Novel delivery systems in contraception

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Contraception has mainly remained the responsibility of women. The sexually active time during the fertile period of life may last over 30 years and, increasingly, it is more than 10 years before the first baby. It is, therefore, natural that convenient long-acting contraceptive methods are becoming more and more appealing. The discovery of poly(dimethylsiloxane) as a carrier, and controlled release polymers for small molecule drugs allowed the development of contraceptive devices releasing steroids for several years. While contraceptive implants and intra-uterine systems are already marketed in many countries, contraceptive vaginal rings are in their late development phase. The key features of these long acting delivery systems are convenience, efficacy, reversibility and positive long-term health effects. Since these methods are based on new concepts, the provider needs to be prepared for extensive counselling.

General aspects of controlled release

The discovery of poly(dimethylsiloxane) as a carrier and controlled release polymers for small molecule drugs allowed the development of contraceptive methods releasing steroids for several years. Another polymer commercially used in implants is ethylenevinylacetate (EVA). While contraceptive implants and intra-uterine systems are already marketed in many countries, contraceptive vaginal rings are in their late development phase.

Contraceptive implant systems have features that reflect those of an endocrine gland. Release of the active ingredient, a progestin, mimics the release of progesterone from the corpus luteum, thus inhibiting gonadotropin secretion and ovulation. Although contraceptive implants of the first generation cannot change their release rate in response to changing needs, as do real endocrine glands, technology will solve this problem in regard to indications and drugs that need to be released in a changing fashion. An intra-uterine system acts similarly to an implant placed at the target organ. Vaginal rings releasing hormones function on the same principles as implants (Fig. 1).

A typical sustained hormone-releasing system consists of a core where the drug is suspended in a polymer matrix, and a release-regulating membrane (Fig. 2a). The active ingredient, such as levonorgestrel, can also be in the
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Fig. 1 Examples of long acting contraceptive implants, vaginal ring and intra-uterine system. For size comparison, a match is shown on the right.

Form of crystals inside polymer tubing. Several factors govern the release of active ingredient from such a polymer system: the surface area, solubility of the ingredient in the polymer, speed of diffusion and concentration of the ingredient in the core. Hence, the speed of the release of a certain active ingredient from a polymer system can be regulated by changing the thickness of the rate-limiting membrane, by changing the surface area or by modifying the polymer. In Figure 2b is

Fig. 2 (a) Cross section of contraceptive implant and the concentration profile of dissolved active ingredient in the device (core and membrane are made of the same polymer). (b) Typical in vitro release profile of active ingredient from contraceptive implant.
presented a typical *in vitro* release profile of a contraceptive implant. The effective life-span of the system is dependent on the speed of release and the load of the drug in the implant. The maximal load of a drug in the core matrix depends on the polymer, but it can exceed 50%. Although the release rate of the delivery system after insertion quickly assumes near zero order kinetics, there is an initial burst of the drug from the membrane of the system. The duration and magnitude of the burst depends on the solubility and diffusion characteristics of the active ingredient in the membrane polymer. The active ingredient dissolves in excess in the membrane during the storage thus reaching the same concentration both at the inner and outer wall of the membrane. This dissolved extra loading of the membrane, compared to the dynamic situation where the concentration of active ingredient at the outer wall is markedly lower, is released right after the insertion.

Convenience and improved compliance from controlled release contraceptive systems

The increased number of new contraceptive options has empowered women to make educated choices concerning their own contraceptive methods, thus decreasing the role of her doctor in the decision-making process. The expert is increasingly needed to confirm or correct the expectations of the client, to inform about adverse effects and screen the contra-indications. Convenience, such as decreased duration and flow of menstruation, and freedom from daily motivation as regards pill intake, is becoming an important factor in the decision-making of women who need long-term contraception. This convenience is provided by the new controlled release contraceptive systems.

Combined oral contraceptives will remain the first option in contraception for many years, especially among young women. This is also medically well-founded because of the positive health effects that have been extensively documented. However, the tendency to forget to take the pills is much more common than earlier thought. A recent study shows that after the first few cycles up to 50% of pill users may forget more than three pills per cycle.

Once the family size has been completed, there is a good chance that a woman wants a long acting method, often sterilisation. Since the effects of controlled release steroid contraceptive systems are reversible and they also provide health benefits, they should be considered for contraception before sterilisation. Divorce, death or serious illness of a child may often result in a desire for another child.
Two generations of contraceptive implants

The first generation contraceptive implant method is represented by Norplant® (Norplant® is a registered trademark of contraceptive implants from the Population Council, New York, USA). It was first introduced in 1983 in Finland. It is currently marketed in North America by Wyeth Ayerst, whereas the marketing rights elsewhere belong to Leiras Oy, Finland, a subsidiary of Schering AG, Germany. Leiras Oy is also the manufacturer of the implants. Currently, over 6 million women are using Norplant® implants globally. The Norplant® method involves the use of six capsules 3.4 cm in length, each having 36 mg of crystalline levonorgestrel in a poly(dimethylsiloxane) tubing. Levonorgestrel is released initially at 85 μg per 24 h and at the end of 5-year use at about 25–30 μg per 24 h. The capsules are placed subcutaneously in the upper arm.

The second generation contraceptive implant, the two-rod levonorgestrel-releasing contraceptive implant method was also developed by the Population Council. Levonorgestrel is mixed with poly(dimethylsiloxane) in a 1:1 ratio to make a rod of 4.4 cm in length containing 70 mg of active hormone, covered with a rate-limiting membrane. Two implants are placed under the skin of the arm. The product is on the market in Finland under the name Jadelle®, and application for marketing authorisation for a 5-year product has been submitted for a mutual recognition procedure in Europe (Leiras Oy, Turku, Finland). The levonorgestrel release profile is indistinguishable between Norplant® and the two-rod system.

Introduction of the first one-implant method Implanon® (Organon, Oss, The Netherlands) was started recently in Europe. It makes use of etonogestrel, the active metabolite of desogestrel, which is widely used in oral contraceptives. This implant utilises ethylenevinylacetate as a polymer. The product is licensed for 3 years’ use. The implant is in a preloaded trocar to facilitate the insertion procedure.

At least three other controlled release contraceptive implants are sold locally or are at the late stage of clinical development. These are a generic copy of the two-rod levonorgestrel implant system in China, the Nestorone® progestin releasing implant in Brazil and the nomegestrol acetate-releasing implant developed by Theramex, France. Biodegradable implants such as Capronor, releasing levonorgestrel have not so far been successful in making their way to the market.

The mechanism of contraceptive action is, at least partly, different between the two implant systems. Use of levonorgestrel implants is not aimed at total inhibition of ovulation. Only about half of the cycles are ovulatory during the first year of use. As a consequence, serum oestradiol concentrations tend to be lower in etonogestrel users than in levonorgestrel implant users. Both implant types also make the cervical
mucus scanty and dry. Normal development of the endometrium is disturbed by continuous progestin administration. The return of fertility takes place quickly after removal of the implants.

**Intra-uterine steroid-releasing systems – targeted progestin delivery**

Progesterone and levonorgestrel are utilised for intra-uterine administration of progestins. The progesterone-releasing device Progestasert® (Alza Corp., Palo Alto, CA, USA) has small markets in North America and in France\textsuperscript{12}. Due to the relatively low potency of progesterone, the clinical contraceptive efficacy of Progestasert® starts to decrease after 12 months, thus limiting its value as a real long-term contraceptive option\textsuperscript{13}. The levonorgestrel-releasing intra-uterine system (LNG IUS) Mirena® (Leiras Oy) initially releases 20 μg/24 h and, at the end of its effective life-span of 5 years, still more than 10 μg/24 h of levonorgestrel\textsuperscript{14}. Local changes on the endometrium during use of the LNG IUS maintain contraceptive efficacy comparable to female sterilisation, with an annual Pearl rate of 0.1\textsuperscript{14,15}. Both progesterone and levonorgestrel inhibit endometrial proliferation which is clinically seen as decreased menstrual blood flow and decreased number of days of bleeding\textsuperscript{13}. The changes are reversible, and the fertility returns after removal of the system comparable to the situation with copper IUDs\textsuperscript{16}.

It is not possible to demonstrate single mode of action of the levonorgestrel intra-uterine system. Local levonorgestrel prevents endometrial growth\textsuperscript{14} and creates a hostile environment for fertilisation\textsuperscript{17}. The local progestin effect causes thickening of the cervical mucus.

Contraceptive efficacy with intra-uterine systems is achieved without major systemic effects. For instance, ovarian function remains mainly undisturbed, although luteinised unruptured follicles may be seen during the first year of use\textsuperscript{18}.

**Health benefits are also associated with controlled release systems**

The importance of positive health effects is increasing when it comes to the choice of contraceptive methods. Strong evidence of beneficial protective effects of oral contraceptives favours their choice among young women. Implants and intra-uterine systems are associated with decreased dysmenorrhea and number of days of menstrual bleeding (Fig. 3). By
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Fig. 3 Number of days of bleeding per month of the users of levonorgestrel intra-uterine system. The continuous line denotes the median, the broken lines denote the 25th and 75th percentiles, and the dotted line denotes the 5th and 95th percentiles (data from Suvisaari and Lähteenmäki 1996)

decreasing the flow of menstruation they result in increased blood haemoglobin concentrations and body iron storage.

A targeted local effect of levonorgestrel with an intra-uterine system gives additional benefits. It appears to give protection against pelvic inflammatory disease, similarly to oral contraceptives. It can be effectively used in the treatment of menorrhagia, reducing the volume of menstrual blood loss by 80–90%. A recent study shows that it could prevent half of the hysterectomies scheduled for menorrhagia patients.

Continuation rate is the ultimate measure of acceptability

The continuation rates associated with all implants and the levonorgestrel intra-uterine system are in general high. Exact comparison of these methods is currently difficult since there are no data available for each method from the same randomised prospective study. The first year continuation rates associated with each of the three implant methods are usually above 90%, and for the levonorgestrel intra-uterine system it is about 80%. In comparative studies between Implanon® and Norplant®, the percentages of women discontinuing use due to adverse experiences
were 5.6 and 2.8, respectively. It can be concluded that all these methods are well accepted by the users. The most important clinical reason for discontinuation appears to be the changes in the profile of bleeding. Appropriate counselling can improve the continuation rate13.

The continuation rates associated with other hormonal methods are clearly lower than those associated with implants and intra-uterine systems. One study showed that only 57% of women returned for the second injection of depot medroxyprogesterone acetate (Depo-Provera®)22. The overall 1-year continuation rate was 23%. A recent study in the UK confirmed a high continuation rate for Norplant® while the first year pill continuation rate was only 60%23. These data together with other results, indicate that the continuation rates and thus long-term acceptability of implants and intra-uterine systems are far better than those of other hormonal methods.

Contraceptive vaginal rings give control of a long-term method to the user

Contraceptive steroids are absorbed well through the vaginal epithelium and circumvent the first pass effect of the liver. Since the first human study testing medroxyprogesterone acetate in 1970, the results of several clinical studies involving different steroids have been published24. At least two different rings are in phase III development, thus giving hope for the first long-acting hormonal contraceptive method that is user-controlled, provider- and coitus-independent.

Both progestin-only and combination rings are under development. The World Health Organization started the development of a vaginal ring releasing 20 μg/24 h of levonorgestrel25. Two large multicentre studies with a total of 2700 women were conducted, but development was discontinued because local changes in the vaginal epithelium were observed. Since then, the polymer used in the original ring has been replaced with a softer polymer and the release rate increased to 35 μg/day. The Population Council, New York, USA, is developing a ring that releases the progestin Nestorone®. Its development is still at phase II. The progestin Nestorone® is highly potent and also suitable also for use during lactation, since the infant can metabolise the drug from breast milk during the first pass through the liver26. This progestin is orally inactive due to this inactivation by the liver. Progesterone-releasing vaginal rings appear to be effective only during lactation and are, therefore, perhaps of more limited commercial interest than others with a larger potential target group.

The technology needed for oestrogen-progestin combination rings is more demanding than that associated with progestin only rings. However, there are at least three different combination rings under development.
The great advantage of combination rings over progestin-only rings is much better control of menstrual bleeding. Since the steroids released from vaginal rings bypass the portal circulation, smaller doses are needed than are ingested in oral contraceptives, thus making adverse effects less probable.

Implants are also a new lead to male hormonal contraception

Oral administration of sex steroids to men has proven to be an almost unsurpassable challenge, mainly due to the first pass effect and liver toxicity of the steroids tested. Therefore, it seems unlikely that hormonal oral contraceptives will be developed. Subdermal implants releasing potent androgens are a promising lead for male contraception. One such candidate is 7-α-methyl-19-nortestosterone (MENT). It is about 10 times more potent than testosterone. While the low potency of natural androgens makes the implant approach with them impractical, sufficient MENT can be loaded into 2–3 implants to provide androgen substitution for about 1 year. Ethylenevinylacetate implants releasing MENT acetate have been shown to suppress serum LH, FSH and testosterone levels by 93–97% in healthy volunteers. Although clinical data on its efficacy as regards spermatogenesis in men are still lacking, these hormonal changes give good reason to believe that suppression of spermatogenesis is also achieved. Clinical development is still in its early phase, and many years are needed to test this lead.

Points of clinical consideration

The two most important key success factors as regards long-acting delivery methods are a correct insertion technique and client counselling. The placement of implants too deep, even inside the underlying muscle, results in problems in removal of the implants. Incorrect insertion of an intra-uterine system leading to misplacement, and even perforation, may result in symptoms such as pain, cramps and prolonged bleeding. The first two symptoms should alert the provider to ascertain the location of the intra-uterine system.

Controlled release contraceptive systems change the menstrual bleeding pattern in almost all women. These changes as a group are the most important cause of early discontinuation, but this can be decreased by adequate counselling. Amenorrhea is common, but welcomed by many women if carefully explained beforehand. The spotting and sometimes prolonged bleeding associated with an intra-uterine system
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decreases within the first 3–6 months in most users (Fig. 3). It is important
to give enough time for questions at the 3-month control visit and encourage
also for earlier contacts if necessary.

Contraceptive implants and the levonorgestrel intra-uterine system are
highly effective in contraception, comparing well with the efficacy of female
sterilisation. When available, contraceptive vaginal rings will represent the
first long-acting method that is under total control of the user. The steroid
load to which the user is daily exposed is less than that from oral
contraceptives and injectables. In addition, women who have contra-
indications to oestrogens or dislike them, can here find an effective
hormonal contraceptive.

Perhaps the most valued aspect from the user’s point is the convenience
that the implants and intra-uterine systems bring about. Once the method
has been inserted, contraception is taken care of for 3–5 years.

The choice between an implant and an intra-uterine system is most often
down to the personal preference of the client, naturally assuming that the
provider can carry out both types of insertion. The late fertile period may
tilt the balance towards the intra-uterine system because this method is also
effective in treating menorrhagia.

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