



# IPPF Medical Bulletin

## Contents

<b>IMAP statement on hormonal methods of contraception</b> .....	1
--	---

## IMAP statement on hormonal methods of contraception

*The statement below was developed by the IPPF Medical Advisory Panel (IMAP) at its meeting in May 2002.*

### INTRODUCTION

Over the past decade there has been an increase in the number of hormonal methods of contraception. In addition to having a broader range of methods, we now have more evidence on safety, efficacy, and issues relating to user satisfaction.

This revised statement is designed to emphasise for both clients and providers the wide range of choice of hormonal methods of contraception now available and to enable a woman who wishes to use one of them to choose the most appropriate.

All hormonal contraceptives are highly effective when used correctly.

Currently available hormonal contraception falls into two broad categories:

- Combined hormonal contraception which contains both an oestrogen and a progestogen
- Progestogen-only contraception which does not contain oestrogen.

Within each of these categories, methods differ in terms of type and dose of hormone and mechanism of action. They also differ in terms of their mode of administration (pills, injectables, implants, intrauterine devices, vaginal rings, transdermal patch) and their duration of action. These factors largely determine which method a woman prefers. There are differences in the health benefits and in the risks associated with the two broad categories of hormonal contraception.

Women who are young and healthy can use all hormonal methods of contraception safely.

A counsellor should explain to the woman the full range of contraceptive choices available to her, including non-hormonal methods. Counselling should then focus on issues that will assist informed choice. Three fundamental questions should be asked:

1. Which method would she prefer to use?
2. Are there any medical reasons why she should not use this method?
3. Are there any other reasons why another method might be more appropriate?

Most medical conditions that might influence choice of a hormonal method can be excluded by taking a thorough medical history and measuring blood pressure.

Reproductive goals and lifestyle factors (such as risk of sexually transmitted infection [STI], smoking, and occupation) are also important in the choice of method and discussion of these should be part of routine counselling.

Hormonal contraceptives do not protect against STI/HIV. If there is risk of exposure to STI/HIV, the correct and consistent use of condoms is recommended either alone or in addition to any hormonal method.

### COMBINED HORMONAL CONTRACEPTIVES

Combined oral contraceptives (COCs) were first marketed in the early 1960s, and at present more than 100 million women are using them. The combined injectable contraceptives (CICs) appeared in the late 1980s and, more recently, combined contraceptive vaginal rings and transdermal patches have become available. The combined pill has been more thoroughly studied than any other medication; other combined hormonal methods have been closely investigated but not yet so extensively. The first COCs to be introduced contained high doses of oestrogen and progestogen, but there has since been a gradual and substantial reduction in both components. Current COCs are safer than the older ones and, because of their safety and efficacy, can be obtained in many countries without prescription.

From the extensive studies on COCs it is apparent that the health benefits of combined hormonal contraceptives far outweigh the health risks for most women.

#### Methods

##### *Combined oral contraceptives*

*Monophasic COCs* – These are usually a combination of ethinylestradiol in doses of 20–50 µg and a progestogen. One pill is taken daily for 21 days followed by an interval of 7 days during which either no pills or inactive pills are taken. The dose of both steroids in the active pills is constant for the 21 days. The progestogens contained in existing pills include levonorgestrel, norethisterone, desogestrel, gestodene, cyproterone acetate, drospirenone, and norgestimate.

*Multiphasic COCs (biphasic and triphasic)* – These are a modification of the combined OC where varying dose combinations of oestrogen and progestogen are used throughout the cycle. There is no evidence that multiphasic COCs are more effective or safer than monophasic COCs, and their clinical effects are similar.

*New methods* – A combined contraceptive vaginal ring releasing 120 µg etonogestrel (the active metabolite of desogestrel) and 15 µg ethinylestradiol per 24 hours, and a transdermal contraceptive patch releasing 20 µg ethinylestradiol and 150 µg norelgestromin (active metabolite or norgestimate) per 24 hours, have been marketed in a few countries. These methods provide promising new options for women's contraceptive choice. However, experience with these methods is still very limited and they will not be discussed in this review.

##### *Combined monthly injectables*

There are two combinations of combined monthly injectables:

- 25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate (Cyclofem, Cycloprovera, Lunelle, Novafem)
- 50 mg norethisterone enanthate and 5 mg estradiol valerate (Mesigyna, Norigynon).

In some countries, other combined injectable contraceptive formulations are available but they have not been tested sufficiently to be recommended by IPPF.

### **Mechanism of action**

The primary mode of action of COCs and CICs is suppression of ovulation by inhibition of pituitary follicle-stimulating hormone and luteinising hormone. In addition, thickening of the cervical mucus (mainly due to progestogen) presents an obstacle to sperm penetration. Although the histology of the endometrium is altered, there is no evidence that this contributes to the contraceptive effect.

### **Efficacy**

The failure rates of COCs and CICs when they are used according to instructions are very low, varying between 0.1% and 0.5%. With typical use the failure rate for CICs is 0.3% and for COCs 6–8%. The higher typical failure rate for COCs is due to the greater likelihood of users' deviating from instructions.

### **Beneficial effects**

The beneficial effects of COCs are well documented. CICs have been available for a much shorter time so that there are fewer data. However, on the basis of theoretical considerations and existing data, the health benefits for CICs are expected to be similar to those of COCs.

### **Prevention of pregnancy**

The most important benefit of the use of COCs is the prevention of pregnancy, including ectopic pregnancy.

### **Ovarian cancer**

COC use decreases a woman's risk of developing ovarian cancer by about 40%. The longer that COCs are used the greater the protective effect, which persists for at least 10 years after COCs are stopped.

### **Endometrial cancer**

COCs also lower the risk of endometrial cancer, by about 50%. The longer that COCs are used the greater the protective effect, and protection seems to continue for up to 15 years after stopping.

### **Menstruation-related disorders**

Since COCs usually lessen menstrual blood loss, they decrease the chance of anaemia developing or worsening. Where cycles have been irregular before, the artificial cycle produced by the pill may provide regularity. Mid-cycle pain, premenstrual tension, and dysmenorrhoea are often relieved.

### **Pelvic inflammatory disease**

The incidence of symptomatic pelvic inflammatory disease is lower in users of COCs than in non-users or in users of other methods with the exception of barrier methods. However, COCs do not protect against sexually transmitted infections, including HIV.

### **Ovarian cysts**

Use of monophasic COCs protects against functional ovarian cysts. Protection is lower with pills containing doses less than 50 µg ethinylestradiol and may not occur with triphasic pills.

### **Benign breast disease**

Use of COCs protects against certain types of benign breast disease.

### **Possible benefits**

Less clearly documented than the above benefits is possible protection against uterine fibroids and osteoporosis.

### **Side-effects**

Low-dose COCs and CICs are well tolerated by most women; however, side-effects can be a reason for discontinuation. Breakthrough bleeding or spotting may occur with either method, particularly during the first three cycles of use. CICs are more likely than COCs to result in prolonged irregular bleeding, heavy bleeding, or amenorrhoea. Bleeding irregularities are less common with combined contraception than with progestogen-only methods. Some women report nausea, dizziness, breast tenderness, headache, fluid retention, or weight gain. Existing data, however, suggest that weight gain is seldom attributable to COC use. These self-reported symptoms tend to improve over time, and some can be alleviated by treatment.

### **Adverse effects**

Serious adverse effects of either COCs or CICs are very uncommon in young healthy women. As with data on beneficial effects, information on adverse effects is more complete for COCs than for CICs. Again, existing data and theoretical considerations suggest that the adverse-effect profiles will be similar.

### **Circulatory system disease**

Any excess morbidity or mortality from cardiovascular disease (myocardial infarction, stroke, venous thromboembolism) attributable to low-dose COCs is very small in women who do not smoke and do not have other risk factors for cardiovascular disease such as diabetes or hypertension.

The excess mortality risk increases with age; but, at any given age, a non-smoking woman who uses COCs has a smaller risk of death from arterial disease than a smoker who does not use COCs.

### **Myocardial infarction**

Myocardial infarction (MI) is rare in women of reproductive age, and the use of COCs does not increase the likelihood that it will occur in a young healthy woman without risk factors. However, COCs do increase the risk in women with an existing risk factor such as smoking, diabetes, or hypertension. In young women with risk factors the absolute risk of MI is still very low, but in older women (35 and over) risk factors become much more important. For example, in women aged 40–44 years who use COCs and smoke, the risk of MI is 25 per 100 000 woman-years – ie, more than 10 times greater than that for women aged 30–35. The more risk factors a woman has, the greater the risk of MI.

Data are limited and inconsistent regarding whether COCs containing desogestrel or gestodene carry a lower risk of MI than COCs containing levonogestrel.

### **Stroke**

*Thrombotic stroke* is a rare condition in women of reproductive age. For instance, in women aged 40–44, the annual risk for thrombotic stroke is 1 per 100 000 woman-years. The risk in healthy women is slightly higher (about 1.5-fold) in current users of low-dose COCs than in non-users. The risk is further raised if the woman smokes, and is at least three times higher if she is hypertensive.

*Haemorrhagic stroke* is also very rare in this age-group. In women aged less than 35 years who do not smoke and are not hypertensive, the risk is not increased by use of COCs. However, the risk is doubled if a COC user is aged 35 or more, is approximately 2.5 times greater if she smokes, and is about 10 times greater if she has a history of hypertension.

#### *Venous thromboembolism*

COC use increases the risk of venous thromboembolism (VTE) by 3–6 times, but this translates into an extremely low absolute risk of death from this cause because of the rarity of this event among non-pregnant women of reproductive age. COCs containing the newer progestogens desogestrel and gestodene may carry a slightly greater risk of VTE (1.6-fold) than COCs containing levonorgestrel. Existing data allow no conclusions on the risk associated with COCs containing norgestimate. The absolute risk of VTE attributable to use of COCs rises with increasing age, obesity, recent surgery, and certain forms of thrombophilia. In Caucasian women the baseline risk of VTE is 5 per 100 000 woman-years. This can be compared with a risk of 60 per 100 000 woman-years during pregnancy. In women using pills containing levonorgestrel the risk is 15 per 100 000 and in those using desogestrel or gestodene it is 20–30 per 100 000. There are no data of this kind for non-Caucasian women.

#### *Raised blood pressure*

A clinically significant rise in blood pressure is sometimes observed in COC users and usually disappears on discontinuation.

#### *Lipids*

Although use of the combined pill is associated with minor alterations in lipid profiles, there are no data to suggest that these changes are clinically important.

#### *Liver disorders*

Benign liver cell adenoma is very rare, but the risk of developing such a tumour is higher in COC users than in non-users. Tumour rupture, with haemorrhage, can endanger life. Cholestatic jaundice develops in some COC users, especially those who have had cholestatic jaundice of pregnancy.

#### *Possible carcinogenicity*

The possible causal association between COCs and various cancers has been a major concern; nevertheless, COC use is known to decrease the risk of cancers of the ovary and endometrium (see beneficial effects above) and has not, to date, been proved to cause any cancers.

#### *Breast*

Numerous studies of the relation between COCs and breast cancer have been conducted, and collectively suggest the following:

- Past users (>10 years since use) are at no increased risk for breast cancer
- Current and recent users (<10 years since stopping) have a small increase in risk of breast cancer.
- This effect is not related to duration of use
- The small excess risk seems largely confined to tumours localised in the breast. Such tumours have a better prognosis than those which have spread beyond the breast

- The findings among current and past users are not modified by known or suspected risk factors for breast cancer; specifically, the effects of COCs are identical in women with and without a family history of breast cancer.

Taken together, these observations indicate that COCs are unlikely to cause new cancers to develop.

#### *Cervix*

Studies in both developed and developing countries have shown a modest increase in the risk of cervical cancer (1.3–1.8 fold) among women who have used COCs for more than 5 years. However, it is not clear whether the increased risk is due to a direct effect of the pill or to some characteristics of pill-users such as age at first intercourse, number of sexual partners, parity, and smoking status. A meta-analysis has indicated that long-term use of oral contraceptives may be a cofactor that increases risk of cervical carcinoma in women who have had persistent human papillomavirus (HPV) infection of the cervix. The highest excess cancer risk, 4-fold, was seen in women who had used such contraception for 10 or more years. This finding does not, however, call for routine HPV-DNA testing. Women taking oral contraceptives should use the screening services, when these are available, in the same way as other women.

#### *Liver*

Several early studies suggested that in countries where primary liver cancer is rare, the risk was increased among women who used COCs. In countries where primary liver cancer is more common, more recent evidence suggests no increase in risk associated with COC use.

#### *Carbohydrate metabolism*

Although minor changes in plasma insulin and glucose tolerance occur in COC users (possibly an effect of the progestogen), there is no evidence of an increase in the incidence of clinical diabetes. COCs can be used by diabetic women under medical supervision, except those with severe complications such as nephropathy, retinopathy, and neuropathy, associated with increased risk of thrombosis. Diabetic women who use COCs should have their blood pressure taken periodically and they should discontinue the COC if hypertension develops, because this will substantially increase their risk of arterial disease.

#### *Pituitary adenomas*

Large studies have yielded no evidence of a causal relation between use of COCs and development of pituitary adenomas.

#### *Gallbladder disease*

Some studies point to an increased risk of gallbladder disease in COC users; the mechanism may be an acceleration of previous subclinical disease.

#### *Vitamins*

Changes in blood biochemical indicators of vitamin status have been observed during COC use but are of no clinical significance.

#### *Return of menstruation and fertility*

Six months after stopping COCs, most women have normal menstrual cycles. There is no evidence of decreased fertility in former COC users. CICs may be associated with a longer delay in return to fertility, but this is substantially less than that associated with progestogen-only injectables.

#### *Pregnancy outcome*

There is no excess rate of either spontaneous abortion or fetal abnormalities in former users of COCs, including those

who conceive soon after stopping COCs. The same is true for women who have inadvertently started COCs while pregnant or in whom the pregnancy began during COC use.

### Medical eligibility criteria

The International Planned Parenthood Federation and other international bodies have collaborated with the World Health Organization (WHO) in the development of eligibility criteria for the use of various contraceptive methods. The following classification was agreed:

- *Category 1:* A condition for which there is no restriction for the use of the contraceptive method
- *Category 2:* A condition where the advantages of using the method generally outweigh the theoretical or proven risks
- *Category 3:* A condition where the theoretical or proven risks usually outweigh the advantages of using the method
- *Category 4:* A condition in which the health risk increases unacceptably if the contraceptive method is used.

Pregnancy is no longer listed as a contraindication to initiation or continued use of a method of contraception since women who are already pregnant do not require contraception. If, however, COCs are used in the unknown presence of pregnancy, there is no reason to expect harm to the woman, to the course of her pregnancy, or to the fetus.

The eligibility criteria for COCs and CICs are at present similar with a few exceptions.

### Contraindications (category 4)

COCs or CICs should not be used in the presence of:

- Breastfeeding and less than 6 weeks postpartum
- Cerebrovascular or coronary artery disease
- Hypertension with BP >160/100 mm Hg
- Hypertension with vascular disease
- Migraine with focal neurological symptoms
- Diabetes with vascular complications (including hypertension, nephropathy, retinopathy, neuropathy) or of >20 years' duration
- Past or present evidence of deep venous thrombosis or pulmonary embolism
- Complicated valvular heart disease
- Acute liver disease
- Malignant liver tumour
- Breast cancer in the past 5 years.

The following conditions are also category 4 only for COCs:

- Smoking 15 or more cigarettes per day in women aged 35 or more (this condition is category 3 for CICs, which are thought to have less effect on coagulation factors)

- Severe decompensated cirrhosis (category 3 for CICs, which have little effect on liver function and no first-pass effect)
- Benign liver tumour (category 3 for CICs, for reasons above).

**Conditions requiring careful consideration (category 3)**  
COCs or CICs should generally not be used in the presence of:

- Breastfeeding from 6 weeks to 5 months postpartum
- Hypertension with BP 140–159/90–99 mm Hg
- History of hypertension where blood pressure cannot be evaluated
- Known hyperlipidaemia
- Migraine without focal neurological symptoms in women aged 35 or more (if it develops during use of COCs or CICs, it becomes category 4)
- History of breast cancer with no evidence of disease for past 5 years.

The following conditions are also category 3 only for COCs:

- Smoking less than 15 cigarettes per day in women aged 35 or more (category 2 for CICs, because of lesser effects on coagulation)
- Chronic liver disease other than severe cirrhosis, including mild cirrhosis (category 2 for CICs, for reasons above)
- Symptomatic gallbladder disease (category 2 for CICs, for reasons above).

When a woman wants to use COCs or CICs in the presence of a category 3 condition, the potential risks should be explained to her and alternative contraceptive methods should be recommended. If the client chooses a COC because other contraceptive options are not available or are unacceptable, the method should be provided by a properly qualified practitioner and she should remain under medical supervision. If a woman has more than one category-3 condition that increases the risk of cardiovascular disease, clinical judgment must be exercised. In most instances, the combination of conditions should be regarded as belonging to category 4 (contraindication).

### Other conditions (category 2)

These are:

- Smoking in women aged less than 35
- Migraine without focal neurological symptoms in women under 35 years (if it develops during COC use, it becomes category 3)
- Diabetes without vascular complications
- Family history of venous thromboembolism (first-degree relative)
- Superficial thrombophlebitis

- Uncomplicated valvular heart disease
- Cervical intraepithelial neoplasia
- Undiagnosed breast mass
- Asymptomatic gallbladder disease
- Sickle-cell disease.

When any of the above conditions are present, careful screening and monitoring will allow the benefits of COC use to outweigh potential risks. However, when a woman has more than one of the first three conditions, which increase the risk of cardiovascular disease, clinical judgment must be exercised. In most instances the combination of conditions should be regarded as category 3.

## PROGESTOGEN-ONLY CONTRACEPTIVE METHODS

Research on progestogen-only contraceptive methods started in the 1960s, shortly after the introduction of combined oral contraceptives. Such methods, including pills, injectables, implants, vaginal rings, and intrauterine devices, are now registered in many countries and are being used by millions of women.

### Methods

The various progestogen-only methods provide different progestogens, different dosages, different routes of administration, and different durations of action. All these characteristics influence the biological effect.

#### *Progestogen-only pills (POPs)*

The most commonly available pills contain levonorgestrel, desogestrel, norethindrone, or lynestrenol. Progestogen-only pills are taken continuously throughout the cycle without a break between cycles.

#### *Progestogen-only injectables (POIs)*

*Depot medroxyprogesterone acetate (DMPA)* is a 1 mL injection containing 150 mg DMPA in an aqueous microcrystalline suspension, given every three months.

*Norethisterone enanthate (NET-EN)* is a 1 mL injection containing 200 mg NET-EN in an oily preparation, given every two months; with administration every three months higher pregnancy rates have been observed.

#### *Progestogen-only implants*

Implants are placed subdermally and release the progestogen at a constant rate allowing the use of very small daily doses to achieve the desired contraceptive effect.

*Norplant* implants consist of six silastic capsules that release around 30 µg levonorgestrel a day and have an effective life of 5 years.

*Jadelle* consists of two silastic rods containing levonorgestrel and has a clinical performance similar to that of *Norplant*, for up to 5 years.

*Implanon* is a single capsule releasing etonogestrel and has a lifespan of 3 years.

### Mechanism of action

Injectable preparations release a much higher dose of progestogens than other methods and are very effective in inhibiting ovarian function and preventing ovulation.

With implants and POPs the daily dose of progestogens is much lower. With these methods, the main mechanism of action is thickening of the cervical mucus, which presents an obstacle to sperm penetration. With *Norplant* (and probably also *Jadelle*) approximately half the cycles are

anovulatory, and with *Implanon* nearly all. With POPs the inhibition of ovulation varies for different preparations.

Progestogens also cause histological changes in the endometrium according to the dose and steroid administered and these are most pronounced with injectables. There is no evidence that these changes contribute to the contraceptive effect.

### Efficacy

Although POPs are generally considered less effective than the COCs, the observed failure rates are only 2–8%, and during breastfeeding 1% or less.

The reported failure rates of POIs are low, and come within the narrow range of 0.1–0.6% during the first 12 months of use.

Implants are highly effective contraceptives with failure rates ranging between 0% and 0.2% during the first 12 months of use and remaining at approximately 0.2% per year for the duration of prescribed use.

### Beneficial effects

#### *Benefits common to all methods*

Progestogen-only methods are suitable for many women with conditions that preclude the use of oestrogens.

Progestogen-only methods can be used during breastfeeding since they have no harmful effects upon the duration of lactation, infant growth, or early development. They are a good option for lactating women when effective non-hormonal methods are contraindicated or not acceptable. To avoid early transfer of small amounts of steroid to the infant, women are advised to delay the use of these methods until six weeks postpartum.

#### *Method-specific benefits*

*POPs* – POPs have a short duration of action. An important factor in their efficacy is the way a client adheres to the instructions.

*Parenterally administered methods* provide medium or long term contraception and are easy to use, preventing failures due to forgetfulness. They avoid the first passage through the liver, allowing administration of lower doses of steroids. *Norplant* is suitable for most women of reproductive age. It is particularly recommended for women who wish to obtain highly effective long-term protection against pregnancy but contemplate having more children in the future or for those who do not wish to undergo sterilisation.

*POIs* provide highly effective medium-term contraception. Delivery is simple. *DMPA* may provide some non-contraceptive health benefits – for example, fewer acute crises in women with sickle-cell disease, higher haemoglobin by inducing amenorrhoea.

### Side-effects

The side-effects of progestogen-only methods differ with the preparation, the biological properties, the dose of steroid, and the characteristics of the user.

#### *Bleeding irregularities*

Progestogen-only methods are associated with disruptions of the menstrual cycle including amenorrhoea, prolonged menses, spotting between periods, and heavy bleeding. Bleeding problems are the most common reason for discontinuation related to side-effects during the first year of use.

For users of *Norplant*, *Jadelle*, and *Implanon*, disruption of the menstrual cycle is the most frequently reported side-effect, with about 60% of *Norplant* users reporting irregular bleeding patterns during the first year of use; some report increased bleeding, others decreased bleeding. The irregularities tend to decrease with duration of use.

With DMPA amenorrhoea is the most common side-effect and its occurrence increases with duration of use from about 50% at the end of one year to 80% by the end of 5 years. Women using NET-EN are less likely to experience amenorrhoea. Heavy vaginal bleeding occurs in 1–2% of users. Less than one-third of women receiving DMPA report having normal menstrual cycles during the first year of use.

Careful counselling of new acceptors can diminish the proportion of women who discontinue the method because of amenorrhoea or bleeding problems: if clients know what to expect, they are better able to understand and cope with side-effects. When bleeding becomes too heavy, treatment with oestrogens, combined oral contraceptives, or non-steroidal anti-inflammatory drugs may be tried. If these measures are not effective or the woman's health is threatened, progestogen-only methods should be discontinued.

When symptoms suggestive of pregnancy and/or delay in menses are reported by a woman with previously regular menstrual cycles, steps should be taken to exclude pregnancy. If the woman is pregnant, the method must be discontinued. Whenever pregnancy is suspected, the possibility of an ectopic pregnancy must be ruled out.

#### **Other side-effects**

Some women using progestogen-only methods report other conditions that may be method-related. Common complaints include headache, acne, breast tenderness, weight gain, mood change, nervousness, nausea, and dizziness, all of which tend to more frequent in the first months of use. Hirsutism and hair loss are also reported. Among these side-effects, weight gain is the most common reason for discontinuation.

#### **Adverse effects**

Serious adverse effects are rare with progestogen-only methods and few conditions prevent their use. For this reason, the eligibility criteria for these methods differ substantially from those for combined oestrogen-progestogen oral and injectable contraceptives. However, the safety issues differ between progestogen-only methods.

#### **Ectopic pregnancy**

When the user of an implant or a POP does become pregnant, the pregnancy is more likely to be ectopic than a pregnancy developing in a woman using no method. However, because pregnancies are infrequent with progestogen-only methods, the overall risk of ectopic pregnancy is considerably less than that in women using no method.

#### **Benign ovarian cysts**

Among users of implants and POPs, there is a higher incidence of benign ovarian cysts than among users of injectables and other contraceptives. These cysts are due to incomplete suppression of ovarian activity; they regress spontaneously in the large majority of women and seldom require treatment.

#### **Bone metabolism**

DMPA decreases the endogenous production of oestrogens more strongly than other progestogen-only methods. For this reason, there is concern about the impact of this method on bone mass, particularly when it is used by adolescents (see section on Special Situations).

#### **Possible carcinogenicity**

The Collaborative Group on Hormonal Factors in Breast Cancer indicated that women who used progestogen-only injectables in the past but stopped more than 10 years ago are not at increased risk of breast cancer. However, current

and recent users do seem to be at slightly increased risk. These findings are similar to those for COC users and the evidence argues against progesterone-only contraception increasing the risk of new breast cancers. No increased risk of breast cancer has been detected in POP users. There are no long-term data on breast cancer in Norplant users.

No increases in the frequency of cervical, ovarian, or liver cancer have been found in women who have used progestogen-only methods.

#### **Metabolic changes**

There is little information on metabolic effects of POPs. However, since these provide about the same low dose of progestogen as Norplant, no clinically important changes are to be expected.

No important changes have been found in liver, kidney, adrenal, or thyroid function among Norplant users. Small and negligible effects on lipid metabolism, and a slight increase in serum glucose concentrations that does not progress in magnitude with time and is of no clinical importance, have been described with this implant.

Among DMPA users, minor alterations of lipid metabolism, fluid/nitrogen balance, glucose tolerance, steroid metabolism, and immune function have been recorded but seem to be of no clinical relevance. Fewer data have been published on the metabolic effects of NET-EN, but its effect on most biochemical functions appears to be similar to that of DMPA.

#### **Cardiovascular**

Data are insufficient to indicate whether there is any relation between use of progestogen-only methods and cardiovascular complications. Results of a WHO study suggest that there is little or no increased risk of cardiovascular disease associated with the use of progestogen-only injectables, although further investigation is needed into a possible increased risk of stroke among women with high blood pressure. POMs do not produce the type of changes in blood clotting factors which in COC users are associated with cardiovascular complications. Most studies show no significant change in systolic or diastolic blood pressure in women using DMPA or Norplant.

#### **Return of fertility**

Fertility is not impaired after discontinuation of DMPA or NET-EN although its return is delayed. The average time between the last DMPA injection and conception is about nine months, including the three months during which the injection is effective; more than 80% of women become pregnant within one year of discontinuing DMPA and 90% within two years. The few data on NET-EN suggest that fertility returns more quickly with this agent.

Because of the short duration of action, fertility returns rapidly after discontinuation of POPs. Of women from whom Norplant was removed in order to conceive, 40% became pregnant within three months, 76% by one year, and 90% by 24 months – rates similar to those observed after discontinuation of non-hormonal methods.

#### **Eligibility criteria**

Where these criteria refer to Norplant, the advice can be taken to apply also to Jadelle, with its similar progestogens.

#### **Contraindications (category 4)**

Progestogen-only methods should not be used in the presence of:

- Breast cancer within the past 5 years.

### **Conditions requiring careful consideration (category 3)**

Progestogen-only methods should generally not be used in the presence of:

- Current deep venous thrombosis or pulmonary embolism
- Acute liver disease
- Liver tumour (benign or malignant)
- Severe decompensated cirrhosis
- History of breast cancer with no evidence of disease for the last 5 years.
- Breastfeeding and less than 4 weeks postpartum.

The following condition is also category 3 for progestogen-only injectables and Norplant:

- Unexplained vaginal bleeding suspicious for serious underlying condition.

In addition, the following conditions are category 3 for progestogen-only injectables:

- Cerebrovascular or coronary artery disease
- Hypertension with BP  $\geq 160/100$  mm Hg
- Hypertension with vascular disease
- Diabetes with vascular disease (including nephropathy, retinopathy, neuropathy) or of >20 years' duration.

When a category 3 conditions is present, the potential risks should be explained to the client and alternative contraceptive methods should be recommended. If a progestogen-only method is chosen because other contraceptive options are not available or not acceptable to the client, she should remain under medical supervision.

### **Other conditions (category 2)**

These are:

- Cerebrovascular or coronary artery disease (if it develops during use of progestogen-only method it becomes category 3; this condition is category 3 for injectables)
- Hypertension with BP  $\geq 160/100$  mm Hg (category 3 for injectables)
- Hypertension with vascular disease (category 3 for injectables)
- Migraine with focal neurological symptoms (if it develops during POP use it becomes category 3)
- Diabetes (if diabetes with vascular disease [including nephropathy, retinopathy, neuropathy] develops during POM use it becomes category 3)
- History of deep venous thrombosis or pulmonary embolism
- Mild compensated cirrhosis
- Gallbladder disease

- Undiagnosed breast mass
- Previous ectopic pregnancy
- Known hyperlipidaemias
- Irregular, heavy, or prolonged vaginal bleeding.

The following conditions are also category 2 for progestogen-only injectables and Norplant:

- Obesity
- Cervical intraepithelial neoplasia and cervical cancer.

The following condition is also category 2 for progestogen-only pills:

- Past ectopic pregnancy.

In addition, the following condition is category 2 for progestogen-only injectables:

- Hypertension with BP 140–159/ 90–99 mm Hg.

When a category 2 condition is present, careful and appropriate monitoring will allow the benefits of using progestogen-only methods to outweigh any potential risks. However, for POIs, if a woman has more than one of the first five conditions above, which may increase the risk of arterial cardiovascular disease, the combination should be regarded as category 3.

## **SPECIAL SITUATIONS FOR ALL HORMONAL METHODS**

### **Adolescents**

The high efficacy of hormonal contraceptives is especially important for adolescents. Indications and eligibility criteria are the same in this age group as for older women. There are concerns regarding the hypo-oestrogenic effect of progestogen-only injectables on women under 18 years of age, which may affect bone mass and density. Any obvious risk factors for osteoporosis, such as chronic therapy with corticosteroids, should be taken into account when advising such young women on the use of progestogen-only injectables. Where available, a CIC may be a more suitable injectable.

### **Breastfeeding**

Progestogen-only methods have no negative influence on the duration of lactation, and infants whose mothers received these methods while breastfeeding appear to develop normally both physically and mentally. However, a cause for concern is the transfer of steroids to breastfed infants when their mothers initiate hormonal contraception early. Therefore, no progestogen-only method should be started before the sixth week postpartum by breastfeeding women.

Use of combined hormonal contraceptives during breastfeeding diminishes the quantity of breast milk, decreases the duration of lactation, and may thereby adversely affect the growth of the infant. Therefore combined hormonal contraception should generally be withheld until six months after delivery or until the infant is weaned, whichever is the earlier.

### **Abnormal vaginal bleeding**

Irregular bleeding patterns are common in healthy women. Hormonal methods should not be withheld unless there is

reason to suspect a pathological condition but the client must be advised that her bleeding problem may increase with the use of any of these methods, particularly low-dose progestogen-only methods, and if she chooses to use one she should be monitored closely.

If a woman has vaginal bleeding that is suspicious of a condition related to pregnancy, or of disease such as pelvic cancer, it should be investigated before the method is initiated. Progestogen-only methods can cause irregular bleeding patterns that mask symptoms of underlying disease.

### **Malignant disease of the genital tract**

Users of hormonal methods who are diagnosed with cancer of the genital tract may continue to use these methods while awaiting treatment.

With most genital tract malignancies, the treatment is such that there will be no further pregnancies. However, if the condition is diagnosed at a time when the woman is using no contraceptive methods, she may need contraceptive protection while awaiting treatment. Under these circumstances any hormonal method is recommended except implants (women with this type of malignancy do not need such long-term contraception).

Women who have been successfully treated for premalignant disease of the cervix will generally preserve their fertility and can use any hormonal method, including implants. The treatment of choriocarcinoma may not preclude further pregnancies but pregnancy should be avoided during treatment and follow-up so that the disease can be monitored properly. Any hormonal method may then be used if this is the choice of the woman.

### **Drug interaction**

Drugs that are liver enzyme inducers may reduce the efficacy of hormonal methods of contraception. Such drugs commonly used in long-term treatments include the antibiotics rifampicin and griseofulvin and the anticonvulsants phenytoin, carbamazepine, primidone, and barbiturates. Alternative contraceptive methods should be encouraged for women who are on long-term use of any of these drugs. If nonetheless a woman opts for hormonal contraception, she should be advised to use a back-up non-hormonal method while taking the medication.

### **Prevention of sexually transmitted infections including HIV**

Although there is evidence that hormonal contraceptives protect against symptomatic pelvic inflammatory disease, they do not protect against sexually transmitted infections, including HIV. Therefore women should be advised to use condoms whenever there is a risk of sexual transmission of such infection. Observational studies have raised concern that women using DMPA may be at higher risk of acquiring HIV than users of non-hormonal contraception. However, the findings must be interpreted with caution because they are possibly influenced by factors such as use of condoms. There are also some indications that, among women infected with HIV, DMPA users have higher viral loads in the genital tract than women using non-hormonal methods. Data on the relation between other hormonal methods and HIV transmission are very limited.

### **Women living with HIV/AIDS**

Though there are few scientific data, current opinion is that hormonal methods of contraception are safe for use by HIV-positive women.

### **Parasitic diseases**

The use of hormonal methods of contraception has not been found to have any interaction with parasitic diseases, although more research is needed in this area, including possible interrelations with drugs used for treatment.

### **Sickle-cell disease**

Women with sickle-cell disease can use hormonal methods of contraception. POIs seem preferable to combined hormonal methods not only because of their lack of effect on coagulation and blood viscosity but also because they seem to have favourable effects on the disease itself.

## **SELECTION OF HORMONAL CONTRACEPTIVES FOR SERVICE PROGRAMMES**

### **Combined oral contraceptives**

There are programmatic advantages in limiting the number of COCs available in a family planning programme. It is recommended that, in clinical facilities, not more than four combined formulations be available – two, or at the most three, low-dose pills ( $\leq 30\text{--}35\ \mu\text{g}$  oestrogen); and not more than one type of high-dose ( $50\ \mu\text{g}$ ) pill. Pills containing  $50\ \mu\text{g}$  oestrogen should not be used, except for emergency contraception and in the rare cases where specific conditions make this dose necessary (eg, drug interaction or when the lower-dose pill does not provide adequate cycle control).

The progestogens contained in existing pills include levonorgestrel, norethisterone, desogestrel, gestodene, norgestimate, and drospirenone. There is no good evidence that any particular progestogen in a combined pill regimen is clinically superior to others. Differences in price between pill formulations should be a consideration in their selection. The pill containing  $30\ \mu\text{g}$  ethinylestradiol and  $150\ \mu\text{g}$  levonorgestrel is the combination for which there is most information on safety, is the most widely used, and in general should be the pill of first choice.

### **Progestogen-only pills**

It is recommended that one type of POP be available in family planning programmes for lactating women and women for whom the oestrogen component of the COC is contraindicated or not desirable.

### **Injectable contraceptives**

Difficulties can arise and mistakes can occur if different formulations of injectables are used in the same family planning programme. Therefore, programme managers should select one POI formulation and keep to it, or ensure that only one formulation is used in a particular geographical area. The same recommendations apply to CICs when they are available.

### **Implant contraceptives**

The two newer implants Jadelle and Implanon are easier to insert and remove than Norplant. Therefore, wherever possible, service programmes should replace Norplant with Jadelle or Implanon. Selection of the implant will depend mainly on the availability, the cost, and the characteristics of the methods. The lifespan of Jadelle (5 years), its efficacy, and its side-effects are similar to those of Norplant. Implanon has a lifespan of 3 years and although data on this product are much less extensive than for Norplant and Jadelle, existing information on safety and efficacy are reassuring.

In countries where Norplant is already available, a change to Jadelle would require little retraining of providers. Implanon insertion requires a different technique, and additional training would be necessary.