Human Reproduction Update, Vol.9, No.4 pp. 373–386, 2003 DOI: 10.1093/humupd/dmg025

Hormonal contraception without estrogens

The ESHRE Capri Workshop Group

A meeting was organized by ESHRE (Capri, August 29–30, 2002) with financial support from Schering S.p.A. to discuss hormonal contraception without estrogens. The speakers included G.Benagiano (Rome), M.Bygdeman (Stockholm), E.Diczfalusy (Rönninge), A.Glasier (Edinburgh), P.Lähteenmäki (Turku), C.La Vecchia (Milan), M.Oettel (Jena), S.Skouby (Copenhagen) and J.E.Schmidt (WHO). The discussants included E.Arisi (Trento), M.Cesaretti (Milan), J.Collins (Hamilton), P.G.Crosignani (Milan), D.T.Baird (Edinburgh), G.C.Frigerio (Milan), J.Harlin (Stockholm) and A.Volpe (Modena). The report was prepared by J.Collins (Hamilton) and P.G.Crosignani[1] (Milan)

[1]To whom correspondence should be addressed at: Department of Obstetrics and Gynaecology, University of Milan, Via Della commenda 12, 20122 Milan, Italy. E-mail: piergiorgio.crosignani@unimi.it

The long-term clinical effects of ethinyl estradiol and the impact on environmental safety of the alkylated estrogen components used in combined contraceptive pills remain the subject of debate. The development of improved methods for the use of progestogen-only contraception would represent a viable and desirable option. Several progestogen compounds are not alkylated, and these can be delivered through a variety of routes. Some of the progestogen-only methods are well established in clinical use. Estimates for both perfect and typical effectiveness are less than one pregnancy per 100 woman-years with oral, injectable, implantable and intrauterine methods. In practice, with the oral progestogen-only method, perfect and typical effectiveness range from three to five pregnancies per 100 woman-years. The main side effect with all progestogen-only methods is unpredictable vaginal bleeding during the first months of use, and this may lead to discontinuation. Nevertheless, continuation of use is more frequent if patients are well informed of this side effect before treatment begins. No cardiovascular- and cancer-related side effects have been proven.

Key words: estrogens/ethinyl estradiol/hormonal contraception/progestogen/side effects

Introduction

The introduction of combined (estrogen-progestogen) oral contraceptives some 40 years ago was a gigantic step towards the improvement of reproductive health, gender equity and quality of life for women worldwide. It also contributed significantly to a marked change in the world's population structure. Fortunately, the history of combined oral contraceptives is not yet finished, but continues as an ongoing evolution involving major changes in science, culture and society. The need for new contraceptive methods is evident in both developed and developing countries. Hundreds of millions of couples have an unmet family planning needs, and up to 40% of pregnancies are still unplanned. Many promising developments have not yet completely met their potential: the full value of emergency contraception remains to be established, hormonal contraception for men is still in its infancy, and so are the so-called 'local' methods of contraception for women that would also interfere with sexually transmitted diseases. Hence, during the next few decades alternate means of achieving effective and safe contraception must be sought in order to ensure that optimal choices and options are available. There is an unfinished research and development agenda facing the scientific community: the development of contraceptives for the male; a variety of improved emergency contraceptives; new types of vaginal microbicides; non-alkylated orally active estrogens; improved female and male condoms; and last—but not least—improved 'progestogen-only' methods. Recent advances in the last-mentioned area constituted the topic of the present workshop, which discussed developments in the delivery of progestogens, the safety and efficacy of the various methods, and the contraceptive potential of anti-progestogens and selective progesterone receptor modulators.

Contraception and population trends

In 2001, 62% (650 million among more than 1 billion) of women of reproductive age who live in a marital or consensual union were using contraception; 70% of the 170 million in the more-developed and 60% of the 880 million in the less-developed regions (United Nations, 2001). Today, nine out of ten contraceptive users worldwide rely on modern methods, such as female sterilization, intrauterine devices, oral contraceptives, condoms, male sterilization and injectable and implantable progestogens. In the developed regions, contraceptive users rely mostly on oral

contraceptives and condoms, whereas female sterilization and intrauterine devices are the most important methods used in the developing regions (Table I).

There are major regional and national differences in the use of modern methods; the United Nations estimates for the various European regions are shown in Table II.

Female and male sterilization is used most extensively in Northern Europe (11 and 13% respectively), and least in Southern and Eastern Europe (2 and 0.1% respectively in both regions). Oral contraceptive use is greatest in Western Europe (48%) and lowest in Eastern Europe (8%); use of the rhythm method is greatest in Eastern Europe (14%) and least in Northern Europe (1%), whereas withdrawal is highest in Southern Europe (30%) and least in Northern Europe (1%). It is likely that these regional differences will diminish with time.

The optimal use of contraception may influence future evolution of global and European populations, for which trends are shown in Table III (Johnson, 1987; United Nations, 2001). The United Nations projects that between 2000 and 2050, the world population will increase by 55%, from 6057 to 9322 million people (United Nations, 2001). Virtually all this increase will take place in less-developed regions (from 4865 to 8141 million), whereas the *total* population of the more-developed regions will not increase (1191 million in 2000 and 1181 million in 2050). The projected increases in North America (from 314 to 438 million) and in Australia/New Zealand (from 23 to 31 million), will be counterbalanced by decreases in Europe (from 727 to 603 million) and Japan (from 127 to 109 million). In Europe, the population of Eastern Europe is projected to diminish by 81.5 million, that of Southern Europe by 28.0 million, of Western Europe by 12.4 million, and of Northern Europe by 2.3 million people.

To illustrate the changing geopolitical reality of our world, it may be recalled that in the year 1950, the European population (548 million) was 2.5-fold greater than that of Africa (221 million), whereas by the year 2050 the African population (2000 million) is projected to be 3.3-fold greater than that of Europe (603 million people). The future consequences of this shift in terms of increasing migratory pressures remain to be seen.

The demographic changes indicated above reflect major changes in fertility rates. In the 30-year time period, from 1965 to 1995, the fertility rate declined from 4.9 to 2.8 children per woman worldwide, and from 2.7 to 1.4 in Europe. European fertility fell below replacement level (2.1 children per woman) at about 1975 and remained so during the subsequent decades (United Nations, 2001). Of course, whenever the total fertility rate of a region remains below replacement level for an extended period of time, the result is a diminished population size.

Table I. Level of current contraceptive use and use of modern methods in developed and developing countries (United Nations, 2001)

Method	Percentage of couples	
	Less developed	More developed
Female sterilization	22	10
Male sterilization	4	7
Intrauterine device	16	8
Oral contraceptive	6	17
Condom	3	15
Injectable hormones	3	0.1
Others	6	13
None	40	30

Table II. Level of current contraceptive use and use of modern methods in Europe (United Nations, 2001)

Region	Percentage of couples		Percentage of users employing modern methods
	Any method	Modern method	
Eastern Europe	69	31	44
Northern Europe	78	77	98
Southern Europe	69	31	46
Western Europe	75	71	94
Total	72	45	64

Table III. Estimates of the populations (in millions) of the World and Europe during two millennia (Johnson, 1987; United Nations, 2001)

Year	World	Europe
14	256	37
1000	280	32
1500	427	62
1750	731	102
1900	1660	284
1960	3020	605
2000	6057	727
2050	9322	603

Impact of contraceptive prevalence on fertility rates

In general, there is an inverse relationship between contraceptive prevalence and fertility levels. On average, total fertility rate decreases by one child for every 15 percentage point increase in contraceptive prevalence. Contraceptive use is the most important of the direct determinants of fertility, and this association is stronger than the association between fertility and other proximate determinants, such as the pattern of marriage and sexual activity outside marriage, the duration of breast-feeding and the practice of induced abortion (United Nations, 1999). Other important factors, such as education and desired family size are among the indirect determinants that must operate through the proximate determinants to influence fertility.

Hence, contraception is the most important *means*, but not the *cause* of low birth rates. The causes are manifold and complex societal changes, including rapidly increasing female autonomy, gains in female education, increasing female participation in the labour force, the changing pattern of union formation and the increasing stability of those unions, as well as changes in the public perception of the role of women in society and in the family (Lesthaeghe and Willems, 1999). Other important contributors to fertility are the marked rise in life expectancy, urbanization and densification, elimination of

Table IV. Population structure (% of all ages) of Europe, 1950–2050 (United Nations, 2001)

Age group (years)	Year		
	1950	2000	2050
0–14	26.2	17.5	14
15–60	61.7	62.2	29.9
61–79	11	17.3	26.6
>80	1.1	3	10

Table V. Effectiveness of progestogen-only contraceptive methods (Benagiano and Primiero, 1983a; McCann and Potter, 1994; Lahteenmaki *et al*., 2000; Meirik *et al*., 2001)

Progestogen-only method	Pregnancy per 100 woman-years	
	Ideal efficacy	In-use efficacy
Pill	0.5	3–5
Injectable	–	0.5–1.00
Implant device	–	0.1
LNG-IUS	–	0.1

illiteracy, social atomization and related feminism, globalized nomadism, the youth loss of majority and a general shift from tradition and social stability to uncertainty and instability (Chesnais, 1999). The overall result of all these changes is expected to be a major reduction in birth rates. As late as 1975, 37% of the global population and 24% of the European population consisted of children (persons aged ⩽14 years). By 2050, these percentages are projected to decline to 21 and 14% respectively (Table IV).

Population structure and contraceptive need

The adversaries of contraception may wonder whether there remains any necessity at all for the further development of improved contraceptives in a future world, where the number of elderly persons could outweigh that of children. The answer is simple: yes. Fertility regulation is a human right enshrined in several instruments of the United Nations. Up to 40% of all pregnancies—estimated at 210 million per year—are unplanned, and about 45 million abortions are carried out each year. Furthermore, in 1990 at least 100 million couples had an unmet family planning need and about 300 million couples were using contraceptive methods with which they were dissatisfied, or which they considered unreliable (World Health Organization, 2000). There is an unfinished research and development agenda facing the scientific community: the development of contraceptives for the male, a variety of improved emergency contraceptives, new types of vaginal microbicides, non-alkylated orally active estrogens, improved female and male condoms, and last—but not least—improved 'progestogen-only' methods.

Oral progestogen-only contraception

Although used mainly in developed countries, progestogen-only contraception has the potential to improve safe effective contraceptive use in the regions of the world with the highest levels of population growth (Table V). Progestogen-only pills (POPs), sometimes called 'minipills', were first licensed in 1973. They contain no estrogen and usually have a lower dose of progestogen than that in combined pills. The prevalence of POP use varies widely around the world, but it is much lower than for combined oral contraceptive pills. In Scotland in 2000, 7% of women using contraception used the POP, while in the USA it is used by less than 1% of such women. The main disadvantages of the POP are the associated high incidence of irregular vaginal bleeding and the need for very careful compliance. The method tends to be used (certainly in the United Kingdom) mainly by women who have contraindications to estrogen (including breastfeeding) and by women in the perimenopause who are perceived to be at lower risk of pregnancy.

Mechanism of action

Traditional POPs [containing levonorgestrel (LNG) or norethisterone] prevent pregnancy through a combination of:

- suppression of ovulation (Landgren and Diczfalusy, 1980);
- suppression of normal luteal activity (Landgren and Diczfalusy, 1980);
- production of hostile mucus which impairs sperm penetration;
- changing the histology of the endometrium presumably impairs implantation (Kim-Bjorklund *et al*., 1991); and
- possibly altering tubal motility.

The ovarian response to traditional POPs varies widely among individuals, with ovulation occurring in between 14% and 84% of cycles. A new POP containing desogestrel 75 μg/day (Cerazette®; Organon) suppresses ovulation in almost every cycle (Rice *et al*., 1999), and is available in some parts of Europe.

Efficacy

The accidental pregnancy rate among perfect users of the POP is said to be 0.5 per 100 during their first year of use (McCann and Potter, 1994). The failure rate during typical use is usually cited as between 3 and 5%. Since the new desogestrel-containing POP inhibits ovulation in almost every cycle, it is likely to have a lower failure rate. In a randomized controlled trial comparing desogestrel 75 μg/day with LNG 30 μg/day, the Pearl Indices were 0.14 and 1.17 respectively (Collaborative Study Group on the Desogestrel-containing Progestogen-only pill, 1998). It is controversial whether body weight influences the failure rates with use of classical POPs.

Side effects

Ectopic pregnancy

An increased risk of ectopic pregnancy is associated with the traditional POP. Up to 10% of pregnancies that occur during POP use are ectopic—an incidence which is similar to that among women using no method of contraception (McCann and

Potter, 1994). The ectopic pregnancy rate is likely to be much lower with a POP which consistently inhibits ovulation.

Irregular bleeding

Incomplete suppression of ovarian activity is a recipe for irregular bleeding. Episodes of follicle growth and atresia result in irregular and unpredictable vaginal bleeding and spotting. For individual women using the POP, bleeding patterns are probably largely determined by their ovarian response to the progestogen, but we cannot rule out an endometrial effect. Women who continue to ovulate normally will have regular cycles, while those who experience variable suppression of ovarian activity will bleed erratically. It is not possible to predict how an individual woman will respond; for example, there does not appear to be any association with either body weight or age. Irregular bleeding is the commonest reason for discontinuation of the POP (McCann and Potter, 1994). It is often said that bleeding patterns improve with time; however, since discontinuation rates are high it may simply be the case that the removal of women with chaotic bleeding patterns from study populations distorts the overall picture.

Persistent follicles

Incomplete inhibition of ovulation is also a recipe for the development of persistent ovarian follicles (commonly referred to as ovarian cysts; Tayob *et al*., 1985) which occur in up to 20% of cycles, but usually resolve rapidly.

Serious risks

The POP is associated with fewer established health risks than the combined pill, having no significant association with either breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 1996a) or cardiovascular disease (World Health Organization, 1998).

Injectable progestogens

During the 40 years in which hormonal contraceptives have been in clinical use, it has become clear that the 'ideal' contraceptive method will never be discovered. Therefore, a method of fertility regulation which is effective, acceptable and safe can become a reality for all users only when they can select from a large variety of methods. The need for choice arises in part because cultural, socioeconomic and psychological factors play an important role in determining the overall acceptability and use-effectiveness of a given contraceptive regimen. For instance, some women have difficulty in storing pills and others cannot remember to take their medication daily; some users need methods which allow complete privacy, because members of their families may oppose the concept of birth control. Unfortunately, this need for choice was not recognized when hormonal methods were first introduced in the developing world, thus undermining major efforts to organize family planning in Asia and Africa.

This demand for options has fostered the development of long-acting methods that can provide contraceptive protection without forcing users to adhere to a strict daily administration schedule. Two classes of contraceptives have these characteristics: (i) intrauterine devices; and (ii) hormonal methods based on long-acting substances. Both of these methods allow administration at infrequent intervals.

Long-acting contraceptive steroids can be injected intramuscularly; alternatively, they can be released by delivery systems inserted subcutaneously, intravaginally or in the uterine cavity. At present, for clinical use, the intramuscular injection is by far the most important of these routes of administration.

Long-acting hormonal contraceptives present several advantages:

- they are highly effective, especially in terms of use-effectiveness;
- they rely minimally (depot medroxyprogesterone acetate – DMPA) or not at all (the others) on compliance with the administration schedule, and therefore conceptions due to user's error are reduced or eliminated;
- absorption is not dependent upon normal gastrointestinal functioning, and there are few gastrointestinal adverse effects;
- they are simple to administer, even by paramedical personnel;
- they avoid the first pass through the liver.

In order to prolong the duration of action of an injected steroid, three major approaches have been followed in separate developments. The first technique is based upon the chemical modification of the molecule; examples of this procedure are the synthesis of esters in which the steroid is conjugated with a fatty acid (Dorfman and Shipley, 1956; Junkmann and Witzel, 1958), or the synthesis of enol-ether derivatives (Meli *et al*., 1963).

The second approach, which was utilized for the preparation of the best-known injectable contraceptive, DMPA, involves a modification of the physical form of the steroid, so that it dissolves very slowly, thereby producing a depot at the site of injection. This is achieved by formulating the steroid as microcrystals (Babcock *et al*., 1958).

A third method utilizes polymeric devices that can be injected (Anderson *et al*., 1976); the steroid is either mixed with a biodegradable and biocompatible polymer to form injectable micropellets, or it is encapsulated in suspension into polymeric microspheres. So far, only the first two approaches have reached the market and have been used for contraceptive purposes.

The first progestogen utilized as a long-acting injectable contraceptive was 17α-hydroxyprogesterone caproate in 1963 (Siegel, 1963). Only two of the many steroids tested are today marketed around the world: DMPA and norethisterone enanthate (NET-EN).

- Medroxyprogesterone acetate: this is a synthetic progestogen derived from progesterone, with a solubility in water of <1 mg/ml. This property has been utilized to formulate it as an aqueous suspension; microcrystals containing 150 μg of the steroid suspended in 1 ml of aqueous medium provide an effective protection against unwanted pregnancy for at least 90 days. The mechanism of action is centrally exerted at the hypothalamic level, with complete block of ovulation (Benagiano and Primiero, 1983a).
- Norethisterone enanthate: this is an acid ester of norethisterone, and its prolonged effect is due to a slow hydrolysis occurring mainly in the liver (Fotherby *et al*., 1980). When administered at the dose of 200 mg every 60 days, NET-EN

inhibits fertility through a mixed, two-phase mechanism: during the first portion of the drug's life-span the contraceptive effect is exerted at the hypothalamic level, whereas later on when ovulation is restored the action is likely to be 'peripheral', on the cervical mucus and/or the endometrium (Benagiano and Primiero, 1983a).

Both progestogens are extremely effective in preventing pregnancy, with a pregnancy rate close to zero. The most important side effect observed with these two agents is a complete disruption of the menstrual bleeding pattern leading to a high incidence of amenorrhoea (particularly with DMPA) or spotting and breakthrough bleeding (Benagiano and Primiero, 1983a).

Use-effectiveness

From its very early days in clinical practice, DMPA has proven to be a very effective contraceptive; the majority of published clinical trials (conducted in the 1970s and 1980s) have reported pregnancy rates at 12 months not exceeding 0.5 per 100 woman-years (see Benagiano and Primiero, 1983a). Most of these studies also reported that the continuation rates at 12 months were >50%, indicating that women from different ethnic, social and cultural backgrounds find the overall clinical profile of the drug acceptable, in spite of the major cycle disruption that almost invariably follows its injection.

In contradistinction to DMPA, the evaluation of the contraceptive use-effectiveness with NET-EN underwent several changes and nowadays it is injected every 2 months, with pregnancy rates of less than 1 per 100 woman-years (Benagiano and Primiero, 1983b).

Risk of osteoporosis

In recent years, attention has been drawn to possible negative effects of DMPA on bone turnover, especially in young women. Conclusions from several studies claim that DMPA should be used with caution in young subjects, and in adults with other risk factors for osteoporosis. In particular, one group (Cundy *et al*., 1991) found that DMPA users had a 7.5% lower mean lumbar and a 6.6% lower mean femoral neck bone density than matched premenopausal controls, whereas they had an 8.9% greater mean lumbar and a 4.0% lower femoral neck bone density than post-menopausal controls. In a separate study (Cundy *et al*., 1994), these authors found that at 1 year following discontinuation of the medication there was a significant increase in lumbar, but not femoral neck, bone density.

Increased risk of sexually transmitted infections (STIs) and HIV

It has been suggested that hormonal contraceptives may alter the susceptibility to STIs, which may in turn influence transmission of HIV-1 (Baeten *et al*., 2001). An increased shedding of HIV-infected cells from the cervix and vagina of women taking hormonal contraceptives has also been observed (Mostad *et al*., 1997). These findings lend credibility to the concept of 'dual protection' (namely, the use of two methods to protect against STIs and against pregnancy) especially in adolescence, when young women are particularly prone to STIs (Carlin and Boag, 1995).

A few studies have now addressed the question of a possible facilitating effect of DMPA on the acquisition of STIs, including HIV. One group (Baeten *et al*., 2001), in a prospective study, found that women utilizing the depot-progestogen had a significantly increased risk of *Chlamydia* infection [hazard ratio (HR) 1.6], which was associated with a significantly decreased risk of bacterial vaginosis (HR 0.75), trichomoniasis (HR 0.6) and pelvic inflammatory disease (HR 0.4). Another group (Martin *et al*., 1998) found that women injected with DMPA had an increased incidence of HIV-1 infection (HR 2.2); after multivariate analysis adjustment, the HR remained at 2.0 with regard to HIV/AIDS.

Progestogen implants

It is almost two decades since contraceptive implants were first approved by a regulatory agency. Norplant® was the first implant to be developed, and is now approved in more than 60 countries. To date, 11 million women are estimated to be using, or to have used, Norplant. Norplant is a six-capsule LNG-releasing implant with a record of good safety and high contraceptive effectiveness (Meirik *et al*., 2001). It has, however, been associated with considerable bleeding disturbances and with difficult and time-consuming removals (Hickey and d'Arcangues, 2002). Several newer implant systems that release different types of synthetic progestogens have been developed, or are under development. Nestorone and Elcometrine are single-unit implants that contain the same progestogen known as ST1435. Nestorone is currently under development by the Population Council and has an effective life span of 2 years; Elcometrine has been licensed for use during 6 months in Brazil. Uniplant, another single-unit system, releases nomegestrel acetate and is recommended for use over 12 months, but it is currently not available on the market.

Jadelle® and Implanon® have been approved by the regulatory authorities of several countries. Jadelle is a two-rod LNG-releasing implant approved for use over 5 years, while Implanon consists of only one rod releasing etonogestrel and is approved for use over 3 years. The smaller number of units makes Implanon insertion and removal simpler, faster, less traumatic, and therefore more acceptable. Two generic products made in the People's Republic of China, called Sino-implants Domestic No. 1 and 2, have been designed to imitate the performance parameters of Norplant and Jadelle respectively (Croxatto, 2002a).

Current evidence suggests that the implants currently available in more than one country—that is, Norplant, Jadelle and Implanon—are highly effective and generally safe (Post-marketing Surveillance of Norplant contraceptive implants I, 2001a). The clinical performance of Norplant (soft-tubing formulation) and Jadelle over 5 years is comparable (Sivin *et al*., 1998). Annual pregnancy rates for up to 5 years are below 1 per 100 woman-years; the cumulative pregnancy rate at the end of 5 years is below 1.5 per 100 woman-years. No method failures have been reported by women using Implanon (Glasier, 2002), though disturbances of the menstrual bleeding pattern may place considerable strain on the women's lives (Hickey and d'Arcangues, 2002).

As far as the mechanisms of contraceptive action are concerned, Norplant, Jadelle and Implanon interfere, to varying degrees, with key steps in the physiology of reproduction. They suppress the

ovulatory process through partial or complete inhibition of the gonadotrophin surge. In addition, they alter the consistence of cervical mucus, thereby restricting the ascent of sperm to the site of fertilization. Finally, changes in endometrial morphology also occur (Croxatto, 2002b).

Quality implant services must meet a number of essential requirements including a sufficient number of staff adequately trained in the correct techniques of insertion and removal, and in counselling of prospective clients. Good pre-insertion counselling is crucial to quality services as it can greatly enhance the acceptability of the devices (Chikamata and Miller, 2002). Counselling should therefore address:

- advantages and disadvantages of implants compared with other available methods (Post-marketing Surveillance of Norplant contraceptive implants II, 2001b);
- the fact that current implants are highly effective and generally safe, but that disruptions of the menstrual bleeding pattern are likely to occur during the first months of use;
- the duration of device efficacy as well as the need to return for removal at the end of the implant's life span;
- the option of removal at any time and for any reason; and
- the fact that implants do not protect against STIs, including HIV/AIDS.

In conclusion, the good efficacy and safety profile of implants must be coupled with quality implant services for them to be a viable option for long-term contraception, especially in developing country settings.

Intrauterine systems

The first intrauterine system was made available more than 30 years ago, released 65 μg progesterone over a 24 h period, and was approved for contraception for 1 year. The product is no longer marketed, however. At present, the only widely used intrauterine system releases 20 μg LNG in 24 h (Luukkainen *et al*., 1987), is approved for 5 years as a contraceptive device, and is marketed in over 100 countries with over 3 million users. Other systems which release LNG at a different rate, or have a different frame or a different progestogen, are either experimental or in development.

LNG-releasing intrauterine system (LNG-IUS)

The system consists of a polyethene T-shaped frame, both arms of which are 32 mm long, and a reservoir containing 52 mg of LNG homogeneously mixed with polydimethylsiloxane and covered with a rate-limiting membrane made from the same polymer. The LNG-IUS was first approved for contraception in Finland in 1990, and by the Food and Drug Administration (FDA) in the USA in 2000. It is marketed under the name Mirena®. In some countries the LNG-IUS is also approved for menorrhagia, dysmenorrhoea and endometrial protection during estrogen replacement therapy (ERT).

Mode of action

No single mechanism can be identified for the high efficacy of LNG-IUS, which seems to arise from several local factors. Local release of 20 μg LNG in 24 h gives a 100-fold higher concentration in the endometrium than can be achieved by oral administration of therapeutic LNG doses. The cervical mucus becomes thick, scanty and difficult to penetrate by sperm. The LNG-IUS inhibits sperm motility and function inside the uterus and Fallopian tubes, thus reducing the probability of fertilization. The morphology and function of the endometrium becomes dramatically altered, with the epithelium including the glands becoming thin and inactive. On occasion, the whole functional layer becomes atrophic, but this is totally reversible and the morphology and function fully recover soon after removal of the LNG-IUS. This is best indicated by an immediate return of fertility.

Insertion

Most commonly, the LNG-IUS is inserted post-menstrually within 7 days after the onset of menstruation. Other choices include: immediately after a first-trimester abortion procedure; and 6–8 weeks after delivery. After 5 years' use, a replacement LNG-IUS can be inserted after removal at any time during year 6. A thorough training in insertion technique is necessary for optimal performance of the LNG-IUS and to avoid complications.

Efficacy

The LNG-IUS has been studied in more than 10 000 women in randomized comparative studies (Sivin *et al*., 1991; Andersson *et al*., 1994), and the Pearl rate has been almost uniformly between 0.1 and 0.2. A large post-marketing surveillance study of over 17 000 women gave a Pearl rate of 0.17. The efficacy of the LNG-IUS does not depend on the age of the woman, and the system is also highly effective in preventing ectopic pregnancy (Pearl rate 0.02).

Menstrual bleeding

The LNG-IUS will change the profiles of bleeding in every user, this being characterized by a reduction in both the number of bleeding days and volume of bleeding. After the first year of use, between 25 and 60% of the women have amenorrhoea (Diaz *et al*., 2001). More than 90% of women reported a decrease in menstrual blood loss during the first year, the mean volume decreasing by 40 ml. The mean number of bleeding days decreases to less than one after 1 year of LNG-IUS use. In the majority of LNG-IUS users, monthly menstruation is reflected by no more than a few days of scanty spotting.

One characteristic of LNG-IUS use, however, is frequent spotting during the first 3 months. After 5 months of use, the number of bleeding and spotting days combined is, on average, less than five. There is no effective treatment for this spotting; women must be counselled, and studies have shown that this improves satisfaction with the system (Luukkainen *et al*., 2001).

Other adverse effects

During the first months of use, women may experience transient hormonal adverse effects including oedema, headache, breast tenderness, acne and other skin effects. Lower-

abdominal or back pain, vaginal discharge and nausea have been described in some studies. Enlarged ovarian follicles/cysts are more common in women on progestin-only contraception. These have been observed by ultrasonography in between 7 and 30% of LNG-IUS users during the first 3–6 months of use, and they may or may not lead to symptoms, though they (usually) disappear spontaneously. Therefore, observation is indicated rather than active treatment. A body weight gain of 0.5 kg per year reported in one large study was found in both copper intrauterine device (IUD) and LNG-IUS users, and so does not appear to be related to LNG-IUS use. Other adverse effects are rare.

Continuation/user satisfaction

The annual total discontinuation rate in comparative clinical studies has typically varied between 10 and 20%, these being similar to values obtained with a copper IUD. Apart from personal reasons/planning pregnancy, the most common reason for discontinuation during the first year of use is bleeding disturbance. Good counselling at the insertion visit, especially about the local nature of amenorrhoea/no bleeding and later improvement of frequent spotting, improves user satisfaction (Backman *et al*., 2002). More than two-thirds of users are more satisfied with LNG-IUS than with their earlier method of contraception. Satisfaction with the LNG-IUS is also found to increase with age.

Safety

Pelvic inflammatory disease (PID) is associated with the insertion of either an IUD or an IUS. Therefore, local infections must be treated before insertion, and an aseptic technique should be followed for insertion. One large comparative study reports significantly less PID in LNG-IUS users than in copper IUD users, but this finding could be explained by the changes caused by LNG IUD to cervical mucus and endometrium, together with reduced menstrual flow. LNG-IUS does not prevent sexually transmitted diseases.

If perforation occurs, it usually does so during insertion and may not show any symptoms. Perforation should be suspected if the insertion is difficult and/or painful, if pain continues after insertion, and if menstrual flow does not decrease. Ultrasonography, X-radiography or hysteroscopy may help in the diagnosis of penetration or perforation. The removal and correct insertion of a new IUS is needed in order to prevent pregnancy.

Health benefits

Several health benefits have been associated with the use of LNG-IUS (Pakarinen *et al*., 2001): high efficacy results in fewer accidental intrauterine and extrauterine pregnancies and abortions. Decreased menstrual flow improves the body iron balance and reduces dysmenorrhoea. The LNG-IUS improves the quality of life by reducing the number of days of bleeding, and the cost of menstrual hygiene.

The use of LNG-IUS seems to reduce the incidence of PID (Toivonen *et al*., 1991).

Contraindications

Contraindications for LNG-IUS use include diagnosed or suspected pregnancy, untreated genital infection, cervical or uterine malignancy, undiagnosed abnormal uterine bleeding, uterine anomaly, active liver disease, and active thromboembolic process.

Side effects of progestogen-only contraceptives

Progestogen-only contraceptives (i.e., POPs or mini-pills and injectable contraceptives such as DMPA) are used by a minority of women. Only 5 to 15% of women reported ever using such contraceptives in Northern Europe or New Zealand (World Health Organization-IARC, 1999), and data on the potential side effects are consequently scattered.

Most of the published information on side effects of progestogen-only contraceptives concerns cancer risk, and this has been reviewed in the IARC Monograph, 72 (World Health Organization-IARC, 1999). Available data are largely based on case-control studies, as well as—for breast cancer—on a collaborative re-analysis of 27 individual studies providing some information on progestogen-only oral contraceptives (OC) (Collaborative Group on Hormonal Factors in Breast Cancer, 1996b).

Breast cancer

Information on breast cancer risk with POPs is available from seven case-control studies (Vessey *et al*., 1983; CASH, 1986; Meirik *et al*., 1986; UK National Case-Control Study Group, 1989; Clavel *et al*., 1991; Ewertz, 1992; Skegg *et al*., 1996). All relative risks (RR) of individual studies were close to unity for ever-use, and none of them was significant. When data from these studies, together with those of other studies providing some information were pooled in the collaborative re-analysis (Collaborative Group on Hormonal Factors in Breast Cancer, 1996b), the overall RR based on 725 ever-user cases and 528 controls was 1.1, of borderline statistical significance. There was some indication for the RR of breast cancer to rise with duration of use (RR = 1.2 for $\geqslant$4 years) and, most important, with recency of use (RR = 1.2 for <5 years since stopping). Although the latter estimate was not significant, the point estimate is compatible with the modest excess breast cancer risk observed among current and recent users of combined OC (Collaborative Group on Hormonal Factors in Breast Cancer, 1996b; La Vecchia, 2001).

Information on injectable depot-progestogen and breast cancer risk comes from two studies (World Health Organization, 1991a; Skegg *et al*., 1995), as well as the collaborative re-analysis (Collaborative Group on Hormonal Factors in Breast Cancer, 1996b). On the basis of 339 cases and 1935 controls, the RR for ever-use was 1.0, and there was no indication of a trend in risk with duration. However, there was some indication of excess risk for women who had first (RR = 1.5) or last (RR = 1.2) used injectable progestogen-only contraceptives since less than 5 years, again reflecting the pattern observed for other hormonal contraceptive preparations. However, an additional study from South Africa

Table VI. Relative risk of acute myocardial infarction in studies considering second- and third-generation oral contraceptives

Study	Second generation		Third generation	
	RR	No. of cases	RR	No. of cases
Lewis *et al*. (1997) (Transnational)	3.0	28	0.9	7
World Health Organization (1997)	1.6	13	1.0	3
Dunn *et al*. (1999) (MICA)	1.1	20	2.0	20
Tanis *et al*. (2001)	2.5	59	1.3	20
Average (95% CI)	2.3 (1.8–2.8)	120	1.5 (1.1–2.3)	50

CI = confidence interval; RR = relative risk.

(Shapiro *et al*., 2000), including 484 breast cancer cases and 318 injectable progestogen ever-users, found a RR of 0.9 for ever-users, and no relation with duration, time since first or last use.

The data on progestogen-only contraceptives and breast cancer risk are therefore limited, and compatible with the absence of any association, or a modest association among current or recent users, which would remain therefore of limited public health relevance—at least for use among women aged below 35 years.

These inferences on breast cancer are based on multivariate risk estimates which allow for the potential confounding effect of parity and lactation—factors that have a recognized favourable influence on breast cancer risk (Collaborative Group on Hormonal Factors on Breast Cancer, 2002).

Endometrial cancer

Data on progestogen-only contraceptives and endometrial cancer risk come from at least two studies. The RRs for ever-users were 0.6 (95% CI = 0.1–5.0) (CASH, 1987) and 0.2 (95% CI = 0.1–0.8) (World Health Organization, 1991b). Although overall there were only four users among the cases and 91 among the controls, these findings are therefore compatible with the well-known protection of combined OC against endometrial cancer risk (La Vecchia, 2001).

Other cancers

Ovarian cancer risk with progestogen-only contraceptives was estimated in three studies. (Liang *et al*., 1983; World Health Organization, 1991c; Rosenberg *et al*., 1994) The RRs were 0.8, 1.1 and 0.3, which is similar to the reduced risk of ovarian cancer with use of combined OC (La Vecchia *et al*., 2001).

Risk of cervical neoplasm was estimated in four progestogen-only contraceptives studies, mainly for DMPA and other injectable contraceptives. Overall, there was no evidence of excess risk for ever-users (La Vecchia, 1994; World Health Organization-IARC, 1999), but the RR was 2.4 (95% CI 1.0–5.7) for women who had used injectable contraceptives for 5 or more years in the largest study, conducted in Latin America (Herrero *et al*., 1990). There was no indication of a differential risk between adenocarcinomas and adenosquamous cervical carcinomas (Thomas *et al*., 1995).

Only scattered data were available on risks of other neoplasms, such as liver cancer or malignant melanoma, but these do not indicate any excess risk. Overall, therefore, there is inadequate evidence in humans for the carcinogenicity of progestogen-only contraceptives (World Health Organization-IARC, 1999).

Cardiovascular effects

With reference to venous thromboembolism (VTE), before 1995 the progestogen component of OC was not generally thought to be associated with the risk of thrombosis. However, the observation that desogestrel and gestodene in combined OC may be associated with a greater risk of VTE than LNG suggests that the progestogen component of OC may also be involved in the risk of VTE (Skegg, 2000; Vandenbroucke *et al*., 2001). Consequently, it is conceivable that progestogen-only contraceptives have some influence on the risk of VTE, particularly for women with inherited clotting defects (Bloemenkamp *et al*., 2000), although the available epidemiological data are too limited to provide adequate quantitative evaluation of the issue.

There are, moreover, limited data (Lewis *et al*., 1996; 1997; World Health Organization, 1997; Dunn *et al*., 1999; Tanis *et al*., 2001) to compare the risk of acute myocardial infarction (AMI) in current users of third- versus second-generation OC, but these suggest that the RR for AMI may be lower with third-generation products. This could be compatible with the more favourable lipid profile of third-generation OC, with a slight increase in high-density lipoprotein (HDL)-cholesterol (Vandenbroucke *et al*., 2001).

At least five published studies have considered the issue. One of these (Jick *et al*., 1995) compared AMI risk of current users of third- versus second-generation OC: the RR (0.7) was based on only two current users of third-generation OC. The main results of four other studies giving the RRs for users of second- and third-generation OC versus non-users are given in Table VI. These include the Transnational case-control study from 16 centres in Europe (Lewis *et al*., 1997), the World Health Organization Study (World Health Organization, 1997), conducted in 21 centres from Africa, Asia, Europe and Latin America, the MICA study from the UK (Dunn *et al*., 1999), and the Dutch study (Tanis *et al*., 2001).

Overall in the four studies, there were 120 AMI cases in current users of second-generation OC and 50 in third-generation users. The pooled RR was 2.3 for users of second-generation OC, and 1.5 for users of third-generation OC, and the confidence intervals overlapped. These pooled estimates are only indicative, given the small number of user cases and the heterogeneity of the results across studies and populations, and so any comparative assessment of the excess risk of VTE and the potentially reduced risk of AMI in users of third-generation OC remains open to further evaluation. A much greater amount of data on progestogen-only contraceptive use is required before an accurate assessment of the VTE or AMI risk can be made.

Specific indications

Compared with modern combined estrogen-progestogen contraceptive preparations, progestogen-only contraception (POC) may be associated with even fewer health risks, as it contains no estrogen and usually a lower dose of progestogen than would be found compared with hormonal contraception of the combined type. Thus, POC may be preferred as a contraceptive method by women with medical problems or higher risk of medical conditions than may be associated with use of combined contraceptives. Medical eligibility criteria address contraceptive use in women with such specific medical conditions. Decisions on appropriate contraception must take into account the patient's baseline risk, whether an increased risk is associated with a given method, and the expressed desires of the individual. Medical eligibility describes the range of options and is therefore a better description of the available choices than simply listing contraindications or relative contraindications. The first attempt to develop a worldwide consensus on eligibility criteria for contraceptives was made when the World Health Organization established a scientific working group in 1994 with the subsequent report: ''Improving Access to Quality Care in Family Planning: Medical Eligibility Criteria for Contraceptive Use'' (World Health Organization, 1996). Another effort was made by the Royal College of General Practitioners (RCGP) and the European Contraceptive Society (ESC) in 1996 to establish evidence-guided prescription of the pill (Hannaford and Webb, 1996). The World Health Organization has set up specific classification categories based upon the type of evidence available. Medical criteria for the use of any method of contraception may be classified under one of four categories:

1. A condition for which there is no restriction on the use of the contraceptive method.

2. A condition where the advantages of using the method generally outweigh the theoretical or proven risks.

3. A condition where the theoretical or proven risks usually outweighs the advantages of using the method.

4. A condition which represents an unacceptable health risk if the contraceptive method is used.

More recently, the evidence-based approach has been incorporated into a practice bulletin from the ACOG (American College of Obstetricians and Gynecologists, 2000). The World Health Organization has also conducted a systematic review to address the controversies encountered when providing contraception to women with medical problems (Curtis *et al*., 2002). The following recommendations on specific indications for POC compared with combined hormonal contraception are based on the principles from these publications.

Post-partum and breastfeeding

Guidelines indicate that, at less than 6 weeks post-partum, women should not use hormonal contraceptive methods because of theoretical concerns about adverse effects on the health and growth of the infant, though no studies have shown such adverse effects from POC. In contrast to combined OC, the use of POC does not increase risk of deep venous thrombosis (DVT) during the post-partum period. POC will not diminish the quantity of breast milk.

Age and smoking

There are theoretical concerns that POCs may cause a hypoestrogenic effect among women aged under 18 years and above 45 years. The effects of POCs on bone mineral density may be particularly important for adolescents who have not yet reached peak bone mass. In women aged less than 18 years who use DMPA, bone mineral density is lower compared to non-users, but the clinical significance of this effect is uncertain. In contrast to combined OC use, POC use with increasing age and increasing number of cigarettes is not associated with any statistical increased risk of cardiovascular disease.

Cardiovascular disease (CVD)

- DVT: there is no significant increase in DVT risk for POC users compared with non-users of any type of steroid hormone contraceptive. In women with a current or past history of DVT, POC may in theory increase the risk of DVT, but less than combined OCs
- Hypertension: combined OC users are at increased risk of stroke and AMI. Limited evidence does not rule out a small rise in stroke risk from POC use in hypertensive women.
- Current or prior ischaemic heart disease or stroke: there is concern about reduced HDL-cholesterol levels in POC users. Thus, in theory, POC use may increase the risk of arterial thrombosis, though to a lesser degree than combined OCs, and data to assess this risk are needed.
- Diabetes with vascular complications: although combined OC use is acceptable in women with diabetes, theoretical concerns indicate that such use should be limited to non-smoking, otherwise healthy women aged less than 35 years. It is not known whether POC use would be safer than combined OC use in diabetic women with vascular complications.

Breast cancer

As noted above, the data on progestogen-only contraceptives and breast cancer risk are limited, and consistent with no increase or a modest increase in risk among current or recent users. Although POC use may in theory worsen the prognosis in women with current or previously treated breast cancer, the known effects on breast cancer are less than those associated with combined OCs.

Table VII. Contraceptive efficacy of mifepristone

Mifepristone dose (mg)	Time of treatment	Subjects (*n*)	Cycles (*n*)	Pregnancy (*n*)	Pregnancy rate (%)	Reference
200	LH + 2	21	161	1	0.01	Gemzell Danielsson *et al*. (1993)
200	LH + 2	32	178	1	0.01	Hapangama *et al*. (2001)
0.5	Daily	32	141	4	0.04	Marions *et al*. (1999)
2 or 5	Daily	50	200	0	0	Brown *et al*. (2002)

Liver disease

In women with active hepatitis, cirrhosis and adenoma there is concern about the additional metabolic burden from the hormones associated with combined OC or POC use, although no evidence currently exists of an increased risk of serious liver disease among present or former users.

HIV

There is no evidence for an association between HIV-1 infection and either combined OC or POC use.

Antiprogestogen

Because progesterone is essential for ovulation, endometrial development, implantation and the establishment of pregnancy, it has long been recognized that a substance which antagonizes the action of progesterone would have a potential as an antifertility agent. Although a large number of antiprogestogens have been synthesized, most studies to date have been focused on the prototype compound, mifepristone (RU 486; Exelgyne, Paris, France). Mifepristone and similar antiprogestogens bind strongly to both the progesterone and glycocorticoid receptor, and to a lesser extent to the androgen receptor. Although mifepristone functions predominantly as an antiprogestogen, it may also (under specific conditions) display progesterone agonistic and even anti-oestrogen properties, though mifepristone does not bind to the estrogen receptor (Hodgen *et al*., 1994).

Extensive trials conducted over the past 15 years have established that a single dose of mifepristone followed 36–48 h later by a prostaglandin is an effective and safe method for termination of early pregnancy (Von Hertzen, 2000). Mifepristone is also very effective in the management of prostaglandin-induced mid-trimester abortion. By sensitizing the uterus to prostaglandin and ripening the cervix, the prostaglandin dose can be reduced and the prostaglandin to abortion interval significantly shortened (Tang *et al*., 2001).

Mifepristone has a number of effects which could be regarded as useful for a contraceptive compound. Long-term (3- to 6-month) daily treatment with mifepristone in doses which inhibit ovulation is effective in the treatment of endometriosis and uterine fibromata (Kettel *et al*., 1994). Preliminary studies also indicate that treatment with antiprogestogens may have beneficial effects in tumours that contain steroid receptors, such as breast cancer (Klijn *et al*., 2000).

The contraceptive potential of antiprogestogens depends on their effects during the menstrual cycle. Following the administration of a single dose of 5–10 mg or daily doses as low as 2 mg mifepristone in the mid to late follicular phase, follicular development is delayed or arrested, estrogen levels fail to increase, and the LH peak is delayed or inhibited. Consequently, ovulation and menstruation are postponed, with the effect depending on the duration of treatment. Once the treatment is interrupted, the growth of the follicle will resume or a new follicle be recruited. The following secretory phase will be essentially normal (Spitz *et al*., 1996; Bygdeman *et al*., 1999). If the daily dose is <1 mg, ovulation is not influenced but the secretory transformation of the endometrium is altered (Marions *et al*., 1999). Similar findings have been demonstrated in subhuman primates using other antiprogestogens such as ZK 137316 (Slayden *et al*., 1998).

That the inhibition of ovulation could be used for contraceptive purposes was illustrated in a study performed in Edinburgh and Shanghai in which 90 women were treated with either 2 or 5 mg mifepristone daily for 4 months. Almost 90% of the women became amenorrhoeic during treatment with the higher dose. Biochemical evidence of ovulation was found on 12 occasions with 3 mg and on six occasions with 5 mg mifepristone during the 360 months of treatment. In total, 50 women used this treatment as their only contraceptive method during 4 months (totalling 200 months of use) and there were no pregnancies (Brown *et al*., 2002).

During treatment with mifepristone, the estrogen levels are sufficient to allow a gestagen withdrawal bleeding. One possibility of inhibiting ovulation and maintaining regular bleeding is to combine mifepristone and gestagen treatment. This was demonstrated by one group (Croxatto *et al*., 1998) who gave 10 mg mifepristone daily for 15 days followed by nomegestrel acetate 5 mg/day for the next 13 days to 10 sterilized subjects during three treatment cycles. Echographic and endocrine features of ovulation were present in 13.3% of the cycles. The development of a secretory endometrium was achieved in all cases, but it was always irregular. Although the contraceptive effect of the treatment was not tested, it was suggested that the ovarian and endometrial effect of the treatment would be sufficient to prevent pregnancy.

If mifepristone in a high dose (200 mg) is given immediately after ovulation, on day LH+2, the secretory development of the endometrium is inhibited without disturbing the normal menstrual cycle. In addition, the normal down-regulation of progesterone and estrogen receptor concentration is inhibited as well as the expression of several progesterone-regulated factors which are of importance for implantation (Spitz *et al*., 1996; Bygdeman *et al*., 1999). This effect on the endometrium seems sufficient to prevent pregnancy, and was demonstrated in two studies including 53 women and 339 cycles where once-monthly treatment with 200 mg mifepristone on day LH+2 was used as their only contraceptive method. Only two pregnancies occurred, corresponding to a Pearl Index of 7. Among a control group of women who did not use any contraceptive method there were 12 pregnancies during a total of

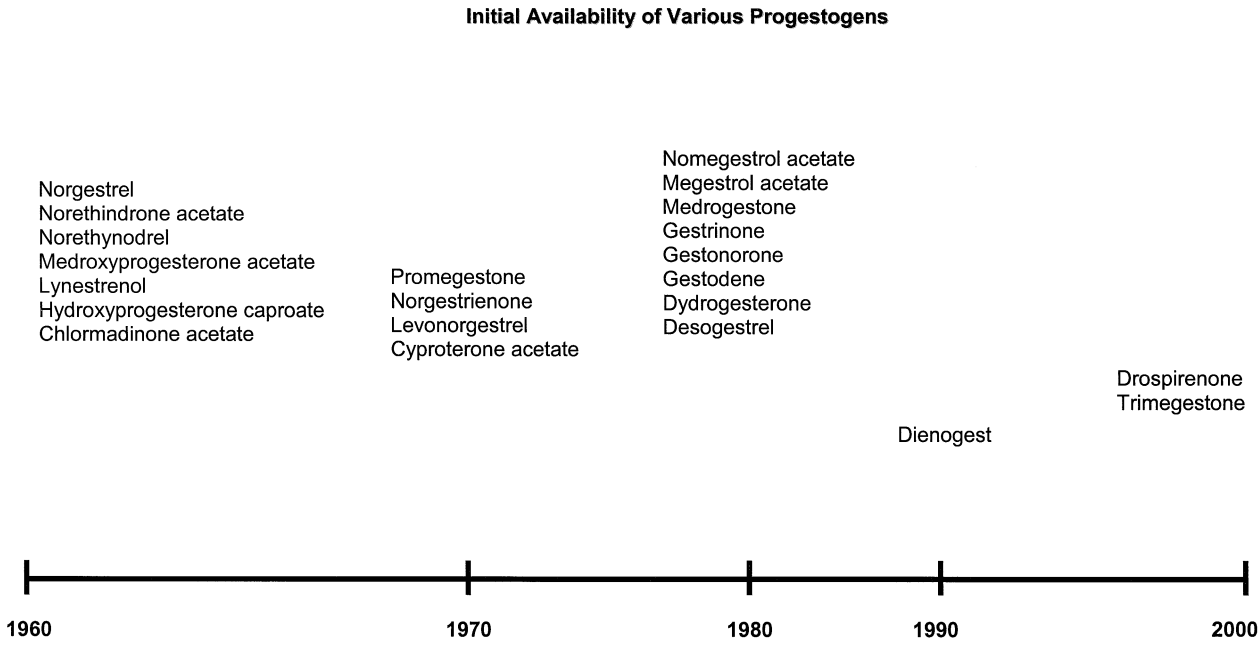

Figure 1. Initial availability of various progestogens.

50 cycles (Gemzell Danielsson *et al*., 1993; Hapangama *et al*., 2001).

Endometrial development seems more sensitive to mifepristone than follicular development and ovulation. While a daily dose of 0.5 mg mifepristone will not influence ovulation or the menstrual cycle, endometrial development will be retarded. The contraceptive effect of a daily dose of 0.5 mg mifepristone was evaluated in 32 women over 141 cycles. The pregnancy rate was significantly reduced (five pregnancies; expected pregnancy rate 40), but the efficacy was not sufficiently high for routine clinical use (Marions *et al*., 1999). Other antiprogestogens with a more specific effect on the endometrium might be more useful (Table VII).

As mifepristone both delays ovulation and inhibits implantation, it seems an ideal drug for emergency contraception. A dose of 600 mg mifepristone was also shown as highly effective (Glasier *et al*., 1992; Webb *et al*., 1992). Even if the dose was reduced to 10 mg and administered within 120 h after a single unprotected intercourse, 85% of expected pregnancies were prevented (World Health Organization, 1999). The side effects were few, other than a delay of the first menstruation for more than 1 week in 18% of the women receiving the 10 mg dose.

The most frequently used method for emergency contraception is two doses of 0.75 mg LNG administered with a 12 h interval and within 72 h of unprotected intercourse. How mifepristone compares with LNG for this purpose is unclear. In an unpublished study (performed by Wu and colleagues in 1324 Chinese women) cited in a recent Cochrane review (Cheng *et al*., 2001), the two-dose regimen of LNG (0.75 mg, 12 h apart) was compared with a single dose of 10 mg mifepristone with a placebo tablet taken 12 h later. Twenty pregnancies occurred in the LNG group, and nine in the mifepristone group. Within the LNG and mifepristone groups, 59.2 and 79.7% of the pregnancies respectively were prevented, the difference being statistically significant. The side effects were mild in nature and occurred in fewer than 10% of each treatment group. More mifepristone subjects (19%) had delayed menstruation than did LNG subjects (11%), while more women in the LNG group than the mifepristone group had early menstruation (17% versus 11%).

Considering the effect of antiprogestogens on the endometrium, an IUD releasing the compound would be an interesting possibility, but as yet this does not appear to have been evaluated.

Thus, if research in this area is promoted and other antiprogestogens not used for abortion are evaluated, a number of possibilities exist for the development of an estrogen-free contraceptive method based on antiprogestogens.

New preparations and delivery systems

New compounds for hormonal contraception are rather rare, with only 22 progestogens (norprogestogens as well as derivatives of 17α-hydroxyprogesterone) having been launched worldwide since the 1960s. The launch of the different progestogens can be seen as two large waves in the 1960s and 1980s (Figure 1), whilst the most recent developments have been dienogest, drospirenone and trimegestone (Oettel *et al*., 2001; Sitruk-Ware, 2002). At present, the pharmaceutical industry commits only a small amount of capacity to the search for and development of new progestogens. On the other hand, several companies are making considerable efforts to develop antiprogestogens, selective progesterone receptor modulators (mesoprogestogens; SPRMS) and ligands for the progesterone receptor isoform A (Conneely and Lydon, 2000). It is hoped that mesoprogestogens in particular may overcome the most pronounced deficiency of conventional POPs, namely bleeding control. These compounds bear the potential to induce amenorrhoea while exerting antifertility effects via reduced endometrial receptivity, generation of sticky cervical mucus and inhibition of ovulation (Chwalisz *et al*., 2002).

Also in contrast to the relatively low emphasis on novel progestogens, important innovations are evolving in the pharmaceutical technology of non-oral contraceptives. Methods are being discovered for the delivery of new compounds by injection, implants, intrauterine systems and transdermal systems (patches) as well as different intravaginal and intranasal dosage forms. In a final area of development it appears that, for now at least, practical methods for male contraception are only available through non-oral administration.

The use of drug delivery systems (DDS) for sex steroids including transdermal patches has led to specific advantages for contraception (Lipp, 2001; Fauth *et al*., 2002). The main benefits are tight control of drug uptake and avoidance of the hepatic first-pass effect (despite the absence of classical progesterone receptors in the liver, there are numerous specific hepatic effects of progestogens). Also advantageous are the long (and, in several cases, extremely long) application intervals, the use of non- or minimally invasive routes of administration, and (depending on the specific characteristics of user groups) overall enhancement of the quality of life. Nevertheless, even the latest insights into polymer technology only partly attain the extremely demanding goal of family planning in the future—that is, user-friendly and effective contraception with a low incidence of side effects, whilst at the same time, and with the same system, providing reliable protection against sexually transmitted diseases, notably HIV.

References

American College of Obstetricians and Gynecologists (2000) The use of hormonal contraception in women with coexisting medical conditions. ACOG Practice Bulletin No. 18. American College of Obstetricians and Gynecologists, Washington, DC.

Anderson, L.C., Wise, D.L. and Howes, J.F. (1976) An injectable sustained release fertility control system. *Contraception*, **13**, 375–384.

Andersson, K., Odlind, V. and Rybo, G. (1994) Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomised comparative trial. *Contraception*, **49**, 56–72.

Babcock, J.C., Gutsell, E.S., Herr, M.E. *et al*. (1958) 6α-Methyl-17α-hydroxyprogesterone 17-acytates: a new class of potent progestatins. *J. Am. Chem. Soc.*, **80**, 2902–2907.

Backman, T., Huhtala, S., Luoto, R. *et al*. (2002) Advance information improves user satisfaction with the levonorgestrel intrauterine system. *Obstet. Gynecol.*, **99**, 608–613.

Baeten, J.M., Nyange, P., Richardson, B.A., Lavreys, L., Chohan, B., Martin, H.L., Mandaliya, K., Ndinya-Achola, J.O., Bwayo, J.J. and Kreiss, J.K. (2001) Hormonal contraception and risk of sexually transmitted disease acquisition: results from a prospective study. *Am. J. Obstet. Gynecol.*, **185**, 380–385.

Benagiano, G. and Primiero, F.M. (1983a) Long-acting contraceptives. Present status. *Drugs*, **25**, 570–609.

Benagiano, G. and Primiero, F.M. (1983b) Norethindrone enanthate. In: Mishell, D.R., Jr (ed.), *Long-acting Steroid Contraception*. Raven Press, New York.

Bloemenkamp, K.W.M., Rosendaal, F.R., Helmerhost, F.M. and Vandenbrouche, J.P. (2000) Higher risk of venous thrombosis during early use of oral contraceptives on women with inherited clotting defects. *Arch. Intern. Med.*, **160**, 49–52.

Brown, A., Cheng, L., Lin, S. and Baird, D.T. (2002) Daily low dose mifepristone has contraceptive potential by suppressing ovulation and menstruation: a double-blind randomized control trial of 2 and 5 mg per day for 120 days. *J. Clin. Endocrinol. Metab.*, **87**, 63–70.

Bygdeman, M., Gemzell Danielsson, K., Marions, L. and Swahn, M.L. (1999) Contraceptive use of antiprogestogen. *Eur. J. Contracept. Reprod. Healthcare*, **4**, 103–107.

Carlin, E.M. and Boag, F.C. (1995) Women, contraception and STDs including HIV. *Int. J. STD-AIDS*, **6**, 373–386.

CASH, Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development (1986) Oral contraceptive use and the risk of breast cancer. *N. Engl. J. Med.*, **315**, 405–411.

CASH, Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development (1987) Combination oral contraceptive use and the risk of endometrial cancer. *JAMA*, **257**, 796–800.

Cheng, L., Gulmezoglu, A.M., Ezcurra, E. and Van Look, P.F.A. (2001) Interventions for emergency contraception (Cochrane Review). In: The Cochrane Library, Issue **2**, 2001. Oxford: Update Software.

Chesnais, J.-C. (1999) Determinants of below-replacement fertility. Pop. Bull., ST/ESA/SER.N/**40-41**, 126–136.

Chikamata, D.M. and Miller, S. (2002) Health services at the clinical level and implantable contraceptives for women. *Contraception*, **65**, 97–106.

Chwalisz, K., Garg, R., Brenner, R.M., Schubert, G. and Elger, W. (2002) Selective progesterone receptor modulators (SPRMs): a novel therapeutic concept in endometriosis. *Ann. N. Y. Acad. Sci.*, **955**, 373–388.

Clavel, F., Andrieu, N., Gairard, B., Brémand, A., Piana, L., Lansac, J., Bréart, G., Rumeau-Rouquette, C., Flamant, R. and Renaud, R. (1991) Oral contraceptives and breast cancer: a French case-control study. *Int. J. Epidemiol.*, **20**, 32–38.

Collaborative Group on Hormonal Factors in Breast Cancer (1996a) Breast cancer and hormonal contraceptives. Collaborative re-analysis of individual data on 53297 women with breast cancer and 100,239 without breast cancer from 54 epidemiological studies. *Lancet*, **347**, 1713–1727.

Collaborative Group on Hormonal Factors in Breast Cancer (1996b) Breast cancer and hormonal contraceptives: further results. *Contraception*, **54** (Suppl. 3), 1S–106S.

Collaborative Group on Hormonal Factors on Breast Cancer (2002) Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50,302 women with breast cancer and 96,973 women without the disease. *Lancet*, **360**, 187–195.

Collaborative Study Group on the Desogestrel-containing Progestogen-only pill (1998) A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 μg or levonorgestrel 30 μg/day. *Eur. J. Contracept. Reprod. Healthcare*, **3**, 169–178.

Conneely, O.M. and Lydon, J.P. (2000) Progesterone receptors in reproduction: functional impact of the A and B isoforms. *Steroids*, **65**, 571–577.

Croxatto, H.B. (2002a) Progestogen implants for female contraception. *Contraception*, **65**, 15–20.

Croxatto, H.B. (2002b) Mechanisms that explain the contraceptive action of progestin implants for women. *Contraception*, **65**, 21–28.

Croxatto, M.B., Salvatierra, A.M., Fuentealba, B. and Massai, R. (1998) Contraceptive potential of a mifepristone-nomegestrel acetate sequential regimen in women. *Hum. Reprod.*, **13**, 3297–3302.

Cundy, T., Evans, M., Roberts, M. *et al*. (1991) Bone density in women receiving depot medroxyprogesterone acetate for contraception. *Br. Med. J.*, **303**, 13–16.

Cundy, T., Cornish, J., Evans, M.C. *et al*. (1994) Recovery of bone density in women who stop using medroxyprogesterone acetate. *Br. Med. J.*, **308**, 247–248.

Curtis, K.M., Chrisman, C.E. and Peterson, H.B. (2002) The WHO Programme for Mapping Best Practices in Reproductive Health. *Obstet. Gynecol.*, **99**, 1100–1112.

Diaz, J., Bahamondes, I., Monteiro, C.A., Petta, M. and Hidalgo, C.E. (2001) Acceptability and performance of the levonorgestrel-releasing intrauterine system (Mirena®) in Campinas, Brasil. *Contraception*, **62**, 59–61.

Dorfman, R.I. and Shipley, R.A. (1956) *Androgens*, *Biochemistry*, *Physiology and Clinical Significance*. J. Wiley & Sons, New York.

Dunn, N., Thorogood, M., Faragher, B., de Caestecker, L., MacDonald, T.M., McCollum, C., Thomas, S. and Mann, R. (1999) Oral contraceptives and myocardial infarction: results of the MICA case-control study. *Br. Med. J.*, **318**, 1579–1584.

Ewertz, M. (1992) Oral contraceptives and breast cancer risk in Denmark. *Eur. J. Cancer*, **28A**, 1176–1181.

Fauth, C., Wiedersberg, S., Neubert, R.H.H. and Dittgen, M. (2002) Adhesive backing foil interactions affecting the elasticity, adhesion strength of laminates, and how to interpret these properties of branded transdermal patches. *Drug Dev. Ind. Pharmacy*, **28**, 1251–1259.

Fotherby, K., Saxena, B., Shrimanker, K. *et al*. (1980) A preliminary

pharmacokinetic and pharmacodynamic evaluation of depot medroxyprogesterone acetate and norethisterone oenanthate. *Fertil. Steril.*, **34**, 131–139.

GemzellDanielsson, K., Swahn, M.L., Svalander, P. and Bygdeman, M. (1993) Early luteal phase treatment with mifepristone (RU 486) for fertility regulation. *Hum. Reprod.*, **8**, 870–873.

Glasier, A. (2002) Implantable contraceptives for women: effectiveness, discontinuation rates, return of fertility, and outcome of pregnancies. *Contraception*, **65**, 29–38.

Glasier, A.F., Thong, K.J., Dewar, M. *et al*. (1992) Mifepristone (RU 486) compared with high-dose estrogen and progesterone for emergency postcoital contraception *N. Engl. J. Med.*, **327**, 1041–1044.

Hannaford, P. and Webb, A. (eds) (1996) *Evidence-Guided Prescribing of the Pill*. Parthenon Publishing, Carnforth, England.

Hapangama, D.K., Brown, A., Glasier, A.F. and Baird, D.T. (2001) Feasibility of administering mifepristone as a month contraceptive pill. *Hum. Reprod.*, **16**, 1145–1150.

Herrero, R., Brinton, L.A., Reeves, W.C., Brenes, M.M., de Britton, R.C., Tenoio, F. and Gaitan, E. (1990) Injectable contraceptive and risk of invasive cervical cancer: evidence of an association. *Int. J. Cancer*, **5–7.**

Hickey, M. and d'Arcangues, C. (2002) Vaginal bleeding disturbances and implantable contraceptives. *Contraception*, **65**, 75–84.

Hodgen, G., van Uem, J.F.H.M., Chillick, S. *et al*. (1994) Non-competitive anti-oestrogenic activity of progesterone antagonists in primate models. *Hum. Reprod.*, **9** (Suppl.), 77–81.

Jick, H., Jick, S.S., Myers, M.W. and Vasilakis, C. (1995) Risk of idiopathic cardiovascular death and non-fatal venous thrombolism in women using oral contraceptive with differing progestagen components. *Lancet*, **346**, 1589–1593.

Johnson, S.P. (1987) *World population and the United Nations – Challenge and Response*. Cambridge University Press, Cambridge, UK.

Junkmann, K. and Witzel, H. (1958) *The Chemistry and Pharmacology of Steroid Esters. Monographs on Therapy*, *Volume 3*. The Squibb Institute for Medical Research, New Brunswick, NJ.

Kettel, L.M., Murphy, A.A., Morales, A.J. and Yen, S.S.C. (1994) Clinical efficacy of the antiprogesterone RU 486 in the treatment of endometriosis and uterine fibroids. *Hum. Reprod.*, **9** (Suppl.), 116–120.

Kim-Bjorklund, T., Landgren, B.M. and Johannisson, E. (1991) Morphometric studies of the endometrium, the fallopian tube and the corpus luteum during contraception with the 300 μg norethisterone (NET) minipill. *Contraception*, **43**, 459–474.

Klijn, J.G.M., Setyono-Han, B. and Foekens, J.A. (2000) Progesterone antagonists and progesterone receptor modulators in the treatment of breast cancer. *Steroids*, **65**, 825–830.

LaVecchia, C. (1994) Depot-medroxyprogesterone acetate, other injectable contraceptives, and cervical neoplasia. *Contraception*, **49**, 223–230.

LaVecchia, C. (2001) Oral contraceptives, cancer and vascular disease. *Eur. J. Cancer Prev.*, **10**, 303–305.

LaVecchia, C., Altieri, A., Franceschi, S. and Tavani, A. (2001) Oral contraceptives and cancer. An update. *Drug Safety*, **24**, 741–754.

Lahteenmaki, P., Rauramo, I. and Backman, T. (2000) The levonorgestrel intrauterine system in contraception. *Steroids*, **65**, 693–697.

Landgren, B.M. and Diczfalusy, E. (1980) Hormonal effects of the 300 μg norethisterone (NET) minipill 1. Daily steroid levels in 43 subjects during a pre-treatment cycle and during the second month of NET administration. *Contraception*, **21**, 87–113.

Lesthaeghe, R. and Willems, P. (1999) Is low fertility a temporary phenomenon in the European Union? *Pop. Dev. Rev.*, **25**, 211–228.

Lewis, M.A., Spitzer, W.O., Heinemann, L.A., MacRae, K.D., Bruppacher, R. and Thorogood, M. (1996) Third generation oral contraceptives and risk of myocardial infarction: an international case-control study. *Br. Med. J.*, **31**, 88–90.

Lewis, M.A., Heinemann, L.A., Spitzer, W.O., MacRae, K.D. and Bruppacher, R. (1997) 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*, **56**, 129–140.

Liang, A.P., Levenson, A.G., Layde, P.M., Shelton, J.D., Hatcher, R.A., Potts, M. and Michelson, M.J. (1983) Risk of breast, uterine corpus, and ovarian cancer in women receiving medroxy-progesterone injection. *JAMA*, **249**, 2909–2912.

Lipp, R. (2001) Novel drug delivery systems for steroidal hormones. *Expert Opin. Ther. Patents*, **11**, 1291–1299.

Luukkainen, T., Allonen, H., Haukkamaa, M. *et al*. (1987) Effective contraception with the levonorgestrel-releasing intrauterine device. A 12-month report of a European multicenter study. *Contraception*, **36**, 169–179.

Luukkainen, T., Pakarinen, P. and Toivonen, J. (2001) Progestogen-releasing intrauterine systems. *Semin. Reprod. Med.*, **19**, 355–363.

Marions, L., Viski, S., Gemzell Danielsson, K. *et al*. (1999) Contraceptive efficacy of daily administration of 0.5 mg mifepristone. *Hum. Reprod.*, **14**, 2788–2790.

Martin, H.L., Nyange, P.M., Richardson, B.A., Lavreys, L., Mandaliya, K., Jackson, D.J., Ndinya-Achola, J.O. and Kreiss, J. (1998) Hormonal contraception, sexually transmitted diseases and risk of heterosexual transmission of Human Immunodeficiency Virus Type 1. *J. Infect. Dis.* **178**, 1053–1059.

McCann, M.F. and Potter, L.S. (1994) Progestogen-only oral contraception: a comprehensive review. *Contraception*, **50** (Suppl. 1): S1–S198.

Meirik, M., Farley, T.M.M., Sivin, I., for the International Collaborative Post-marketing Surveillance of Norplant® (2001) Safety and efficacy of levonorgestrel implants, intrauterine device, and sterilization. *Obstet. Gynecol.*, **97**, 539–547.

Meirik, O., Lund, E., Adami, H.O., Bergstrom, R., Christoffersen, T. and Bergsjo, P. (1986) Oral contraceptive use and breast cancer in young women. *Lancet*, **ii**, 650–654.

Meli, A., Wollf, A. and Howarth, W.L. (1963) The mechanism by which 3-esterification with cyclopentyl alcohol enhances the oral activity of ethinyl oestradiol. *Steroids*, **2**, 417–422.

Mostad, S.B., Overbaugh, J., DeVange, D.M., Welch, M.J., Chohan, B., Mandaliya, K., Nyange, P., Martin, H.L., Ndinya-Achola, J., Bwayo, J.J. and Kreiss, J.K. (1997) Hormonal contraception, vitamin A deficiency and other risk factors for shedding of HIV-1 infected cells from the cervix and vagina. *Lancet*, **350**, 922–927.

Oettel, M., Elger, W., Gräser, T., Holz, C., Lähteenmäki, P. and Patchev, V. (2001) What is past is prologue: estrogen/progestogen replacement tomorrow. *Gynecol. Endocrinol.*, **15** (Suppl. 4), 68–90.

Pakarinen, P., Toivonen, J. and Luukkainen, T. (2001) Therapeutic use of the LNG-IUS, and counselling. *Semin. Reprod. Med.*, **19**, 365–372.

Post-marketing Surveillance of Norplant contraceptive implants: I (2001a) Contraceptive efficacy and reproductive health. International Collaborative Post-marketing Surveillance of Norplant®. *Contraception*, **63**, 167–186.

Post-marketing Surveillance of Norplant contraceptive implants: II (2001b) Non-reproductive health. International Collaborative Post-marketing Surveillance of Norplant®. *Contraception*, **63**, 187–209.

Rice, C.F., Killick, S.R., Dieben, T. and Coelingh Bennink, H. (1999) A comparison of the inhibition of ovulation achieved by desogestrel 75 μg and levonorgestrel 30 μg daily. *Hum. Reprod.*, **14**, 982–985.

Rosenberg, L., Palmer, J.R., Zauber, A.G., Warshauer, M.E., Lewis, J.L., Jr, Strom, B.L., Harlap, S. and Shapiro, S. (1994) A case-control study of oral contraceptive use and invasive epithelial ovarian cancer. *Am. J. Epidemiol.*, **139**, 654–661.

Shapiro, S., Rosenberg, L., Hoffman, M., Truter, H., Cooper, D., Rao, S., Dent, D., Gudgeon, A., van Zyl, J., Katzenellenbogen, J. and Baillie, R. (2000) Risk of breast cancer in relation to the use of injectable progestogen contraceptives and combined estrogen/progestogen contraceptives. *Am. J. Epidemiol.*, **151**, 396–403.

Siegel, I. (1963) Conception control by long-acting progestogens: preliminary report. *Obstet. Gynecol.*, **21**, 666.

Sitruk-Ware, R. (2002) Progestogens in hormonal replacement therapy: new molecules, risks, and benefits. *Menopause*, **9**, 6–15.

Sivin, I., Stern, J., Coutinho, E. *et al*. (1991) Prolonged intrauterine contraception: a seven-year randomised study of the 20 mcg/day (LNg 20) and the Copper T-380Ag IUDs. *Contraception*, **44**, 473–480.

Sivin, I., Campodònico, I., Kiriwat, O. *et al*. (1998) The performance of levonorgestrel rod and Norplant® contraceptive implants: a 5-year randomized study. *Hum. Reprod.*, **13**, 3371–3378.

Skegg, C.G. (2000) Third generation oral contraceptives. Caution is still justified. *Br. Med. J.*, **321**, 190–191.

Skegg, D.C., Noonan, E.A., Paul, C., Spears, G.F.S., Meirik, O. and Thomas, D.B. (1995) Depot medroxyprogesterone acetate and breast cancer. A pooled analysis of the World Health Organization and New Zealand studies. *JAMA*, **273**, 799–804.

Skegg, D.C., Paul, C., Spears, G.F.S. and Williams, S.M. (1996) Progestogen-only oral contraceptives and risk of breast cancer in New Zealand. *Cancer Causes Control*, **7**, 513–519.

Slayden, O.D., Zelinski Wooten, M.B., Chwalisz, K. *et al*. (1998) Chronic treatment of cycling rhesus monkeys with low doses of the

antiprogestogen ZK 137316: a morphometric assessment of the uterus and oviduct. *Hum. Reprod.*, **13**, 269–277.

Spitz, I.M., Croxatto, H.B. and Robbins, A. (1996) Antiprogestogens: mechanism of action and contraceptive potential. *Annu. Rev. Pharmacol. Toxicol.*, **36**, 47–81.

Tang, O.S., Thong, K.J. and Baird, D.T. (2001) Second trimester medical abortion with mifepristone and gemeprost: a review of 956 cases. *Contraception*, **64**, 29–32.

Tanis, B.C., van den Bosch, M.A.A.J., Kemmeren, J.M., Cats, V.M., Helmerhorst, F.M., Algra, A., van der Graaf, Y. and Rosendaal, F.R. (2001) Oral contraceptives and the risk of myocardial infarction. *N. Engl. J. Med.*, **345**, 1787–1793.

Tayob, Y., Adams, J., Jacobs, H.S. and Guillebaud, J. (1985) Ultrasound demonstration of increasing frequency of functional ovarian cysts in women using progestogen-only oral contraception. *Br. J. Obstet. Gynecol.*, **92**, 1003–1009.

Thomas, D.B., Ray, R.M. and the WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1995) Depot-medroxyprogesterone acetate (DMPA) and risk of invasive adenocarcinomas and adenosquamous carcinomas of the uterine cervix. *Contraception*, **52**, 307–312.

Toivonen, J., Luukkainen, T. and Allonen, H. (1991) Protective effect of intrauterine release of levonorgestrel on pelvic infection: three year's comparative experience of levonorgestrel and copper releasing devices. *Obstet. Gynecol.*, **77**, 261–264.

UK National Case-Control Study Group (1989) Oral contraceptive use and breast cancer risk in young women. *Lancet*, **i**, 973–982.

United Nations Department of Economic and Social Affairs Population Division (1999) Levels and Trends of Contraceptive Use as Assessed in 1998. ESA/P/WP.155. United Nations, New York.

United Nations Department of Economic and Social Affairs Population Division (2001) World Population Prospects: The 2000 Revision. ST/ESA/SER.A/204. Sales No. E.01. XIII.12. United Nations, New York.

Vandenbroucke, J.P., Rosing, J., Bloemenkamp, K.V.M., Middeldorp, S., Helmerhorst, F.M., Bouma, B.N. and Rosendal, F.R. (2001) Oral contraceptives and the risk of venous thrombosis. *N. Engl. J. Med.*, **344**, 1527–1535.

Vessey, M., Baron, J., Doll, R., McPherson, K. and Yeates, D. (1983) Oral contraceptives and breast cancer: final report of an epidemiologic study. *Br. J. Cancer*, **47**, 455–462.

Von Hertzen, H. (2000) Research on regimens for early medical abortion. *J. Am. Med. Womens Assoc.*, **55**, 133–136.

Webb, A.M.C., Russel, J. and Elstein, M. (1992) Comparison of Yuzpe regimen, danazol and mifepristone (RU 486) in oral postcoital contraception. *Br. Med. J.*, **305**, 927–931.

World Health Organization (1991a) Collaborative Study of Neoplasia and Steroid Contraceptives. Breast cancer and depot medroxyprogesterone acetate: a national study. *Lancet*, **338**, 833–838.

World Health Organization (1991b) Collaborative Study of Neoplasia and Steroid Contraceptives. Depot medroxyprogesterone acetate (DMPA) and risk of endometrial cancer. *Int. J. Cancer*, **49**, 186–190.

World Health Organization (1991c) Collaborative Study of Neoplasia and Steroid Contraceptives. Depot medroxyprogesterone acetate (DMPA) and risk of epithelial ovarian cancer. *Int. J. Cancer*, **49**, 191–195.

World Health Organization (1996) Improving Access to Quality Care in Family Planning Medical Eligibility Criteria for Contraceptive Use. WHO, Geneva.

World Health Organization (1997) Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. *Lancet*, **349**, 1202–1209.

World Health Organization (1998) Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. *Contraception*, **57**, 315–324.

World Health Organization (1999) Task Force on Postovulatory Methods of Fertility Regulation. Comparison of three single doses of mifepristone as emergency contraception: a randomized trial. *Lancet*, **353**, 697–702.

World Health Organization-IARC (1999) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, *Volume 72. Hormonal Contraception and Post-Menopausal Hormonal Therapy*. International Agency for Research on *Cancer*, Lyon.

World Health Organization Study of Hormonal Contraception and Bone Health (2000) Steroid hormone contraception and bone mineral density: a cross-sectional study in an international population. *Obstet. Gynecol.*, **95**, 736.