new patch should be applied and a new 4-week cycle started; additional contraceptive precautions should be taken for 7 days.
- If there is a delay in removing the third patch, before the patch-free interval, it should be removed as soon as possible and the next cycle started on the usual day; no additional contraception is required.

Postcoital hormonal contraceptives (emergency contraception) should be taken within 72 hours after unprotected intercourse to be most effective (for details see Emergency Contraception, below). A single oral dose of levonorgestrel 1.5 mg may be given within 72 hours of intercourse, or it may be given as a dose of 750 micrograms within 72 hours of intercourse followed by a second dose 12 hours later. An alternative preparation available for such use consists of tablets each containing ethinylestradiol 50 micrograms and norgestrel 500 micrograms or levonorgestrel 250 micrograms. Two tablets should be taken within 72 hours and a further 2 tablets 12 hours later. UK licensed product information for levonorgestrel-only preparations suggests that if vomiting occurs within 3 hours of any dose it can be repeated. However, WHO considers that 2 hours is probably sufficient for hormone absorption and that no action is needed if vomiting occurs after this time. WHO also considers that combined hormonal preparations are more likely to cause nausea and vomiting, and that the use of an antiemetic may be considered before repeating a dose. The efficacy of postcoital hormonal contraception may be reduced in women who are being treated with enzyme-inducing drugs, and a higher dose of levonorgestrel has been suggested (see Interactions, above).

◊ Reviews and guidelines.

1. Department of Reproductive Health and Research. *Selected practice recommendations for contraceptive use*. 2nd ed. Geneva: WHO, 2004. Also available at: http://whqlibdoc.who.int/publications/2004/9241562846.pdf (accessed 14/01/08)
2. Wiegratz I, Kuhl H. Long-cycle treatment with oral contraceptives. *Drugs* 2004; **64:** 2447–62.
3. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. Missed pills: new recommendations. *J Fam Plann Reprod Health Care* 2005; **31:** 153–5. Also available at: http://www.ffprhc.org.uk/admin/uploads/MissedPillRules%20.pdf (accessed 14/01/08)
4. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC guidance (April 2006): emergency contraception. *J Fam Plann Reprod Health Care* 2006; **32:** 121–7. Also available at: http://www.ffprhc.org.uk/admin/uploads/449_EmergencyContraceptionCEUguidance.pdf (accessed 14/01/08)
5. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC guidance (issued July 2006, updated January 2007): first prescription of combined oral contraception. Available at: http://www.ffprhc.org.uk/admin/uploads/FirstPrescCombOralContJan06.pdf (accessed 14/01/08)

Acne. Oral contraceptives have been shown to be effective[1,2] in reducing inflammatory and non-inflammatory lesions in women with acne (p.1577) who require contraception, probably by a multifactorial action on circulating androgens. Studies have used combinations of ethinylestradiol with various progestogens; a systematic review[2] considered that combinations with chlormadinone or cyproterone acetate were more effective than those with levonorgestrel, but noted that this was based on limited evidence. Combination preparations based on cyproterone acetate, that also have a contraceptive effect, have traditionally been favoured for acne management (see also p.2089).

1. Huber J, Walch K. Treating acne with oral contraceptives: use of lower doses. *Contraception* 2006; **73:** 23–9.
2. Arowojolu AO, *et al*. Combined oral contraceptive pills for treatment of acne. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 14/01/08).

Contraception. Contraception is used for fertility control, and some methods have additional non-contraceptive health benefits. There are a wide variety of regular methods including periodic abstinence (natural family planning), male and female barrier methods, intra-uterine devices (IUDs), female hormonal contraceptives, and female or male sterilisation. In addition, female hormonal contraceptives and copper IUDs are available for emergency (postcoital) contraception. The methods used for contraceptive purposes can be grouped into three categories: those that prevent ovulation, those that prevent fertilisation of the ovum, and those that prevent implantation of the fertilised ovum. None of the available contraceptive methods are effective once implantation of a fertilised ovum has occurred, i.e. they are not abortifacients.

A large number of factors will influence the choice of contraceptive method. Those relating to the woman include age (and therefore likely fertility), parity, medical disorders, risk of sexually transmitted diseases, smoking status, breast feeding, and cultural and religious considerations. Those relating to the method include its failure rate, reversibility, ease of use, mechanism of action, adverse effects, and non-contraceptive benefits.

The most reliable reversible methods for contraception are those for which there can be no 'user' failure such as *progestogen injections* and *implants*, and progestogen or copper *intra-uterine devices* (IUDs). When used perfectly, these methods have reported failure rates of between 0.05 and 0.6% during the first year of use; higher rates had been reported with older IUDs. The duration of action of the various progestogen injections is up to 2 or 3 months, whereas progestogen implants and progestogen IUDs can be effective for 1 to 5 years, depending on the preparation. These long-acting progestogen preparations thicken cervical mucus, so preventing sperm penetration, and suppress the endometrium, so preventing implantation. In addition, they suppress ovulation; the degree of suppression is complete for injectable preparations, about 50% for implants, and low for the progestogen IUDs. Copper IUDs were traditionally thought to act by preventing implantation, but it is now thought that the biochemical changes which they produce in the uterus also prevent fertilisation. They are effective and have a prolonged action (up to 5 or 10 years). There is an increased risk of pelvic infection in the 20 days after insertion of an IUD, but the risk is the same as non-IUD users thereafter. An IUD must not be used in women with a current sexually transmitted infection or pelvic inflammatory disease, but it may be considered in those who are no longer at risk after an infection has been treated. For women at increased risk of infection, prophylactic antibacterial therapy may be given before IUD insertion if screening test results are not yet available. In the past, it was recommended that IUDs were not suitable for nulliparous women because of a risk of impaired fertility after removal. However, this may have been biased by other factors such as the increased risk of sexually transmitted infection associated with sexual behaviour in younger women. Nulliparity alone is therefore no longer considered a contra-indication to IUD use, and indeed some IUDs have been designed specifically for this group of women. Although IUDs are effective at preventing pregnancy, in the uncommon event of IUD failure, the risk of ectopic pregnancy is increased and can occur in 6 to 8% of these pregnancies.

Of methods subject to 'user' failure, *combined oral contraceptives* are the most effective. They have a reported failure rate during the first year of 0.3% if used perfectly, but 8% in typical practice. Their principal mechanism of action is to prevent ovulation, and they also decrease the chances of fertilisation and implantation. Combined oral contraceptives offer the non-contraceptive advantages of avoidance of dysmenorrhoea, premenstrual tension, and iron-deficiency anaemia, and in the long-term they protect against endometrial and ovarian cancer. However, they do not protect against sexually transmitted diseases, they are unsuitable for older women who smoke, and long-term use carries a slight increased risk of breast cancer. Other forms of combined contraceptive which have been developed recently include *monthly injection*, *vaginal ring*, and *transdermal patch*.

Progestogen-only oral contraceptives are considered to have a slightly higher failure rate than that for combined preparations because of the need for more accurate dosage timing. A 0.9% failure rate has been given for the first year of use if taken correctly, but in practice failure rates of up to 10% have been reported. Failure rates are lower in women taking these contraceptives during breast feeding, as breast feeding itself provides additional contraception (see also Natural Family Planning Methods, below). Regularity in taking them is essential; a dose should not be delayed for more than 3 hours (up to 12 hours for desogestrel). They act primarily to decrease the chance of fertilisation and implantation since they prevent ovulation in only 14 to 50% of cycles, although desogestrel is said to reliably inhibit ovulation. They are useful for women who are breast feeding, for those who smoke and are more than 35 years of age, and if medical conditions contra-indicate the use of oestrogens.

Barrier methods, including both male and female condoms, vaginal sponges containing spermicide, and diaphragms and cervical caps used with spermicide, act as a mechanical barrier to prevent fertilisation, and inactivate sperm. Barrier methods decrease the risk of sexually transmitted diseases and a shift towards their use has occurred since the emergence of HIV infection in particular. However, barrier methods are not as effective in preventing conception as hormonal contraception and IUDs. Even when used correctly, failure rates in the first year of use vary from 2% for the male condom, to 6% for the diaphragm with spermicide, to 20% for the vaginal sponge in parous women. Spermicides, such as nonoxinol 9, may be used as foam, cream, jelly, dissolvable vaginal tablets or pessaries, or as a spermicide-containing polyvinyl alcohol film placed over the cervix. However, they are generally considered relatively ineffective when used as the sole method of contraception, and such use is not recommended.

Natural family planning methods such as periodic abstinence using the calendar, temperature, cervical mucus ('Billings') or sympto-thermal methods require high motivation to learn and practice effectively. However, they may be the only acceptable method to some people. More recently, daily measurement of urine hormone concentrations has been used as a predictor of the timing of ovulation and hence the risk of becoming pregnant; on 'unsafe' days abstinence or barrier methods are required. Traditional methods such as withdrawal (coitus interruptus) are widely used in some areas, but are considered relatively ineffective. The lactational amenorrhoea method of contraception can be used during breast feeding for up to 6 months after childbirth. For it to be an effective contraceptive method, breast feeding must start immediately after birth, the infant must be fully or nearly fully breast-fed, feedings must be no more than 4 to 6 hours apart, and menstruation must not have restarted. When carried out consistently and correctly, this method has a failure rate of 0.9% in the first 6 months.

Various other methods of contraception are under investigation including the use of the antiprogestogen mifepristone, selective sex-hormone receptor modulators, and contraceptive vaccines. There has also been some investigation of **male contraception**. Weekly intramuscular injection of high-dose testosterone or nandrolone to produce azoospermia has been investigated with some success, but development of an oral contraceptive dosage form for males has been slow. Use of a progestogen with testosterone is being studied, as is the use of implants of synthetic androgens such as trestolone (7-α-methyl-19-nortestosterone; MENT).

The available irreversible methods of contraception are surgical male or female *sterilisation*. The use of mepacrine for non-surgical female sterilisation has been attempted but has proved extremely controversial.

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Emergency contraception. Emergency contraception (postcoital contraception) can be used after unprotected intercourse but before a fertilised ovum has been implanted. Methods that act after implantation are considered abortifacients. The two most commonly used emergency contraceptives are *oral contraceptives* and *copper IUDs*.

Oral contraceptive regimens (the so-called 'morning after pill') have historically used a preparation containing high-dose oestrogen with a progestogen, taken within 72 hours of intercourse, and repeated 12 hours later (the Yuzpe regimen). This preparation is thought to act by a variety of mechanisms, which may depend on when in the menstrual cycle it is used. It may prevent implantation, prevent or delay ovulation, disrupt ovum transport, and alter corpus luteum function. However, levonorgestrel alone (without an oestrogen) is now widely recommended as an emergency contraceptive. A large WHO multicentre study found that levonorgestrel 750 micrograms alone within 72 hours of intercourse and repeated after 12 hours was more effective than the Yuzpe regimen and better tolerated.[1] Both regimens were most effective when given within 24 hours of intercourse.[1,2] A small observational study[3] of the Yuzpe method used between 72 and 120 hours after unprotected intercourse reported a trend towards decrease in effectiveness. A further large study[4] by WHO found that for up to 120 hours after intercourse, a single dose of levonorgestrel 1.5 mg was as effective as two doses of 750 micrograms given 12 hours apart, with a pregnancy rate of about 1.5%.

Efficacy rates vary between studies, but the Yuzpe method has been shown to reduce the risk of pregnancy by about 75% and levonorgestrel by about 89%.[5] Based on its greater efficacy and better tolerability, levonorgestrel is now generally recommended as the hormonal emergency contraceptive of choice that can be offered up to 120 hours after intercourse.[5-9]

Copper, but not progestogen, IUDs can be inserted up to 120 hours after unprotected intercourse for postcoital contraception. They have a failure rate of no more than 1% when used for emergency contraception.[9] Thus, when efficacy is a priority the IUD is the emergency contraceptive method of choice.

Mifepristone is under investigation as an emergency contraceptive. Its action appears to depend on inhibiting ovulation or, if ovulation has occurred, preventing implantation. Early studies used a single dose of 600 mg, but later studies have found 10 mg to be equally effective. Mifepristone also appears to be at least as effective as levonorgestrel but it can delay the onset of subsequent menstruation, which might cause anxiety in some women.[10,11]

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Malignant neoplasms. The prophylactic use of oral contraceptives may protect against ovarian cancer in women with mutations of the BRCA1 or BRCA2 genes, but must be balanced against the risk of breast cancer in these women (see Ovary, under Carcinogenicity, p.2061).

Hormone Replacement Therapy

Hormonersatztherapie; HRT; THS; Traitement Hormonal Substitutif; Tratamiento hormonal restitutivo.

Гормонозаместительная Терапия

The Menopause

The menopause is defined as the permanent cessation of cyclical menstruation due to loss of ovarian follicular activity. It is therefore determined in retrospect, conventionally after 1 year without menstruation. In the few years before the menopause (the menopausal transition), ovarian oestradiol secretion declines, sometimes in a fluctuating manner, and there is a resultant increase in pituitary follicle-stimulating hormone (FSH) secretion. The menopausal transition may be characterised by irregular menstrual cycles and dysfunctional uterine bleeding, and fertility is much reduced compared with the early reproductive years. The term perimenopause is used to cover the menopausal transition and the first year after the menopause, and may last 6 years or more. It has sometimes been referred to as the climacteric. Oestrogen concentrations reach their minimum and FSH concentrations their maximum about 4 years after the menopause. After the menopause the ovaries may continue to produce some androgens; adrenal and ovarian androgens are aromatised to oestrogens (predominantly oestrone) in the periphery, but oestrogen concentrations are much lower than in premenopausal women. The median age for the natural menopause is about 51 years. If the menopause occurs in women aged 40 years or less, it is considered premature. The menopause may be induced by surgical removal of both ovaries, or sometimes by antineoplastic drugs or radiotherapy.

The decline in oestrogen concentrations during the perimenopause may be associated with both acute and long-term effects. However, some of these may be difficult to differentiate from the effects of ageing, and the incidence varies geographically. Established *acute symptoms* can include vasomotor instability, manifesting as hot flushes and night sweats, and vaginal atrophy and dyspareunia. Non-specific symptoms include palpitations, headache, backache, and psychological symptoms such as tiredness, lack of concentration, loss of libido, irritability, insomnia, and depression. Insomnia may occur secondary to night sweats. There is little evidence that depressive illness is disproportionately increased at the menopause. Urinary problems are common in ageing women, and may occur in the perimenopause, but the extent that these are due to lack of oestrogens has not been determined. An established *long-term consequence* of the decline in oestrogen concentrations is an increased risk of bone fractures resulting from an increase in the rate of bone resorption. In addition, decline in oestrogen concentrations is associated with adverse effects on blood lipoproteins, and this may be a risk factor for cardiovascular disease.

Acute and longer-term effects of the menopause may be managed by using hormone replacement therapy (HRT) with oestrogens, with or without progestogens, and nonhormonal therapies (see Menopausal Disorders, p.2077).

Adverse Effects of HRT

When oestrogens are used for menopausal HRT, adverse effects include nausea and vomiting, abdominal cramps and bloating, weight changes, breast enlargement and tenderness, premenstrual-like syndrome, sodium and fluid retention, altered blood lipids, cholestatic jaundice, glucose intolerance, rashes and chloasma (melasma), changes in libido, migraine, dizziness, depression, mood changes, headache, leg cramps, vaginal candidiasis, and decreased tolerance of contact lenses. Transdermal delivery systems may cause contact sensitisation (possibly severe hypersensitivity reactions on continued exposure), and nasal sprays may cause local irritation, rhinorrhoea, and epistaxis. Headache has been reported on vigorous exercise. Use of oestrogen without a progestogen results in endometrial hyperplasia and an increased risk of endometrial carcinoma (see below). The addition of a progestogen for 10 to 14 days of a 28-day cycle reduces this risk but results in regular withdrawal bleeding towards the end of the progestogen. Use of continuous progestogen and oestrogen avoids withdrawal bleeding, but may result in irregular breakthrough bleeding, particularly in the early stages of therapy, or if used within 12 months of the last menstrual period. Current use of menopausal HRT is associated with an increased risk of venous thromboembolism and breast cancer (see below).

◊ Reviews.

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Carcinogenicity. Use of unopposed oestrogen as menopausal HRT in women with a uterus increases the risk of endometrial cancer, irrespective of the route of administration. This risk is reduced, although possibly not eliminated completely, by the concomitant use of a progestogen. There is also evidence that use of HRT, as oestrogen alone or with a progestogen, increases the risk of breast cancer.

Because of continuing modifications in regimens for HRT there is a continuing need to monitor the incidence of various cancers in users of this therapy.

The carcinogenicity of combined menopausal HRT has been reviewed.[1]

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BREAST. Early age at menarche and late age at menopause increase the risk of breast cancer, and surgical oophorectomy at an early age decreases the risk of breast cancer. In addition, higher concentrations of unbound endogenous oestrogens in postmenopausal women appear to increase the risk of developing breast cancer.[1] Such risk factors have prompted concerns that menopausal HRT might be associated with an increased risk of breast cancer.

Reviews and analyses[2-4] of studies published during the 1970s and/or 1980s on the use of **unopposed oestrogen** replacement therapy in postmenopausal women have generally shown that there is an associated moderate increase in the risk of breast cancer; figures for overall relative risk compared with non-oestrogen users ranged from under 1 to up to 2. One of these,[3] a meta-analysis of studies from 1976 to 1989, further showed that although the relative risk of breast cancer rose to 1.3 after 15 years of oestrogen use, it did not appear to rise at all until after 5 years of use. A similar meta-analysis[4] differentiated between low-dose oestrogens and high-dose oestrogens; those taking 625 micrograms daily of conjugated oestrogens had a risk of breast cancer 1.08 times higher than non-oestrogen users, whereas the relative risk in those taking 1.25 mg daily or more was up to 2.0. A subsequent meta-analysis[5] differentiated between current use of HRT, duration of use, and use at any time. The highest relative risk of breast cancer was associated with current use (1.4); use for 10 years or more was associated with a relative risk of about 1.2, and having ever used HRT was not associated with an increased risk. In 1997 the Collaborative Group on Hormonal Factors in Breast Cancer reanalysed about 90% of the worldwide evidence on breast cancer and the use of HRT.[6] They reported that the relative risk of having breast cancer diagnosed was increased by a factor of 1.023 for each year of use, being 1.35 for 5 or more years of use. However, this effect was reduced on cessation of use, and had largely disappeared after about 5 years. In women who started therapy at age 50, the cumulative excess number of breast cancers diagnosed per 1000 women between age 50 and 70 were estimated to be 2, 6, and 12 for 5, 10, and 15 years of use, respectively, from a baseline of 45 per 1000 in never-users.[6] In contrast, the arm of the Women's Health Initiative[7] that compared conjugated oestrogens with placebo over an average of about 7 years found a trend towards a reduction in breast cancer risk with HRT. A Finnish cohort study[8] also found no increase in risk with less than 5 years of oral estradiol or estriol therapy. For women taking unopposed oestrogen in the Nurses' Health Study[9] cohort the linear increase in risk with increasing duration of use did not become statistically significant until current use exceeded 20 years.

Most data relate to the use of unopposed oestrogen. There has been speculation both that the concomitant use of progestogen in HRT could reduce the risk of breast cancer and that it might increase it. Bergkvist *et al.*[10] suggested an increased relative risk of