Expert Opinion on Investigational Drugs

ISSN: 1354-3784 (Print) 1744-7658 (Online) Journal homepage: http://www.tandfonline.com/loi/ieid20

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To cite this article: Megan A Economidis & Daniel R Mishell Jr (2005) Pharmacological female contraception: an overview of past and future use, Expert Opinion on Investigational Drugs, 14:4, 449-456, DOI: 10.1517/13543784.14.4.449

To link to this article: https://doi.org/10.1517/13543784.14.4.449

Published online: 22 Apr 2005.

Expert Opinion

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Pharmacological female contraception: an overview of past and future use

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Female hormonal contraceptive methods have undergone slow change over the past four decades. Due to social, political and legal reasons, as well as medical complications, several new methods have been removed from the contraceptive armamentarium almost as quickly as they have been added. With worldwide unintended pregnancy rates approaching 50% of all pregnancies, there is an increased need for the development of new methods of effective, safe, acceptable hormonal contraception. Pharmacological methods of contraception are reversible and contraceptive steroids are now formulated in pills, patches, intravaginal rings, subdermal implants and injections. All currently marketed formulations are made from synthetic steroids and contain no natural oestrogens or progestins. This article reviews the current state of female contraception and explores future directions.

Keywords: contraception, contraceptive vaginal ring, injectable contraception, IUD, oral contraceptive pill, subdermal contraceptive implant, transdermal contraceptive system

Expert Opin. Investig. Drugs (2005) 14(4):449-456

1. Introduction

In the US, of the ~ 60 million women in the reproductive age group (15 – 44 years) ~ 39 million (65%) use a method of contraception [1]. Worldwide, an estimated 350 million women lack access to modern contraceptive methods. Worldwide, ~ 175 million pregnancies occur, and an estimated 75 million (43%) are unintended. About 45 million of these 75 million unintended pregnancies are terminated by abortion [2]. The rising global unintended pregnancy rate indicates that increased efforts for the development of new methods of effective, safe, acceptable contraception (new hormones, new delivery systems) are needed, but so is greater accessibility to these methods. It is important that individuals have no restrictions to receive these methods.

Pharmacological methods of contraception are reversible and contraceptive steroids are now formulated in pills, patches, intravaginal rings, subdermal implants and injections. In the US, of these reversible pharmacological methods of contraception, combination oral contraceptives (COCs) are the most popular, and are used by 27% of women of reproductive age. More than three-quarters (77%) of US women have taken COCs during their reproductive years [1].

The oestrogen–progestin combination is the most effective type of COC formulation because it consistently inhibits the mid-cycle gonadotropin surge and thus prevents ovulation. The progestin-only oral formulations have a lower dose of progestin than the combined agents and do not consistently inhibit ovulation. Both types of formulations also act on other aspects of the reproductive process by altering cervical mucus, decreasing motility of the uterus and oviduct, diminishing endometrial glandular production of glycogen and decreasing ovarian responsiveness to gonadotropin stimulation.

With both types of formulations, neither gonadotropin production nor ovarian steroidogenesis is completely abolished. Levels of endogenous oestradiol in the peripheral blood during ingestion of high-dose combination COCs are constant and are similar to those found in the early follicular phase of the normal cycle [3].

Contraceptive steroids prevent ovulation by interfering with release of gonadotropin-releasing hormone (GnRH) from the hypothalamus and also by suppressing pituitary release of luteinising hormone (LH) and follicle-stimulating hormone (FSH). Several studies in humans showed most women who had been taking combination COCs had suppression of the release of LH and FSH after infusion of GnRH, thus indicating that the steroids have a direct inhibitory effect on the pituitary as well as on the hypothalamus [4].

The magnitude of the hypothalamic–pituitary suppression is unrelated to the age of the woman or the duration of steroid use, but is related to the potency of the formulation. The effect is more pronounced with formulations containing more potent progestins [5] and with those containing high doses of oestrogen [6]. Transdermal and vaginal methods of hormonal delivery also inhibit ovulation.

Since the introduction of COCs in 1960, development efforts have focused largely on oral formulations. Research has concentrated on reducing the amount of oestrogen to the lowest dose that provides regular bleeding episodes and minimises side effects. The type of progestin used in the formulations has changed to provide agents that are less androgenic.

2. Background

Hormonal contraceptive methods have undergone slow change over the past four decades. Due to social, political and legal reasons, as well as medical complications, several new methods have been removed from the contraceptive armamentarium almost as quickly as they have been added. For example, in 1984 a levonorgestrel subdermal implant was introduced onto the world market, and in 1991 it was approved for use in the US. In 1999 the manufacturer withdrew this method from use for legal reasons. In 2000, in the US, a monthly intramuscular injection containing medroxyprogesterone acetate (MPA) 25 mg and oestradiol cypionate 5 mg was introduced. In 2002 the manufacturer withdrew this method from use in the US; however, it is still in use in other countries. Oral contraceptives containing high-dose oestrogen were withdrawn from the market due to an increased incidence of venous thromboembolic events. The Dalcon shield (intrauterine device [IUD]) was withdrawn from the market due to high rates of upper reproductive tract infections and for legal reasons. In 1968, depot medroxyprogesterone acetate (DMPA) was initially marketed in Europe, but it was not until 1992 that it received approval for use in the US, making DMPA and COCs the longest available hormonal contraceptive methods. Women desire varying contraceptives over their lifetime and they wish to have access to safe, acceptable and effective methods of contraception to meet their ever-changing needs.

3. Oral steroid contraceptives

Oral contraceptives were initially marketed in the US in 1960. The initial formulations contained 150 µg of the oestrogen mestranol (ethinyl oestradiol 3-methyl ether) and 9.85 mg of the progestin norethynodrel. Because contraceptive steroid formulations with > 50 µg of oestrogen are associated with greater incidence of thrombophilic effects without greater efficacy, they are no longer marketed for use in the US, Canada or UK. All current formulations contain ≤ 50 µg of oestrogen, mainly ethinyl oestradiol (EE).

There are three major types of oral contraceptive formulations: fixed-dose combination, combination phasic and daily progestin. The combination formulations are the most widely used and most effective. They consist of tablets containing both an oestrogen and progestin that are given continuously for three weeks. In most formulations, no steroids are given for the next seven days, after which time the active combination is given for an additional three weeks. Uterine bleeding usually occurs in the week when no steroid is ingested.

All currently marketed formulations are made from synthetic steroids and contain no natural oestrogens or progestins. Varying dosages of EE (20 – 35 µg) are mainly paired with synthetic progestins derived from 19-nortestosterone (estranes and gonanes). Most modern oral contraceptives contain progestins derived from norethindrone or norgestrel. These progestins chemically resemble testosterone and have some androgenic activity.

In 2001, a new oral contraceptive pill was introduced containing drospirenone (DRSP), a progestin derived from 17-α-spirolactone and structurally related to spironolactone. This fixed-dose continuous pill containing 30 mg of EE and 3 mg of drospirenone exhibits progestogenic, antimineralocorticoid and antiandrogenic activities.

The EE/DRSP pill carries the same high level of contraceptive efficacy and cycle control as other COCs, with few unwanted side effects [7]. In a European study of ≥ 2000 women, the incidence of intermenstrual bleeding was similar between those randomised to the EE/DRSP COC and those to a formulation containing EE 30 µg and desogestrel 150 µg [8].

Due to the antiandrogenic activity of DRSD, use of this formulation decreases the severity of acne, seborrhoea and related skin conditions, as has been shown with other COC formulations in randomised trials with placebo. The antimineralocorticoid properties lead to decreased water-retention (bloating) and improved sense of well-being. Several clinical trials have shown EE/DRSP oral contraception (OC) use benefits women with premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) by decreasing the incidence and severity of somatic symptoms

related to the menstrual cycle and improving health-related quality of life [9,10].

The use of COC pills continuously for 3 weeks followed by a steroid-free interval of 7 days was originally intended to reflect a woman's natural menstrual cycle. No scientific evidence exists to support the necessity of this practice. Researchers have studied extending the use of COCs to reduce the extent of withdrawal bleeding since the late 1970s.

In 2003 the FDA approved the release of an extended regimen COC product containing 30 µg of EE and 150 mg of levonorgestrel. Active pills are taken for 84 days followed by a 7-day pill-free interval to reduce withdrawal bleeding episodes to four hormone withdrawal bleeding events per year.

A large randomised, parallel, open-label, 1-year study was conducted at 47 sites to examine the safety and efficacy of the extended use of COCs. A total of 682 healthy, reproductive-aged women were randomly assigned to the extended 84/7 day regimen or to the conventional 21/7-day regimen. Results revealed that the extended-phase regimen was as effective in pregnancy prevention as the conventional-cycle regimen. Of the extended-phase participants, ~ 7.7 and 1.8% of the conventional-cycle participants, discontinued pill use secondary to 'unacceptable bleeding'. However, the rate of discontinuation for unacceptable bleeding in the extended-phase group decreased after two treatment cycles. The duration of withdrawal bleeding was comparable between the extended-phase and the conventional-cycle groups. The frequency of unscheduled bleeding episodes was initially higher with the extended regimen than with the conventional regimen, but declined with each successive cycle. With the extended regimen, there were 12 days of breakthrough bleeding in cycle 1, which decreased to 4 days by cycle 4. By cycle 4, breakthrough bleeding was comparable to that in the conventional regimen group. More than half of the days of unscheduled bleeding episodes in the extended group consisted of only spotting [11]. Other advantages of the extended COC regimen include: prevention of follicular growth and endogenous oestrogen synthesis in the pill-free interval; less likelihood of ovulation if pills are missed at the beginning of the cycle, which should result in reduction of typical-use pregnancies; and prolongation of endometrial stimulation with a low dose of oestrogen, which should result in maintenance of the endometrium as well as in a decreased likelihood of adverse symptoms developing in the pill-free interval (e.g., headache and bloating).

Studies have been performed investigating use of COCs containing EE 20 µg at a dosing interval of 24 days active pills and 4 days inactive pills. Shortening of the hormone-free interval should ensure suppression of follicular development, oestradiol synthesis and the risk of ovulation. It has been established that with the lower doses of oestrogen (< 25 µg) used in the more recent formulations, EE is cleared from the circulation 2 – 3 days after the active pill is discontinued, thus allowing several hormone-free days during which FSH levels rise and follicular growth occurs. As with the oestrogen component, with lower doses of progestins, this steroid is cleared from the circulation within a few days of stopping ingestion of the exogenous steroid-containing pills, allowing LH levels to rise. Subsequently, ovulation may occur if the new cycle of active pills is not started precisely 7 days after the last active pill was taken.

4. Long-acting contraceptive steroids

To avoid contraceptive failure associated with the need to remember to take a COC daily, methods of administering contraceptive steroid formulations at less frequent intervals have been developed. Several types of long-acting steroids, including injectable suspensions, subdermal implants, transdermal patches and an intravaginal ring have been developed and are being used by women globally. Subdermal implants are not currently marketed in the US; implants are still available in Europe and elsewhere and should soon be available in the US.

4.1 Transdermal contraceptive system

A transdermal method of delivering contraceptive steroids has been developed and received regulatory approval for use in the US in 2001; initial marketing began in 2002. The transdermal contraceptive system (TCS) consists of a 20-cm^2, beige-coloured, three-layered matrix patch that releases into the systemic circulation a constant rate each day of 150 µg of norelgestromin (the active metabolite of norgestimate) and 20 µg of EE. The three layers of the thin matrix consist of an outer protective layer of polyester, a medicated adhesive middle layer, and a polyester inner liner that is removed just prior to application to the skin.

Circulating blood levels of each steroid remain relatively constant during the 7 days the patch is scheduled to be in place, as well as for an additional 2 days. This is in contrast to the peaks and troughs that occur after ingestion of an oral contraceptive pill [12]. In a pharmacokinetic study, 1 day after placement, steady-state conditions of each steroid were achieved in the serum of women when one patch was placed for 7 days for 3 out of 4 weeks. Each patch releases sufficient steroid that steady-state levels are maintained for 9 days if removal is delayed. Steady-state serum concentrations increased only slightly from the first week of the first treatment cycle until the third week of the third treatment cycle, indicating minimal accumulation. The circulating levels of norelgestromin are sufficient to inhibit ovulation during the 3 weeks the patch is in place as well as during the week it is removed to allow withdrawal bleeding.

Each patch can be applied to the skin of the abdomen, buttocks, upper arm or upper torso (except for the breasts) for one week and then removed. A new patch is applied to a different site for three consecutive weeks; no patch is applied during the fourth week to allow withdrawal bleeding to occur. Withdrawal bleeding similar in duration to that which occurs with COC use usually begins 2 – 3 days after the last patch is removed.

Contraceptive effectiveness of the TCS is similar to COCs. In a pooled analysis from three large clinical studies, the overall

pregnancy rate from > 22,000 treatment cycles was 0.88 pregnancies/100 woman-years [13]. In these studies the pregnancies were uniformly distributed among the 3236 subjects with body weight < 198 lbs (90 kg), but five pregnancies occurred among the 83 subjects weighing ≥ 198 lbs (90 kg). Thus, the TCS may have a lower level of effectiveness in women with body weight of ≥ 198 lbs.

A randomised trial demonstrated that the incidence of perfect compliance with the TCS occurred during 88.2% of cycles, which was significantly better than the 77.77% of cycles observed with COC use [14]. The convenient dosing schedule of the patch probably enhances compliance and may result in greater effectiveness than the COC in actual use. In the clinical trials during which 70,552 patches were worn, the rate of replacement for complete detachment was 2.9% [15]. Various conditions of exercise, heat and humidity did not increase the incidence of detachment or the force required to remove the patch [16].

Adverse effects were analysed in the comparative study with the COC. The patch had a higher incidence of intermenstrual spotting and breast tenderness than the COC in the first two cycles of use, but not thereafter [14]. Of women using the TCS, ~ 20% noted intermenstrual spotting and breast discomfort in the first cycle of use. Application-site reaction also occurred in 20% of the subjects using the TCS. Other adverse effects, such as headache and nausea, were similar with these two methods of steroid contraception [14]. Thus, the TCS is an effective reversible method of steroid contraceptive.

4.2 Contraceptive vaginal ring

A flexible, soft, transparent doughnut-shaped device containing contraceptive steroids received regulatory approval as a contraceptive in the US in 2001 and was initially marketed in 2002. The contraceptive vaginal ring (CVR) is made of a co-polymer of ethinyl vinyl acetate (EVA) and has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. The ring releases 120 µg of etonogestrel (ENG), the biologically active metabolite of desogestrel (formerly known as 3-ketodesogestrel), and 15 µg of EE each day [17]. These steroids are absorbed through the vaginal epithelium into the circulation, where steady levels of EE are reached within 2 days and ENG within 7 days after insertion [18]. Levels of both hormones remain relatively constant for the remainder of the 3 weeks the ring is scheduled to be in place. While the ring is in place as well as the week it is removed to allow bleeding to occur, ovulation is inhibited [19]. The pregnancy rate in a 1-year multi-centre study of 1145 women was 0.65 pregnancies/100 woman-years [17]. The mean duration of withdrawal bleeding, 4.7 – 5.4 days (which usually begins 1 – 2 days after the removal of the ring), is similar to that which occurs with COCs.

The CVR is available in only one size and does not have to be fitted in the vagina because it does not act as a barrier to sperm. A new CVR is used for each treatment cycle and the woman inserts and removes the ring herself. Nearly all women report the insertion and removal process is easy and the woman usually has no discomfort with the ring in place. About 30% of sexual partners reported they could feel the ring during sexual intercourse, but only 6% of males objected to their partner's use of the ring. If desired, the ring can be removed for ≤ 3 h without altering contraceptive effectiveness [17].

In a summary of three trials comparing use of the CVR with a COC containing 30 µg EE and 150 µg levonorgestrel, the incidence of irregular bleeding was less with the CVR than the COC [20]. Intermenstrual bleeding occurred in ≤ 5% of all CVR cycles, while irregular bleeding occurred in 5.4 – 38.8% of COC treatment cycles. The incidence of spontaneous ring expulsion is low, occurring in < 3% of women using the CVR. Fewer than 5% of women using the CVR reported vaginal discomfort or vaginitis. The incidence of other steroid-related symptoms, such as breast tenderness, nausea, headaches and nervousness, occurred with similar frequency among the CVR and COC users. As was observed with the patch, perfect compliance with the CVR was greater than the COC. Perfect compliance occurred in 92.4% of CVR users and 75.4% of COC users.

4.3 Injectable suspension

Three types of injectable steroid formulations are currently in use for contraception throughout the world. These include DMPA, norethindrone enanthate and several once-a-month injections of combinations of different progestins and oestrogens. Only DMPA is currently available in the US, where it is used by ~ 3% of women of reproductive age. DMPA is administered intramuscularly (150 mg) once every 3 months and is a highly effective contraceptive. A new lower-dose formulation of DMPA (104 mg/0.65 ml) administered by subcutaneous injection has been developed and should soon be marketed.

Subcutaneous DMPA provides equivalent high contraceptive efficacy and safety, as occurs with the original formulation, but with a lower steroidal dose. The slower rate of absorption observed with DMPA (C_{max} of 1.56 ng/ml s.c. and 3.73 ng/ml i.m. DMPA) provides a long duration of use and a lower peak serum medroxyprogesterone (MPA) concentration, but one that is still above the minimum concentration needed for ovulation suppression over a targeted period of 3 months [21].

Two 1-year, open-label, noncomparator, multi-centre studies assessed the contraceptive efficacy and safety of DMPA administered subcutaneously once every 3 months for ≤ 1 year [22]. Efficacy was evaluated in a total of 1787 women (18,681 total woman-cycles of exposure and 16,023 at-risk woman-cycles of exposure) with a 0% cumulative pregnancy rate at 1 year. Overweight or obese women were included in those trials. As no pregnancies occurred, subcutaneous DMPA efficacy is maintained in women with high body–mass indices, and dosage adjustments based on body weight are not required. Overall compliance rate was high (> 94%) as was subject satisfaction.

Adverse events accounted for drug discontinuation in 13.9% of subjects. Most common drug-related adverse events

were: weight increase (8.2%), headache (6.1%), amenorrhea (5.8%) and intermenstrual bleeding (6.1%). Over the 12-month study period, American women exhibited a median weight increase of 1.7 kg and European/Asian women exhibited a median increase of 1 kg, which appears to be higher than occurs with COCs. Mild injection-site reactions were experienced by 9.7% of subjects; these included injection-site pain, granuloma or atrophy [22].

Pharmacokinetic studies found that within 24 h of subcutaneous injection, circulating blood levels of MPA (~ 1.25 ng/ml) are much above the 0.2 ng/ml threshold considered sufficient to exert a consistent contraceptive effect. Decreased serum oestradiol and progesterone levels, and suppression of follicular hormones, are observed within 24 h post injection and hormonal activity consistently suppresses ovulation over the 91-day treatment interval [21].

The earliest return to ovulation as marked by serum progesterone levels > 4.7 ng/ml occurs at 106 days post injection. The median time to return to ovulation in subcutaneous DMPA users is 212 days and by the end of 1 year, the cumulative rate of ovulation return is 97%. For users of intramuscular DMPA, the median time to return to ovulation is not statistically significantly different at 183 days and the 1-year cumulative rate of return of ovulation is 95% [21].

Decreased serum oestradiol levels are associated with increased bone resorption. Bone mineral density (BMD) is lower in women using intramuscular DMPA when compared with controls. Studies have shown that current DMPA users have a decrease in BMD in the lumbar spine, femoral neck and distal forearm. The magnitude of reduction in BMD is greater the longer the duration of DMPA use. It is not known whether the effect on BMD increases the risk of osteoporosis or fractures later in life. It has been suggested that the loss of BMD occurs only while using DMPA and is reversible after stopping, but the extent of recovery is unknown. Teenage and young adult women using DMPA should be strongly encouraged to increase dietary calcium intake to 1300 mg/day. Although no data exists regarding the effect of subcutaneous DMPA on BMD, because its mechanism of action is identical to intramuscular DMPA, the same recommendations will apply to users of the subcutaneous formulation.

4.4 Subdermal implant

Subdermal implants of polydimethylsiloxane (Silastic®) capsules containing levonorgestrel were approved by the FDA in 1990 for contraceptive use. Marketing began in 1991, but was discontinued in the US in 1999. However, this method of contraception is still marketed in other countries.

To produce effective blood levels of norgestrel, the original implants required six capsules, each filled with 36 mg of crystalline levonorgestrel. As manufacture, placement and removal of six capsules was complicated, a two rod system was developed. This levonorgestrel-containing implant consists of two solid rods that are each a homologous mixture of Silastic and 75 mg crystalline levonorgestrel covered with Silastic tubing. Because of different properties of diffusion, higher blood levels of norgestrel are achieved with a smaller total surface area of the rods. The two-rod system is approved for 5 years of use, but is not currently marketed in the US. The contraceptive efficacy and the side-effect profile of the two-rod system are similar to the six-capsule implant: 0.1% cumulative pregnancy rate at 5 years, removals for bleeding problems (< 5%), and medical problems (< 4%).

Since 1999, single implants have been manufactured and studied in clinical trials worldwide. The most widely studied single-rod implant is 40 mm long, 2 mm in diameter, and contains 68 µg of ENG, the active metabolite of desogestrel [23]. This rod consists of an EVA copolymer core that is surrounded by an EVA membrane. This implant is inserted through a trocar without the need for a skin incision, but incision is required for removal. The insertion and removal process is rapid, averaging 1 and 3 min for each procedure, respectively [24]. This implant has a 3-year duration of use.

The rod initially releases 60 – 70 mg/day of ENG. The rate of release of ENG then gradually decreases, reaching ~ 40 µg/day at the end of 3 years [23]. Within 8 h of insertion mean serum ENG levels reach 266 pg/ml, which is sufficient to inhibit ovulation. Mean serum concentration of ENG reach 526 pg/ml 24 h after insertion, with the maximum concentrations, a mean of 813 pg/ml, occurring ~ 4 days after insertion. Mean serum ENG levels then gradually decline to 196 pg/ml at the end of 1 year and 156 pg/ml at the end of 3 years [23].

With the rod in place, the cervical mucus remains viscid and sperm penetration is prevented. Endometrial biopsies obtained with this implant in place reveal inactive or weakly proliferative histology [25]. This implant is an extremely effective contraceptive. In multi-centre studies of 2362 subjects, with 73,429 cycles of use of this implant, no pregnancy has occurred [26].

After removal of the rod, serum ENG levels become undetectable within 1 week and ovulation usually resumes in 3 weeks. With this implant in place, the mid-cycle LH surge is always inhibited and consistent prevention of ovulation occurs for 3 years [25]. Ovarian follicular activity is not completely suppressed and mean oestradiol levels range from ~ 50 pg/ml in the first year to 100 pg/ml in the third year [25]. Recently, concern has arisen that ovarian suppression may be associated with lower serum oestradiol levels that could lead to loss of BMD, as has been demonstrated with DMPA. However, the ENG implant does not significantly suppress oestradiol levels and changes in BMD do not occur. In a study comparing implant users with non-medicated IUD users, there were no significant changes from baseline BMD measurements in implant and IUD users [27].

Irregular bleeding is the most common adverse effect of all progestin-only methods of contraception, including this one [25]. Amenorrhea and infrequent bleeding occur in ~ 50% of the women who use the implant, whereas infrequent bleeding and prolonged bleeding occur in 20%. In one multi-centre study in Europe and Canada, discontinuation of this method

due to abnormal bleeding occurring in 23% of women within the first 2 years of use; 2% discontinued use for amenorrhea and 21% for bleeding irregularities [28]. However, in a comparative study of this single implant with the six-capsule levonorgestrel implant, there were fewer bleeding episodes and less blood loss per episode with the single ENG implant than with the levonorgestrel system [29]. The most common adverse effects reported with this implant are acne, breast pain, headache and weight gain [29].

4.4 Intrauterine devices

IUDs are one of the most effective and most cost-effective long-term methods of contraception available to women today. IUDs are as effective as female sterilisation for pregnancy prevention. Additional benefits of IUDs include a rapid return to fertility after the device is removed, few systemic metabolic effects and the need for only a single act of motivation for long-term use.

From 1990 until 2000 only the copper T380A (Cu-T) was available for use in the US. This IUD is a non-hormonal contraceptive device that is approved for use for 10 years, but maintains its effectiveness for at least 12 years. In the first year of use the copper IUD has a 0.5% pregnancy rate, a ~ 6% expulsion rate and a 15% rate of removal for medical reasons (mainly bleeding and pain). In 2000, the introduction of the levonorgestrel-releasing (LNG) IUD expanded women's choices for intrauterine contraception. The LNG-IUD consists of a polyethylene frame that measures 32 mm in both the vertical and horizontal directions. There is a silicone reservoir containing levonorgestrel 52 mg on the vertical stem. The initial release of levonorgestrel is 20 µg/day which gradually declines during its 5-year effective duration of use. The pregnancy rate in the first year of use of the LNG-IUD is about 0.2%. The cumulative 5-year termination rates for the LNG-IUD are 0.5% for pregnancy, 5.8% for expulsion, and 13.8% for bleeding and pain [30].

The LNG-IUD exerts its contraceptive effect through inhibition of fertilisation by thickening cervical mucus, thus preventing sperm transport from the cervix to the uterine cavity; by inhibiting sperm motility and function; by suppressing the endometrium; and by creating a weak foreign body reaction inside the uterine cavity.

The amount of blood lost in each menstrual cycle is significantly reduced in women using LNG-IUDs than in nonusers. In a normal menstrual cycle, the mean amount of menstrual blood loss (MBL) is ~ 35 ml. The copper T380A (Cu-T) IUD is associated with a mean MBL each cycle of about 55 ml. In contrast, the LNG-IUD is associated with a decrease in mean MBL to ~ 5 ml/cycle within a few months following insertion, as the uterus adjusts to the presence of the foreign body [31]. Irregular and frequent bleeding episodes usually occur in the first few months after insertion of the levonorgestrel-releasing IUD. After this time bleeding is usually regular and scant and ~ 20% of users become amenorrheic 1 year after the insertion of the device.

The reduction in MBL and eventual amenorrhea with LNG-IUD use is a result of the local effect of levonorgestrel on the endometrium. Increased endometrial tissue concentrations of progestin lead to inhibition of the synthesis of endometrial oestradiol receptors and subsequent endometrial insensitivity to the effects of circulating oestradiol. As a result, a strong antiproliferative effect is seen. The hypothalamic–pituitary–ovarian axis is not affected by the local release of LNG from the IUD; therefore, ovarian function is preserved as are circulating levels of LH, FSH and oestradiol [32].

Multiple studies have revealed that during the first 24 h after IUD insertion, even after placing an antiseptic agent on the cervix, the normally sterile endometrial cavity is consistently infected with bacteria. From 24 h to ~ 3 weeks following insertion, the woman's natural defence reactions destroy the bacteria and after 3 weeks the endometrial cavity is sterile. Consequently, the rate of pelvic inflammatory disease is highest in the first 3 weeks after IUD insertion, but remains lower and similar to women using no method of contraception during the remaining years of use [33,34].

After removal of the IUD, resumption of fertility is prompt and occurs at the same rate as resumption of fertility after discontinuation of the barrier methods of contraception [35]. The incidence of term deliveries, spontaneous abortion, and ectopic pregnancies in conceptions occurring after IUD removal is the same as in the general population not using any form of contraception.

5. Expert opinion and conclusion

New contraceptive methods are currently or shortly will be available to women in the US and worldwide. The increased availability of contraceptive choices should begin to reduce the high incidence of unintended pregnancies experienced by women globally. New delivery systems in the form of intravaginal rings, subdermal implants and transdermal patches offer women the option of not having to remember to take a pill daily. New formulations of oral contraceptive pills (OCPs) offer women an improved side-effect profile as well as broaden non-contraceptive benefits.

There is neither an ideal nor a complete armamentarium of contraceptive options for women. New methods are needed to help meet the changing needs for contraception throughout a woman's reproductive life. By expanding the number and type of available contraceptives a healthier and more accurate match between method and user can be made, which should improve compliance and typical use efficacy.

Future research endeavours should not only explore new progestin and oestrogen formulations, but also examine the use of selective receptor (progestin or oestrogen) modulators as methods of contraception. However, new developments need to meet continued demand for safety, efficacy, convenience and affordability.

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Pharmacological female contraception: an overview of past and future use

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