Delivery options for contraceptives

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Although a steady increase in contraceptive use has been observed in developed and less-developed countries, the contraceptive needs of a significant proportion of couples have not yet been met, resulting in an increase in unplanned pregnancies. Several new contraceptive products have reached the market during the past few years. Among these are new implants, a medicated intrauterine device, contraceptive vaginal rings, transdermal patches and several new regimen of combined oral contraceptives. These new or improved methods have been developed to expand the contraceptive choices available to women and men as well as to respond to the unmet need for contraceptives with long-term activity. New targets are being identified both in the ovary and the testes for a more specific non-hormonal contraception. This futuristic approach still keeps in mind the need for better access to existing contraceptive methods, as well as the discovery of new contraceptives that are simple to use, safe, reversible and inexpensive. In recent years, there has been great interest in agents that provide dual protection against pregnancy and sexually transmitted infections (STI), especially human immunodeficiency virus (HIV). A contraceptive method providing dual medical benefits might increase motivation for consistent use, thus reducing contraceptive failures and unwanted pregnancies.

Although a wide variety of contraceptive delivery methods are available today, the needs of a significant proportion of couples have not yet been met, as evidenced by the high number of unplanned pregnancies. Between 1995–2000, there were 1.2 billion pregnancies in the world, of which 28%, or 338 million, were unintended [1].

Additional contraceptive options and delivery methods are needed for several reasons. First, the actual usage of any type of contraception differs from country to country for political, sociological, economic and personal reasons. Second, the contraceptive needs of each couple change over time. The basic characteristics of an ideal contraceptive include effectiveness in family planning and minimal side effects. Additional medical benefits can increase compliance and willingness to use such methods. Other desirable characteristics, such as duration of action or easiness of use, depend upon the stage of the family life. For example, couples who wish to postpone pregnancy for several years or who have completed their families, a long-acting contraceptive delivery method requiring little attention by the user for several years such as implants or intrauterine systems could be ideal [2,3]. For couples who wish to begin or add to their families within a short period of time, a contraceptive delivery system that is user-controlled, easy to use, easy to discontinue, such as vaginal rings (VRs) or transdermal systems and has good compliance, could be optimal [4]. For

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couples at high risk of sexually transmitted infections (STIs), a contraceptive delivery method that also protects against the transmission of infections would be highly desirable [5]. Finally, the addition of male hormonal contraceptives to the available options would fill a currently unmet need [6–9].

Of the contraceptives in use today, the most effective are those that deliver hormones . Unlike the traditional barrier methods (male or female condoms, diaphragms and cervical caps), which are associated with one-year unintended pregnancy rates between 15–32% during 'typical' use [10], the real-life one-year pregnancy rates for well-established hormonal contraceptives [combined oral contraceptives (COCs), copper-releasing intrauterine devices (IUDs) or hormone-releasing intrauterine systems (IUSs), subdermal implants] range from 0.1–8.0% [10].

Problems with compliance reduce the effectiveness of many user-controlled hormonal contraceptives. With estrogen-progestin COCs, for example, pregnancies related to method-failures are very rare. With 'perfect use' of COCs, as observed in the clinical trials, the pregnancy rates are very low (in the order of <1% in the first year) [11]. However, with 'typical use' – in real-life settings when women are less compliant than in a clinical trial setting – the first-year pregnancy rate is 8% [12].

Side effects are an important contributor to poor compliance and discontinuation of OC use. The most common side effects are related to hormone use and include nausea, headache, unanticipated bleeding or spotting, weight gain, or breast tenderness [10,11]. Women who discontinue OC use because of severe unscheduled bleeding are at higher risk for pregnancy [13,14]. For these reasons, the development of other hormonal, user-controlled contraceptive delivery systems has been very important.

Between 1960–1990, many new contraceptive delivery options were introduced, but during the early 1990s no new method was introduced, reflecting a period of inactivity in pharmaceutical development over the previous years. However, since the early 2000s, several new delivery options have become available [4,10,15–17]. These include two hormone-releasing CVRs [15,16,18,19], a combined estrogen–progestin injection that lasts one month [20–23], a combined estrogen–progestin transdermal patch [24–26], and an extended cycle OC [27–29]. The pipeline of new or improved contraceptive delivery systems is quite full: some are being evaluated in clinical trials [30–32], whereas others are still in the 'proof-of-concept' stage [7,15,17,28,33–38].

The characteristics of recently introduced and 'in-development' methods of hormonal contraceptive delivery are summarized in Tables 1–4 and some of the new methods of drug delivery are described below.

Intrauterine devices and medicated systems

Contraceptive delivery systems with long durations of action include IUDs, with or without additional medication. The non-medicated systems are numerous and available in most countries. They include the Copper T 200 IUD*, active for four years and the Copper T 380 Ag IUD (Paragard®), active for ten years. Both have been developed initially by the Population Council and are one of the most affordable long-acting method of contraception.

Developed by the Population Council and initially Leiras Oy, then Schering AG, Mirena®, the first medicated IUS, was approved in the USA in 2000. This system was approved for the first time in Finland in 1990. The additional active agent in Mirena is levonorgestrel (LNG). The IUS is a small t-shaped device, similar to many non-medicated IUDs in use today. The IUS is inserted into the uterus by a clinician or, in some countries, by a nurse practitioner or a midwife. LNG is released from the IUS at a slow, steady rate of 20 μg/day, preventing fluctuations in serum LNG levels [39–42]. In the first few weeks after insertion, serum LNG levels range from 150–200 pg/mL. The LNG IUS prevents pregnancy primarily via the local effects of the progestin on the cervix and the endometrium [43]. The cervical mucus is thickened, thus preventing sperm penetration and fertilization. This mechanism of action is valued in countries where religious beliefs lead to a reluctance to use inert IUDs thought to interfere with implantation. The LNG IUS is effective for up to five years [42], with a five-year cumulative pregnancy rate of 0.5% [39].

During use, the LNG IUS reduces menstrual blood loss [41,44,45], beneficial for women with heavy menstrual bleeding, which may cause iron-deficiency anemia [42,45–47]. A reduction in the proportion of women experiencing dysmenorrhea has also been noted [47]. Preliminary studies have suggested that the LNG IUS could also be useful in managing endometriosis in some women [42]. A recent randomized comparative study comparing the LNG IUS and gonadotropin-releasing hormone analogues showed equal improvement of symptoms due to endometriosis with both treatments [48], confirming the earlier observational studies. All these beneficial effects are due to the high progestational effect of levonorgestrel delivered in the endometrium. However, although small amounts of this progestin are found in the systemic circulation, they are able to induce undesirable effects such as acne or oily skin in some women. Another drawback of the system is the need for a skilled health provider to insert it as its size might be difficult to insert in some women with a small uterus.

Implants

Another type of long-acting, sustained-release hormonal contraceptive is the subdermal implant (Table 1). Developed by the Population Council and initially manufactured by Leiras Oy in Finland, the first-generation implant, Norplant®, comprises six capsules containing LNG in a silicone elastomer matrix. At the end of the first year of use, Norplant implants deliver LNG at a rate of ~40–50 μg/day as measured by *in vitro* release tests; the release rate declines to

TABLE 1

Long-term contraceptive delivery systems (little user attention)

Product	Status	Manufacturer/ developer	Active agent(s)	Technology	Duration of action	Preg rate/ 100 women-y* Injectable
Injectables						
Lunelle® [21–23]	Approved Europe (discontinued in USA, 2002)	Pharmacia, Sweden	MPA/E_2C (25/5 mg per 0.5 mL or 0.5mL syringe)	Intramuscular injection	1 month	<1
Implant						
Norplant® [2,3]	First approved 1983 (not available in USA)	Leiras Oy Finland/Population Council USA				
	LNG (40–50 µg/day)	Six-capsule implant (discontinued in USA by Wyeth, sold in Europe and worldwide by Schering AG)	7 years	<1		
Jadelle® [3,49]	First approved 1997, Finland	Leiras Oy then Schering AG/Population Council	LNG (40–50 µg/day)	two-rod implant	5 years	<1
Implanon® [4,50,51]	Approved in many countries; approvable letter FDA 2004	Organon, Oss, Netherlands	ENG (60 µg/day)	Single-rod (ethylene vinyl acetate polymer– 40 mm × 2 mm (l x diam)	3 years	0
Intrauterine device						
Mirena® [39–42]	Approved worldwide, USA (2000) First approved 1990 Finland	Schering AG, (Berlex in USA)	LNG (20 µg/day)	T-shaped polyethylene stem, steroid reservoir cylinder around stem; removal threads	5 years	0.7

Abbreviations: MPA, medroxyprogesterone acetate; E2C, Estradiol cypionate; LNG, Levonorgestrel; ENG, Etonogestrel.

25–30 µg/day in the fifth year of use. Nonetheless, Norplant showed efficacy in preventing pregnancy for a duration of seven years, with a seven-year cumulative pregnancy rate of 1% [2]. The technology of the Norplant implants has changed since this contraceptive method was first introduced in 1983. The tubing has changed and the one used in today's implants of Norplant® is made of a softer, more flexible elastomer with lower silicon content. This technological advance has been associated with lower long-term pregnancy rates [3]. In the USA, Wyeth has stopped the distribution of this system due to litigation issues that were related to technical difficulties in the withdrawal of the implants when the health providers were not trained. Schering distributes the system worldwide outside the USA and this method is still used by millions of women in developing countries and in China.

The second-generation implant, Jadelle®, was also developed by the Population Council and manufactured by Leiras Oy, and now Schering AG, with the goal of reducing the total number of implants. The system is made of an elastomer with improved drug release capability. Therefore, the two-rod Jadelle implant has the same LNG release rates as the six-capsule Norplant. Jadelle is approved for use over five years. Its five-year cumulative pregnancy rate is 1% [49]. Both Norplant and Jadelle have multiple mechanisms of action, including effects on the ovulatory process and alterations of the cervical mucus to render it impenetrable to sperm [50].

More recently Organon (Oss, Netherlands) developed a new technology of implants and introduced Implanon® in Europe. The system is a one-rod implant that delivers the progestin etonogestrel (ENG) at an initial release rate of 60 µg/day. This implant is effective for three years and ovulation inhibition is the primary mechanism of pregnancy prevention [51].

Implants under development include several with nonandrogenic progestins, such as nomegestrol acetate or Nestorone® (NES; 16-methylene-17α-acetoxy-19-norpregn-4-ene-3,20 dione). Non-androgenic progestins are being developed to avoid the side-effects due to androgenic progestins such as acne, oily skin and changes in lipid profiles. Although it is inactive when taken orally, NES is more potent than LNG when administered via non-oral routes [52,53]. Its poor oral bioavailability makes NES suitable as a contraceptive for lactating women because it does not affect the nursing infant [16]. The implant, which is inserted into the upper arm, releases NES from a silicone matrix core containing ~80 mg of the progestin; the initial *in vitro* release rate is ~100 µg/day [31]. In a two-year study evaluating the contraceptive efficacy and safety of the NES implant in post-partum, breast-feeding women, no pregnancies occurred in 2195 women-months of exposure and lactation and infant growth during the first year of life were unaffected. No serious adverse events were observed [31]. Therefore, the NES implant represents a promising long-acting birth control in this special population.

The implant method is used by many women who want to space out pregnancies for several years or have completed their family. The main advantage is the high efficacy rate and the long duration of action without compliance issues. However, the need for a skilled and trained

TABLE 2

User-controlled contraceptive delivery systems

Product	Status	Manufacturer/ developer	Active agent(s)	Technology	Duration of action	Preg rate / 100 women-y* contraceptive vaginal ring
Contraceptive vaginal rings						
NuvaRing® [18,19,61]	Approved Europe, First approved 2002, USA	Organon Oss Netherlands	ENG (120 μg/day) +EE (15 μg/day)	Steroid core in ethylene vinyl acetate copolymer ring; od: 54 mm; c-s d: 4 mm	New ring for each 4 wk cycle	1–2
Progering (lactating women) [60,83]	Approved Chile, Peru	Silesia SA, Chile	Natural P (10 mg/day)	Silicone elastomer	Six months continuous	1.5
NES/EE [4,28,56]	Phase II/III trials	Population Council USA	Nestorone®+ EE (150 μg/15 μg)	Two steroid cores in silicone elastomer ring body; od: 56 mm; c-s d: 8.4 mm	One year (13 cycles)	–
NES, lactating women [30,83]	Phase II	Population Council	NES (50, 75, 100 μg/day)	One steroid core inserted in silicone elastomer ring body; od: 56 mm; c-s d: 8.4 mm	Six months continuous	–
CDB-2914 or VA-2914	Proof of concept	Population Council/ HRA Pharma (Paris FR)	CDB-2914	Proprietary	Three months continuous	–
Transdermal methods						
Transdermal patch (Ortho Evra®) [24,26,65]	First approved 2003 USA, Europe	Ortho McNeil Pharmaceutical, USA	Norelgestromin (150μg/day) + EE (20 μg/day)	Matrix type patch, flexible film, removable inner layer, middle layer with drugs, backing layer	Three patches per cycle (three weeks)	1–2
Transdermal gel	Phase II	Population Council	NES	Proprietary	Daily	–
Transdermal spray	Proof of concept	Acrux Australia/ Population Council	NES	MDTS® spray	Daily	–
Extended-cycle combined oral contraceptive						
Extended-cycle OC (Seasonale®) [27]	Approved USA	Barr Laboratories USA	LNG (0.15 mg)/ EE (0.03 mg)	Oral contraceptive	84 days	1–2

Abbreviations: MDTS, Metered Dose Transdermal System; NES, 16-methylene-17α-acetoxy-19-nor-pregn-4-ene-3,20 dione; o.d., outer diameter; c-s.d., cross-sectional diameter.

health provider for the insertion and withdrawal as well as the frequent bleeding problems are the main drawbacks of this contraceptive method.

Contraceptive vaginal rings

CVRs are another type of sustained-release contraceptive delivery system. Unlike other long-term methods, CVRs don't require involvement of a healthcare professional but can be inserted and removed by the user, allowing flexibility in family planning (Table 2). Steroid hormones are released from a doughnut-shaped ring body composed of a soft, flexible, inert silicone elastomer. The size of CVRs generally range from 54–58 mm in diameter with cross sections between 4.0–8.4 mm [54,55]. The Population Council has developed CVRs that use a proprietary 'core' technology in which hormone-containing rods are inserted into the body of the ring. Other rings contain one or more steroids homogeneously disseminated through the core of the ring, or in a circular system throughout the center of the doughnut [16,56].

To date, two CVRs have reached the market. NuvaRing®, developed by Organon and approved in Europe and the USA, releases ENG (120 μg/day) and ethinyl-estradiol (EE) (15 μg/day). The ENG/EE CVR is inserted for three weeks and then removed for one week. A new ring is required each month [18]. When used properly, Nuvaring has pregnancy rates of 1–2 per 100 women-years of use [55,58].

The second CVR, Progering® was developed by the Population Council and is manufactured and marketed by Silesia in Chile and Peru. This ring releases natural progesterone over a three-month period and is designed for lactating mothers and also for progesterone replacement in *in vitro* fertilization (IVF) programs [57,60]. The use of progesterone in lactating women has the advantage of not affecting the infant as progesterone is quickly metabolized when taken orally. In addition the maintenance of pregnancy after embryo implantation in IVF programs where the mother would need partial or full progesterone replacement is usually ensured by daily injections of progesterone, which are painful and also give peaks and trough levels, whereas the ring releases more constant levels of progesterone for a more physiological delivery of the hormone.

Delivery of steroids by the vaginal route offers many advantages such as a control of the method by the user, the delivery of lower doses of steroids thanks to an

increased bioavailability of the steroids delivered from the vagina and also no need for daily attention to the method, and research continues on refinements of the CVR delivery method. Depending upon the CVR, the steady release of hormones can occur over a period of three weeks to one year. The Nuvaring, which is available in many markets, has been designed for one cycle of use. The NES/EE ring developed by the Population Council has been designed for 13 cycles of use. Other rings under early development are also evaluated for a three-months duration of use. CVRs that can be used for longer periods of time are of particular interest. CVRs with longer periods of hormone release are dependent on two technological advances: the availability of safe, pliable poly (dimethylsiloxane) carriers and the development of new controlled-release polymers capable of releasing hormones for a year or more [28,56].

Timmer and Mulders [61] have demonstrated that the highest serum concentration of ENG and EE released from Nuvaring is ~40% and 30%, respectively, of that observed with a COC containing desogestrel (DSG) and EE. The bioavailability of ENG is higher with the CVR (103%) than with the DSG/EE COC (79%), although the bioavailability of EE is similar with the CVR (55.6%) and the COC (53.8%) [61]. Taking the difference in daily doses into account, systemic exposure to ethinylestradiol with NuvaRing was ~50% of that for the oral pill, thus reducing the effects of this synthetic estrogen on the metabolic markers of cardiovascular risk.

The Population Council is currently developing several CVRs. A combined progestin–estrogen ring containing NES and EE, designed to be active for one year, is in the final stages of clinical development [28]. The steroids are released from two cores in the CVR body: one contains NES alone and the other contains both steroids.

Both the recently approved Nuvaring delivering ENG/EE, and the above mentioned Population Council ring delivering NES/EE use a three-weeks-in/one-week-out regimen. The CVR is inserted into the vagina on the fifth day of the menstrual cycle and left in place for three weeks. It is recommended that the woman uses the same specific day of the week for insertion and withdrawal of the ring [18,62].

Although the compliance is higher with monthly methods compared with daily pills, it can still be difficult for some women to remember when they have to withdraw or to reinsert the ring; they are then exposed to failures. Due to the fact that ethinyl estradiol is delivered from the combined rings, the contra indications are similar to those of oral contraceptives and the method cannot be recommended to women with cardiovascular risk.

Saxena *et al.* [36] recently described a biodegradable CVR designed to deliver a nonhormonal contraceptive. The ring body is composed of biodegradable hydrogel, which consists of a core surrounded by four concentric sheaths containing dextran, a copolymer of polylactide, and epsilon-caprolactone. The hydrogel is impregnated with iron(II) D-gluconate dihydrate, which causes complete spermiostasis due to lipidperoxidation; ascorbic acid, which increases the viscosity of the cervical mucus; and mixtures of polyamino and polycarboxylic acids, which maintain a vaginal pH of ~4.5. When used in rabbits, this system rapidly inactivated the sperm. Unlike the CVRs that deliver steroid hormones to the systemic circulation, this ring is designed for local delivery of a non-hormonal spermicide. The advantage of such system resides in the continuous delivery of a spermicide from the biodegradable material over the mid-cycle days when the cervical mucus is abundant and would be attracting the sperm. The design of the system is such that one of the layer would dissolve and deliver the spermicide during the days of high mucus production.

Contraceptive patches

The transdermal patch is another sustained-release, user-controlled contraceptive method that delivers steroids through the skin to the systemic circulation (see Table 2). Transdermal delivery of steroids has been attempted since the early 1980s. With the successful development of matrix technology, it became possible to deliver both EE and a progestin through the skin over a seven-day period. A combination patch, ORTHO EVRA®–EVRA (Ortho Mc Neil, USA)®, which releases EE (20 μg/d) and norelgestromin (150 μg/d), has been recently approved as a contraceptive worldwide. The patch is applied once weekly for three weeks, followed by a patch-free week [63,64]. This reversible, user-controlled transdermal method is as effective and safe as COCs, with comparable cycle control [65,66]. The probability of method failure is 0.4–0.6% and the overall annual probability of pregnancy is 0.7–0.8%. In recent studies, compliance rates of ~90% have been reported with the patch, exceeding those noted with OC use [24]. Side effects are generally mild to moderate, with application site reaction, breast symptoms, nausea, headache and mood changes being reported more often in women using the patch than in those on OCs [65].

There also as explained for vaginal rings, the ethinyl estradiol component of the patch requires the same contraindications as with COCs and there is no advantage of the liver by-pass by the transdermal route when EE is used contrarily to E2.

The transdermal method is particularly advantageous for delivering orally inactive progestins, such as NES. NES is absorbed effectively via the skin resulting in good systemic bioavailability. A NES transdermal gel for contraception is currently in development. The results of preliminary clinical studies indicated that due to its potent progestational and antiovulatory effects, NES, suppressed ovulation in the majority of subjects when applied transdermally [17,67]. In a dose-finding Phase 2 study with a NES transdermal gel containing 0.3, 0.6 or 1.2 mg/day NES, was applied daily, a dose–response

TABLE 3

Male contraceptive delivery systems

Product	Status	Manufacturer/ developer	Active agent(s)	Technology	Duration of action	Preg rate / 100 women-y*
Subdermal implant [9]	Phase II	Population Council	MENT®	Proprietary	12 months	–
Androgen + progestin or GnRH [37,68,69,84] Implanon + TU injections	Various stages I to III Phase II	Academic centers, WHO, Organon, Netherlands and Schering, Berlin	Various (see text) ENG + TU	Orals + Injections ; Orals + Implants; Implants + injections	Target: 12 months	–

Abbreviations: MENT, 7 α Methyl NorTestosterone; GnRH, Gonadotropin Releasing Hormone; WHO, World Health Organization; ENG, Etonogestrel; TU, Testosterone Undecanoate.

relationship was observed for ovulation inhibition of 53, 64, and 83%, respectively [17].

Male contraception

Although the demand is increasing for male methods of contraception, no male contraceptive other than the condom and vasectomy is available today, and research is ongoing (Table 3). The goal of male hormonal contraceptive methods in clinical development is the suppression of spermatogenesis. Other non-hormonal methods are directed at sperm function and maturation and are still in preclinical development.

Clinical studies in human volunteers have used an androgen alone or a combination of an androgen with a progestin or with a gonadotropin-releasing hormone (GnRH) antagonist [6–9,37,68,69]. The objective of these studies has been the induction of azoospermia, which is achieved when follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are suppressed [37,68]. Androgen therapy with testosterone esters, when given alone, induces a decrease in FSH and LH, while maintaining male habitus and libido. However the testosterone dose needed to ensure these effects is high and induces side-effects such as acne, changes in lipid fractions (such as a decrease in high density lipoprotein) and stimulation of prostate growth [70]. Progestins with high antigonadotropic potency have been shown to suppress FSH and LH, resulting in a decrease in testosterone levels and necessitating replacement therapy with an androgen [68–71].

A testosterone transdermal gel has been shown to be an effective androgen replacement in men with hypogonadism in several clinical trials [72–78]. However, when used in male contraceptive studies, transdermal testosterone has had disappointing results when used alone. Other studies are ongoing combining progestins with transdermal testosterone. [6,79]. Combinations of gonadotropin releasing hormone (GnRH) antagonists and androgens have been tested in clinical trials to decrease quickly and profoundly the FSH levels, hence suppressing the spermatogenesis in a few weeks. The proposed regimen consisted of a 12 weeks GnRH antagonist for an induction phase and then maintenance of the effect with testosterone injections. With this combination, the dose of androgen required for maintenance of the anti-spermatogenic effect was much lower that those required when testosterone injections are used alone [37].

Future studies using GnRH antagonists plus androgen regimen might be dependent upon the development of new antagonists, which could be administered orally or long-acting, possibly non-peptide, which might be more acceptable, and less expensive than the currently available peptide analogs [37].

In the next decade, new androgens will become available for use in male contraception. Orally active selective androgen receptor modulators (SARM) or tissue–selective androgens such as MENT (7α MEthyl Nor Testosterone) delivered from one-year implants [9] are under development. These molecules are designed to have strong gonadotropin suppression activity with the ability to maintain sexual function and bone and muscle mass, but to have little or no effect on the serum lipid profile and the prostate gland. This promising method is being developed and initial studies indicated suppression of spermatogenesis in >80% of the subjects who received four implants. Optimization of the formulation is ongoing to deliver a higher dose of the androgen in a smaller number of implants before undertaking larger dose-finding and efficacy studies.

Other nonhormonal contraceptive methods for men are also under investigation. These include attempts to decrease sperm production or motility or to block the ability of sperm to fertilize the ovum. A new approach to male contraception, which involves perturbing the dynamics of tight junctions and adherens junctions in the testis, has been studied by Cheng *et al.* [80,81]. The movement of germ cells during their development in the testis can be disrupted by perturbing the tight junctions that constitute the blood-testis barrier. The opening and closing of the tight junctions between Sertoli cells can be manipulated by using inhibitors of specific cytokines. The disruption of germ-cell attachment to the seminiferous epithelium of the testes is also being evaluated. Premature detachment of the germ cells results in the release of immature sperm that cannot fertilize an ovum. Eddy *et al.* [82] studied the enzymes involved in the movement of the spermatozoid, which is essential for its migration in the female reproductive tract. Targeting these enzymes might offer a new approach to prevent the

TABLE 4

Dual-protection (microbicide + contraceptive) delivery systems

Product	Status	Manufacturer/ developer	Active agent(s)	Technology	Duration of action	Preg rate / 100 women-y*
Carraguard® + LNG	Proof of concept	Population Council	Carrageenan (adsorption inhibitor) + LNG (progestin)	Vaginal gel (active agent plus progestin delivery method)	Prior to intercourse (TBD)	–
BufferGel™ [33]	Phase II/III	Reprotect/ HIV	Carbopol 974P(acid buffer)	Clear vaginal gel	Prior to intercourse	
Savvy [33]	Phase II/III	Biosyn /HIV Prevention Trials Network/ FHI	1% C31G (surfactant)	Vaginal gel	Prior to intercourse	–
Ushercell [33]	Phase III	FHI/ CONRAD	6% cellulose sulfate	Clear vaginal gel (adsorption inhibitor)	Prior to intercourse	–
PRO2000 [33]	Phase III	Indevus Pharmaceuticals/ Microbicide Development Programme	2% and 5% polynapthalene sulphonate (entry and fusion inhibitor)	Water-based vaginal gel	Prior to intercourse	

Abbreviations: FHI, Family Health International; CONRAD, Contraceptive Network for Research And Development; HIV, Human Immunodeficiency Virus; TBD, To be determined.

motility of sperm without modifying the endocrine environment.

The hormonal methods are closer to become an available method as compared with non-hormonal methods. However the combination of two hormones, requiring also two modes of delivery, is complex and might not appear attractive to the users. An intensive search for a second-generation of male contraceptive drugs is ongoing, supported by several organizations such as the WHO, the NIH, CONRAD, the Population Council and several other Medical research councils [38].

Dual-protection methods

Some dual-protection methods that combine a contraceptive with a microbicide that might protect against STIs, especially HIV infection, are in Phase II or Phase III clinical trials, while others are still in the proof of concept stage (Table 4) [33]. The dual-protection products in advanced clinical development are vaginal gels containing a microbicidal agent. The gels themselves are spermicides. Microbicides with different mechanisms of action are being evaluated, but no preferred agent has yet emerged. The combination agents are badly needed in less developed countries in which medical care is not readily available and HIV prevalence is high.

Conclusion

Future contraceptive research will build upon advances in biomedical research analyzing the biology of reproduction at the cellular level. It is hoped that this research will lead to the discovery of novel targets for contraception. The application of the so-called '-omics' revolution, which has created the tools and technologies of genomics, proteomics, lipidomics, and glycomics, has great potential in the identification of protein targets and their regulatory genes [33].

The extraordinary progress made in the drug delivery area might also facilitate the development of superior contraceptive systems in the future. Sustained-release systems would have a positive impact on compliance and ease of use. The first revolution in drug delivery systems was spearheaded by the first-generation, long-acting systems developed by the Population Council. IUDs and implants, fruits of this research, are now widely available, and a CVR is in the last stages of development. All these delivery systems are based on the use of steroidal hormones delivered continuously at very low doses, which suppresses ovulation in menstruating women. Dual-protection methods which join contraceptives to microbicides to protect women against unwanted pregnancy and STIs, especially HIV infection, would meet a major need.

In other cases, the provision of an extra health benefit might increase compliance with contraceptive use. Current contraceptive methods do have many benefits: some improve menstrual bleeding patterns, alleviate dysmenorrhea, acne, and, sometimes, pre-menstrual syndrome. Others can produce amenorrhea. The protective effect of the COC on ovarian and endometrial cancer is perceived as an advantage by providers and this additional medical benefit might enhance continuation rates among well-informed women. Contraceptive methods that would also provide additional protection against breast or ovarian cancer would also have wide appeal. Above all, new contraceptives, which are designed to be used by healthy men and women, should be very safe. Easy to use, reversible and inexpensive methods are still needed.

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