

Family planning needs: new opportunities, emergency contraception and other new technologies

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ABSTRACT

The advent of modern contraception is considered one the major advances of the 20th century, yet, as the next century begins, it is estimated that there is still a large unmet need for contraception with millions of couples worldwide who express a wish to limit the number of their children but do not use or are not satisfied with their contraceptive method. While the reasons are numerous, it is clear that there is a need for improved and new methods which are easier to use, in the user's control, with less side-effects and responding to the needs of different groups of users, including men.

To respond to this need, current contraceptive research and development efforts focus on five main areas: emergency post-coital methods, user-controlled long-acting methods, dual protection methods against both pregnancy and sexually-transmitted infections, methods for men, and methods with fewer side-effects including some that are more targeted to specific reproductive biological events.

A number of leads are presented which are at various stages of development. Concluding remarks stress the numerous challenges of contraceptive development, not the least of which is the vision required of what the needs of future generations will be, since it takes 10-15 years to bring a new contraceptive to the market. More fundamentally, overall progress towards reducing the unmet need for contraception will depend on the status of women, specifically their decision-making power, and access to education and income.

Key word: contraception

Introduction

The uptake of family planning has been quite dramatic over the past forty years. Globally, contraceptive prevalence has risen from 30% in the early 1960s to 58% in 1998 among married women. This increase has been greatest in developing countries, from 9% to 55% over the same period (Population Division 1999). Such figures clearly show that family planning responds to some of the needs of couples.

Yet, it is also estimated that, upward from 120 million couples worldwide say they want to limit the number of their children but do not use any form of contraception (Robey 1996). They face three major obstacles: they are ambivalent about modern contraception and fear its side-effects; they often do not have access to good quality services; they face strong opposition from family members or influential members of their community.

When it comes to the estimated 570 million of users themselves (Population Division 1999), women for the most part, over 40% of those in developing countries have abandoned their contraceptive method by the end of the first year of use. For 11% of them, this is because of side-effects, for another 11% this is because of an unplanned pregnancy (Shah 2000). Some of these unplanned pregnancies are terminated with an abortion; it is estimated that each year, about 46 million abortions are performed, of which 20 million are done in unsafe conditions and lead to about 78,000 maternal deaths (WHO 1997). This contributes some 15% of the 515,000 maternal deaths that occur each year worldwide (WHO 2001).

Thus, while there is a need for better public information, improved education and counselling of users, and improved access to good quality services, there is also a need for improved or new methods, which are easier to use, in the user's control, with less side-effects and responding to the needs of various groups of users, including men.

Contraceptive research and development attempts to meet these goals by pursuing five main lines:

- a. For cases of unprotected intercourse, contraceptive failure or rape, women need *emergency post-coital methods* to reduce the risk of unintended pregnancies.
- b. Acceptability studies show that women need *long-acting methods*, as these are easier to use than methods that require daily interventions. However, the long-acting methods that are currently available, such as intra-uterine devices and implants, require the intervention of health care providers for removal. This can be a problem where providers are unavailable or unconvinced that removal is needed. Thus there is a need for long-acting methods which are *under the user's control*, that is, that women can discontinue at will.
- c. Every year, there are about 340 million new cases of curable sexually transmitted infections (WHO 2001). In addition, there are about 5.6 million new cases of HIV infections worldwide, and in Africa, the prevalence of HIV infection is higher among women than men (UNAIDS 1999). Women need methods that offer them *dual protection*, against pregnancy and sexually-transmitted infections (STIs). Too often, they are not in a position to negotiate condom use, particularly within marriage and this puts them at risk. For example, two studies conducted in India (George 1997) and in Rwanda (Allen 1991) have shown that, among married women who stated they were monogamous, 22% and 25%, respectively, were HIV-positive.
- d. The burden of contraception needs to be shared more equitably between men and women. Currently, *men* have a choice of methods limited to withdrawal, condom and vasectomy. New methods are needed for them.
- e. Contraception is used by healthy women for several decades of their lives. Side-effects which could be tolerated with short-term treatment courses, are much less acceptable in this context and the strive to develop methods with *less side-effects* needs to continue. This implies a search for *more targeted, less systemic methods*.

1. *Emergency contraception*

Emergency contraception was once called “the best kept secret of family planning”. Indeed, it is in the early 1970s, almost 30 years ago, that Yuzpe and his colleagues tested combinations of ethinyl estradiol (EE) and norgestrel (NG) for post-coital contraception, based on their observation that a single dose of 50 µg EE + 500 µg NG induced significant changes thought to prevent implantation. Subsequent clinical trials (Yuzpe 1977, 1982) led them to conclude that the most successful regimen consisted of two doses of 100 µg of EE and 1 mg of NG administered 12 hours apart within 72 hours of unprotected intercourse.

Practitioners may not have been convinced by this method for two reasons. Firstly, the real efficacy of the method was difficult to estimate. Analysis of recent clinical trials suggests that, when started within 72 hours of unprotected intercourse, it prevents about 74% of pregnancies (Trussell 1996), and thus is considerably less effective than other contraceptive methods. Secondly, it has unpleasant side-effects; about half of the users report nausea and at least 20% experience vomiting (Task Force on Post-ovulatory Methods of Fertility Regulation 1998).

Yet, history shows that women have long sought a post-coital contraceptive. Even with the advent of modern contraception, women still need emergency contraception, either when they have unplanned, thus unprotected, intercourse as is the case for most young couples who have sex for the first time, or in case of a contraceptive problem such as breakage or slippage of a male condom, or in case of rape.

Intra-uterine device (IUD) insertion has been shown to be an effective form of emergency contraception as late as 5 days after unprotected intercourse (Van Look 1990), however it, too, has serious limitations. The IUD may be difficult to insert in young and nulliparous women, it can induce some abdominal discomfort, it carries the risk of spreading an infection acquired during that same act of unprotected intercourse and such long-term contraceptive protection may not be desired at that time.

Thus efforts were made to develop alternative forms of emergency contraception and to increase international awareness for these methods.

Various doses of levonorgestrel have been tested since the 1970s for post-coital contraception. More recently, a large multinational, randomized, double-blind clinical trial (Task Force on Postovulatory Methods of Fertility Regulation 1998) was conducted, comparing the Yuzpe regimen and levonorgestrel treatment (two doses of 750 µg each, taken 12 hours apart) when taken up to 72 hours after unprotected intercourse. Twenty-one centres in 14 countries participated in the study and recruited 1998 women. Results showed that levonorgestrel was not only better tolerated but was also more effective than the Yuzpe regimen, preventing 85% of expected pregnancies. It also showed that the earlier either treatment was taken after the act of unprotected intercourse, the more effective it was.

Because progesterone is known to play a key role in the establishment of pregnancy, the anti-progestin mifepristone was also tested as a post-coital agent. Studies (Task Force on Postovulatory Methods of Fertility Regulation 1999) showed

that a single dose of 10 mg taken within 5 days of unprotected intercourse had an efficacy of 85% and fewer side-effects than the Yuzpe regimen.

Mifepristone treatment has the advantage of requiring a single dose, however, the drug is more expensive and likely to remain less available to countries than levonorgestrel. Thus a study is in progress in 15 centres in 9 countries to compare 10 mg mifepristone with levonorgestrel taken in a single dose of 1.5 mg, or in two doses of 750 µg each, taken 24 hours apart. Some exploratory studies are also being conducted with other compounds, such as gestrinone, in an effort to increase the effectiveness of this approach.

In parallel, a Consortium for Emergency Contraception was created (Mertens 1999), grouping eight organisations, aiming to broaden knowledge and availability of hormonal emergency contraception through model introduction strategies specifically designed to ensure safe, effective and appropriate patterns of emergency contraceptive use. This initiative contributed to the registration of the levonorgestrel regimen in more than 22 countries, in some as an over-the-counter drug to facilitate its use as early after unprotected intercourse as possible. Indeed, a study (Glasier 1998) carried out in Edinburgh suggested that self-administration of emergency contraception could reduce the rate of unwanted pregnancies and induced abortions, without adverse effects.

2. *Long-acting methods under women's control*

2a. Vaginal rings

Most steroid hormones are absorbed efficiently through the vaginal epithelium and can be released from vaginal rings made out of Silastic. As a delivery system, the vaginal ring is the only long-acting method which is under the user's control. It can be easily inserted, checked, removed and replaced by the woman herself. It also has other advantages, namely, it can be worn continuously for a number of weeks; its use is not coitally related; it provides a constant rate of drug release resulting in a steady plasma level of the minimum dose required for contraception; metabolic side-effects are reduced by avoiding the first-pass effect through the liver; and in the case of accidental pregnancy or if protection is no longer required, plasma levels fall rapidly to zero and fertility returns following removal of the ring. Reports of vaginal lesions observed with early ring designs (Bounds 1993) have not been confirmed with newer devices (Fraser 2000, Task Force on Long-acting Systemic Agents for Fertility Regulation 2000).

To date, only one ring is available on the market, for postpartum contraception: it releases natural progesterone at a rate of 10-15 mg/day down to 5 mg/day over 3 months, and is to be worn continuously (Silesia) (Massai 1999).

Other rings are at an advanced stage of development, which release both an estrogen and a progestogen and act by inhibiting ovulation. They are

to be used for three weeks then removed for one week, repeating this schedule over the life-time of the ring. They include rings releasing:

- etonogestrel 120 µg/day + ethinyl estradiol 15 µg/day (Organon) (Olsson 1990, Schindler 1993, Timmer 2000)
- nesterone 150 µg/day + ethinyl estradiol 15 µg/day (Population Council) (Laurikka-Routti 1990, Alvarez-Sanchez 1992)

2b. Transdermal systems

Like vaginal rings, transdermal systems (Sitruk-Ware 1995) have the advantage of avoiding the first-pass effect through the liver, thereby decreasing the metabolic effects of the exogenous steroids. Several types of patches are being tested for weekly use, including:

- combined patches releasing:
 - levonorgestrel + ethinyl estradiol
 - (17-deacetyl) norgestimate + ethinyl estradiol
 - gestodene + ethinyl estradiol
- progestogen-only patches releasing:
 - nesterone
 - norgestimate.

2c. Centchroman

Centchroman (Centron, Saheli) is a novel nonsteroidal chemical, developed and marketed in India as a once-a-week contraceptive pill. It is a potent anti-estrogen with weak estrogenic and antiprogestational actions. A weekly dose of 30mg does not inhibit ovulation but acts by inducing asynchrony between the developing zygote and endometrial maturation, thus preventing implantation. Early studies (Nityanand 1990) have suggested that it is highly effective and that its main side-effect is delayed menses in less than 10% of subjects. These findings need to be confirmed in larger clinical trials.

2d. Monthly combined injectable preparations using disposable syringes

Several once-a-month combined injectable preparations are on the market, used by about 2 million women worldwide. Their provision in disposable non-reusable syringes such as Uniject has increased their safety and studies (Bahamondes 1997) have shown that self-administration with these syringes can increase acceptability of these methods among women who wish to use them without having to access health services on a monthly basis.

3. *Dual protection methods*

3a. Non-latex male condoms

The main advantages of non-latex condoms over latex condoms are that: they are loose-fitting except at the base of the penis; are stronger *in vitro*; do not deteriorate on storage; are not affected by oil-based lubricants and can be used by people with allergy to latex. Polyurethane condoms such as Avanti

and EZON and styrene-based plastic condoms such as Tactylon (Callahan 2000), Unique and Unisex are already on the market, and others are under development. Clinical trials with Avanti (Rosenberg 1996) suggest that it may have higher slippage and breakage rates than the male latex condom, however its acceptability is generally greater. The cost of these devices is likely to remain an obstacle to their widespread use in national family planning programmes.

3b. Female condoms

The first female condom to be available on the market was Femidom, made of polyurethane. It provides a useful alternative to women, particularly when the use of male condoms cannot be negotiated, and provision of both male and female condoms has been shown to increase the number of protected acts of intercourse. Because Femidom remains expensive, alternatives made of latex are being developed (Bounds, 1997). Current research focuses on acceptability and efficacy of these methods, for pregnancy and infection protection.

3c. Microbicides/spermicides

Microbicides (The Population Council and International Family Health 2000) are substances applied in the vagina via a gel, cream, sponge, film or suppository which offer the potential for women to protect themselves, and their sexual partners, against infection with HIV as well as other STIs. A large number of products are under development and, because of their mechanisms of action, many will have both spermicidal and antimicrobial activity, particularly those based on the following approaches:

- surfactant agents such as nonoxynol-9, octoxynol-9, benzalkonium chloride, menfegol, and N-docosanol.
- agents that create a protective physical barrier in the vagina, such as sulphated and sulphonated polymers, e.g. carrageenan.
- agents that enhance vaginal defence mechanisms by maintaining natural levels of acidity which do not allow HIV to survive, and render the vaginal environment inhospitable to sperm. Examples include BufferGel and Acidform.

4. *Male methods*

4a. Hormonal methods

The development of male hormonal methods of contraception has been the subject of research for the past 30 years or more, yet no method is available to date. The ideal method should suppress sperm production while leaving testosterone production intact, in order to render the man infertile but not impotent. It should also be effective shortly after starting treatment and be rapidly reversible

A number of studies in animals and men have shown that the administration of androgens alone (Wallace 1993, Anderson 1997, Zhang 1999, Kamischke 2000, Sundaram 2000), or in combination with GnRH (gonadotropin-releasing hormone) analogues (Behre 1992) or progestogens (WHO 1993, Buchter 1999, Gao 1999, Wu 1999) suppress gonadotrophin secretion and spermatogenesis either to complete azoospermia or to a sufficiently low level of oligozoospermia to render the treated individual infertile. Furthermore, discontinuation of treatment leads to full recovery of gonadotrophin secretion and spermatogenesis and to restoration of fertility (Pangkahila 1991).

A number of clinical trials have proven the feasibility and contraceptive efficacy of this approach (WHO 1990, WHO 1996, Wu 1996) and current research focuses on the use of more potent androgens and on the development of long-acting methods. One such method is the use of a long-acting subcutaneous testosterone pellet and oral desogestrel which results in complete suppression of spermatogenesis for twelve months and maintenance of normal serum testosterone levels for the duration of treatment (Kinniburgh 2000).

4b. Non-hormonal methods

Extracts of the Chinese medicinal plant *Tripterygium wilfordii* have been shown to contain compounds which cause infertility in male rats. One of them, triptolide, appears to be effective in reducing epididymal sperm number and in inducing an almost complete loss of sperm motility (Hikim 2000). These characteristics make it an attractive lead which would induce infertility without suppressing spermatogenesis, would act quickly and would be easily reversible (Lue 1998).

4c. Immunological methods

In a small number of patients attending infertility clinics, the problem is thought to be the presence of anti-sperm antibodies. It was also observed that a proportion of vasectomized men developed anti-sperm antibodies and that this might explain the low pregnancy rate observed after vasectomy reversal. Since the presence of anti-sperm antibodies is not associated with side-effects other than infertility, the possibility of developing an anti-sperm vaccine seems to be a feasible approach. However, to date, the difficulty has been to identify an appropriate antigen and to avoid possible irreversible effects on the testis.

Other approaches based on anti-FSH (follicle-stimulating hormone), anti-FSH receptor, or anti-GnRH are being investigated as possible inhibitors of gametogenesis (Alexander 1994).

4d. Improved methods for male sterilization

Vasectomy is easier to perform and is associated with fewer complications than female sterilization, yet, worldwide, the number of couples

relying on vasectomy was estimated in 1995 to be about 39 million, compared to over 185 million couples relying on female sterilization. The necessity for a skin incision, and the lack of assured reversibility appear to be the main issues of acceptability. Two major techniques have been developed to overcome these problems: the no-scalpel method of vasectomy and the percutaneous, non-surgical vas occlusion technique. The no-scalpel method is gaining in popularity (Liu 1993). However, to date, occlusion techniques based on polyurethane or methylcyanoacrylate have been shown to have too much local toxicity, with local reaction and occlusion on either side of the plug (Chen 1996). Methods using silicone are under evaluation, whereby liquid silicone is injected in the vas then cures *in situ*, or it is pre-formed as plugs which are then inserted (Soebadi 1995).

A new approach to non-surgical vas occlusion under study involves an injection, into the vas deferens, of a preparation of styrene maleic anhydride dissolved in dimethyl sulphoxide. In monkeys, this approach has been shown reversible using a combination of palpation and percutaneous electrical stimulation (Lohiya 2000).

5. *Methods with reduced side-effects*

5a. Immunocontraceptives

Immunocontraceptives have potential for the development of long-acting methods that are free of side-effects and contra-indications currently associated with currently available hormonal contraceptives, do not require the insertion of a device, have a relatively long (6-12 months) but not permanent duration of action and are naturally reversible.

One such preparation is under development (Jones 1988, WHO 2000) based on a double immunogen: the carboxyterminal peptide and the loop peptide of the hCG (human chorionic gonadotropin) molecule, conjugated with diphtheria toxoid. It acts by inhibiting the action of hCG produced by the pre-implantation embryo, thus limiting the production of progesterone by the corpus luteum and making the endometrium unsuitable for implantation. One difficulty with this approach is to ensure that individual women have the needed protective antibody level and this may require the development of a home monitoring test.

5b. Hormonal injectable preparations

A number of approaches are used to improve the pharmacokinetic profile of injectable contraceptives in an effort to reduce their level of side-effects. These include slow-release preparations in the form of microspheres of pure steroids (testosterone, progesterone and a combination of progesterone 200mg + 17 β -estradiol 5mg as a once-a-month method) (Garza-Flores 1991) and the use of esters as depot formulations (Crabbé 1983).

5c. Estrogen-free oral contraceptive preparations

In an effort to develop estrogen-free oral preparations, studies are being conducted to explore the potential of a sequential regimen based on an anti-progestogen and a progestogen (Croxatto 1998). The anti-progestogen is used at a dose that inhibits ovulation and the progestogen allows the development of a secretory endometrium so that vaginal bleeding is induced monthly.

5d. Intrauterine devices (IUDs)

The main reasons for discontinuing IUD use are pain, bleeding and expulsion. These side-effects are thought to be related to the relative size of the frame or shape of the device. A number of frameless IUDs have been developed and are already on the market, which consist of copper sleeves crimped onto nylon suture material anchored into the myometrium. However early devices were not shown to induce significantly less side-effects than other IUDs and had a relatively high expulsion rate, and new designs (Gynefix) are currently being tested (IUD Research Group 1995, Wildemeersch 1999, Batar 2000, Cao 2000).

Other IUDs have been developed which release small amounts of a progestogen continuously. The T-shaped Mirena, which releases 20 µg/day of levonorgestrel (LNG) over 5 years is already on the market (French 2000). It induces significant less blood loss than copper IUDs but, its use is associated with menstrual pattern disturbances and with time, increasing amenorrhea, and this is poorly accepted by women in some cultures. A new system is under development, which combines an absence of frame and release of a progestogen: FibroPlant – an intrauterine system consisting of fibers releasing LNG at a rate of 14 µg/day (Wildemeersch 2000), which in early clinical trials has been found to induce less amenorrhea than Mirena.

6. *New targets for contraception*

The development of totally new approaches to contraception needs a deeper understanding of the mechanisms regulating such processes as gametogenesis, sperm capacitation, acrosome reaction, follicular development and implantation. These are being actively investigated with the aim of identifying new targets that might allow a more focused regulation of fertility, thereby avoiding the systemic side-effects associated with current methods (Harrison 1996).

Concluding remarks

The challenges in developing family planning methods are numerous.

It is generally estimated that it takes 10-15 years to develop a new method and bring it to the market, at a cost of US\$ 200-300 million. Industry is reluctant to make such an investment, particularly since they consider that profit is unlikely outside of

the developed countries where contraceptive use is already very high. Other issues such as product liability, stringent regulatory requirements and competition with the public sector which provides free or low cost contraceptives to developing countries come into play. A number of public sector agencies contribute to the field but their resources are limited.

In contrast to the long lead time to a new method, politics, ethics and assumptions change and the views of users evolve as their experience of fertility regulation increases. Assessing the perspectives and needs of couples from various socio-cultural and economic backgrounds is difficult but it is even more taxing to anticipate those of the generations to come and to predict how a method will be received once it is available on the market.

In developing countries where the unmet need for contraception is the greatest, the capacity of the health systems is an essential factor in the impact of a method, thus low cost and ease of delivery are of paramount importance in selecting leads for development.

More importantly, use of family planning is highly dependent on the status of women, their decision-making power, their access to education and to income and progress in these areas is vital if women are to gain maximum benefit from these technological advances.

References

Alexander NJ 1994 Contraceptive vaccines. In: Van Look PFA, Perez-Palacios G *Contraceptive research and development 1984 to 1994*. Oxford University Press, Delhi, India. 203-213.

Allen S, Lindan C, Serufulira A *et al.* 1991 Human immunodeficiency virus infection in urban Rwanda. Demographic and behavioral correlates in a representative sample of childbearing women. *Journal of the American Medical Association* **266**, 1657-1663.

Alvarez-Sanchez F, Brache V, Jackanicz T *et al.* 1992 Evaluation of four different contraceptive vaginal rings: steroid serum levels, luteal activity, bleeding control and lipid profiles. *Contraception* **46**(4), 387-398.

Anderson RA, Wallace EM, Kicman AT *et al.* 1997 Comparison between testosterone enantate-induced azoospermia and oligozoospermia in a male contraceptive study IV: Suppression of endogenous testicular and adrenal androgens by exogenous testosterone. *Human Reproduction* **8**, 1657-1662.

Bahamondes L, Marchi NM, Nakagava HM *et al.* 1997 Self-administration with Uniject of the once-a-month injectable contraceptive Cyclofem. *Contraception* **56**, 301-304.

Batar I, Gbolade BA, Wildemeersch D 2000 Immediate post-abort insertion of the frameless IUD: review of current experience. *European Journal of Contraception & Reproductive Health Care* **5**(1), 96-98.

- Behre HM, Nashan D, Hubert W *et al.* 1992 Depot-gonadotropin-releasing hormone agonist blunts the androgen-induced suppression of spermatogenesis in a clinical trial of male contraception. *Journal of Clinical Endocrinology and Metabolism* **74**, 84-90.
- Bounds W, Szarewski A, Lowe D *et al.* 1993 Preliminary report of unexpected local reactions to a progestogen-releasing contraceptive vaginal ring. *European Journal of Obstetrics, Gynecology and Reproductive Biology* **48**, 123-125.
- Bounds W 1997 Female condoms. *European Journal of Contraception and Reproductive Health Care* **2**(2), 113-116.
- Buchter D, von Eckardstein S, von Eckardstein A *et al.* 1999 Clinical trial of transdermal testosterone and oral levonorgestrel for male contraception. *Journal of Clinical Endocrinology and Metabolism* **84**(4), 1244-1249.
- Callahan M, Mauck C, Taylor D *et al.* 2000 Comparative evaluation of three Tactylon™ condoms and a latex condom during vaginal intercourse: breakage and slippage. *Contraception* **61**, 205-215.
- Cao X, Zhang W, Gao G *et al.* 2000 Randomized comparative trial in parous women of the frameless Gynefix and the TCU 380A intrauterine devices: long-term experience in a Chinese family planning clinic. *European Journal of Contraception & Reproductive Health Care* **5**(2), 135-140.
- Chen Z, Gu Y, Liang X *et al.* 1996 Morphological observations of vas deferens occlusion by the percutaneous injection of medical polyurethane. *Contraception* **53**(5), 275-279.
- Crabbé P, Archer S, Benagiano G *et al.* 1983 Long-acting contraceptive agents: Design of the WHO chemical synthesis programme. *Steroids* **41**(3), 243-253.
- Croxatto HB, Salvatierra AM, Fuentealba B *et al.* 1998 Contraceptive potential of a mifepristone-nomegestrol acetate sequential regimen in women. *Human Reproduction* **13**(12), 3287-3302.
- Fraser AS, Lacarra M, Mishell DR *et al.* 2000 Vaginal epithelial surface appearances in women using vaginal rings for contraception. *Contraception* **61**, 131-138.
- French RS, Cowan FM, Mansour D *et al.* 2000 Levonorgestrel-releasing (20 microgram/day) intrauterine systems (Mirena) compared with other methods of reversible contraceptives. *BCOG* **107**(10), 1218-1225.
- Gao E, Lin C, Gui Y *et al.* 1999 Inhibiting effects of Sino-implant plus testosterone undecanoate (TU) on spermatogenesis in Chinese men. *Reproduction and Contraception* **10**(2), 98-105.
- Garza-Flores J, Fatinikun T, Hernandez L *et al.* 1991 A pilot study on the assessment of a progesterone/estradiol sustained release as a once-a-month injectable contraceptive. *Contraception* **44**, 45-59.

George S, Jacob M, John TJ *et al.* 1997 A case-control analysis of risk factors in HIV transmission in South India. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* **14**, 290-293.

Glasier A, Baird D 1998 The effects of self-administering emergency contraception. *New England Journal of Medicine* **339**, 1-4.

Harrison PF, Rosenfield A 1996 *Contraceptive research and development - Looking to the future*. National Academy Press, Washington D.C. pp. 519.

Hikim AP, Lue YH, Wang C *et al.* 2000 Posttesticular antifertility action of triptolide in the male rat: evidence for severe impairment of cauda epididymal sperm ultrastructure. *Journal of Andrology* **21**(3), 431-437.

IUD Research Group. UNDP/UNFPA/World Bank/WHO Special Programme of Research, Development and Research Training in Human Reproduction. 1995 The TCu 380A IUD and the frameless IUD "the Flexigard": interim three-year data from an international multicenter trial. *Contraception* **52**(2), 77-83.

Jones WR, Bradley J, Judd SJ *et al.* 1988 Phase I clinical trial of a World Health Organization birth control vaccine. *Lancet* **1**, 1295-1298.

Kamischke A, Plöger D, Venherm S *et al.* 2000 Intramuscular testosterone undecanoate with or without oral levonorgestrel: a randomized placebo-controlled feasibility study for male contraception. *Clinical Endocrinology* **53**(1), 43-52.

Kamischke A, Venherm S, Plöger D *et al.* 2001 Intramuscular testosterone undecanoate and norethisterone enanthate in a clinical trial for male contraception. *Journal of Clinical Endocrinology and Metabolism* **86**(1), 303-309.

Kinniburgh D, Anderson RA, Cheng L *et al.* 2000 Contraceptive potential of oral desogestrel with depot testosterone in men. *International Journal of Obstetrics and Gynaecology* **70**, abstr FCI/22.05.

Laurikka-Routti M, Haukkamaa M, Heikinheimo O. 1990 A contraceptive vaginal ring releasing ethinylestradiol and the progestin ST1435: Bleeding control, serum steroid concentrations, serum lipids and serum chemistry. *Contraception* **42**, 111-120.

Lohiya NK, Manivannan B, Mishra PK 2000 Repeated vas occlusion and non-invasive reversal with styrene maleic anhydride for male contraception in langur monkeys. *International Journal of Andrology* **23**(1), 36-42.

Liu X, Li S 1993 Vasal sterilization in China. *Contraception* **48**(3), 255-265.

Lue Y, Sinha Hikim AP, Wang C *et al.* 1998 Triptolide: a potential male contraceptive. *Journal of Andrology* **19**(4), 479-86.

Massai R, Miranda P, Valdes P *et al.* 1999 Preregistration study on the safety and contraceptive efficacy of a progesterone-releasing vaginal ring in Chilean nursing women. *Contraception* **60**, 9-14.

Mertens W 1999 *Evaluation report on the Emergency Contraception Consortium*. Boston: Management Services for Health, (revised).

Nityanand S, Chandrawati, Singh L *et al.* 1990 Clinical evaluation of Centchroman: a new oral contraceptive. In: Puri C.P. and Van Look P.F.A. (eds) *Hormone Antagonists for Fertility Regulation*. Bombay, ISSRF, 223-230.

Olsson SE, Odland V 1990 Contraception with a vaginal ring releasing 3-keto-desogestrel and ethinyl estradiol. *Contraception* **42**, 563-72.

Pangkahila W 1991 Reversible azoospermia induced by an androgen-progestin combination regimen in Indonesian men. *International Journal of Andrology* **14**(4), 248-256.

Population Division (Department of Economic and Social Affairs, United Nations) 1999 *World contraceptive use in 1998* (document ST/ESA/SER.A/175). United Nations, New York. pp. 261.

Robey B, Ross J, Bhushan I 1996 *Meeting unmet need: new strategies*. Population Reports J-43: pp. 36.

Rosenberg M, Waugh MS, Solomon HM *et al.* 1996 The male polyurethane condom: a review of current knowledge. *Contraception* **53**, 141-146.

Schindler AE 1993 The 3-keto-desogestrel/ethinylestradiol ring: a new parenteral form of hormonal contraception. *European Journal of Obstetrics, Gynecology and Reproductive Biology* **49**(1-2), 13-4.

Shah I 2000 Perspectives of users and potential users on methods of fertility regulation. In : Puri CP, Van Look PFA, eds. *Sexual and reproductive health. Recent advances, future directions. Vol.II*. New Age International Limited publishers, New Dehli:45-91.

Sitruk-Ware R 1995 Transdermal application of steroid hormones for contraception. *Journal of Steroid Biochemistry & Molecular Biology* **53**(1-6), 247-51.

Soebadi DM, Gardjito W, Mensink HJ 1995 Intravasal injection of formed-in-place medical grade silicone rubber for vas occlusion. *International Journal of Andrology* **18**(suppl 1), 45-52.

Sundaram K, Kumar N 2000 7 α -methyl-19-nortestosterone (MENT): the optimal androgen for male contraception and replacement therapy. *International Journal of Andrology* **23**(Suppl.2), 13-15.

Task Force on Long-acting Systemic Agents for Fertility Regulation. United Nations Development Programme (UNDP) / United Nations Population Fund (UNFPA) /

World Health Organization (WHO) / World Bank (WB), Special Programme of Research, Development and Research Training in Human Reproduction. 2000 A randomised comparison of the effects on vaginal and cervical epithelium of a placebo vaginal ring with non-use of a ring. *Contraception* **62**, 93-89.

Task Force on Post-ovulatory Methods of Fertility Regulation 1998 Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. *The Lancet* **352**(9126), 428-433.

Task Force on Postovulatory Methods of Fertility Regulation 1999 Comparison of three single doses of mifepristone as emergency contraception: a randomised trial. *The Lancet* **353**(9154), 697-702.

The Population Council and International Family Health 2000 *The case for microbicides: A global priority*. pp. 27.

Timmer CJ, Mulders TM 2000 Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring. *Clinical Pharmacokinetics* **39**(3), 233-42.

Trussell J, Ellertson C, Stewart F 1996 The effectiveness of the Yuzpe regimen of postcoital contraception. *Family Planning Perspectives* **28**, 58-64,87.

UNAIDS - Joint United Nations Programme on HIV/AIDS 1999 *AIDS epidemic update: December 1999*. Document UNAIDS/99.53, pp. 24.

Van Look PFA. 1990 Postcoital contraception. *Outlook* **8**(3), 2-6.

Wallace EM, Gow SM, Wu FCW 1993 Comparison between testosterone enantate-induced azoospermia and oligozoospermia in a male contraceptive study I: Plasma luteinizing hormone, follicle stimulating hormone, testosterone, estradiol and inhibin concentrations. *Journal of Clinical Endocrinology and Metabolism* **77**(1), 290-293.

WHO. Department of Reproductive Health and Research 2000 *Annual Technical Report 1999*. Document WHO/RHR/00.9, pp. 357.

WHO. Division of Reproductive Health (Technical Support) 1997 Unsafe abortion - Global and regional estimates of incidence of and mortality due to unsafe abortion with a listing of available country data. Third Edition [WHO/RHT/MSM/97.16] pp. 109.

WHO. Task Force on Methods for the Regulation of Male Fertility 1990 Contraceptive efficacy of testosterone-induced azoospermia in normal men. *The Lancet* **336**, 955-959.

WHO. Task Force on Methods for the Regulation of Male Fertility 1993 Comparison of two androgens plus depot-medroxyprogesterone acetate for suppression to azoospermia in Indonesian men. *Fertility and Sterility* **60**, 1062-1068.

WHO. Task Force on Methods for the Regulation of Male Fertility 1996 Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. *Fertility and Sterility* **65**, 821-829.

WHO 2001 *Maternal mortality in 1995. Estimates developed by WHO, UNICEF and UNFPA*. Document WHO/RHR/01.9.

WHO 2001 *Global prevalence and incidence of selected curable sexually transmitted infections*. Document WHO/HIV_AIDS/2001.02, pp. 42.

Wildemeersch D, Batar I, Webb A *et al.* 1999 GyneFix®. The frameless intrauterine contraceptive implant for interval, emergency and post-abortal contraception - an update. *The British Journal of Family Planning* **24**, 149-159.

Wildemeersch D, Schacht E 2000 Endometrial suppression with a new 'frameless' levonorgestrel releasing intrauterine system in perimenopausal and postmenopausal women: a pilot study. *Maturitas* **36**(1), 63-68.

Wu FCW, Farley TMM, Peregoudov A *et al.* 1996 Effects of testosterone enanthate in normal men: experience from a multicenter contraceptive efficacy study. *Fertility and Sterility* **65**(3), 626-636.

Wu FCW, Balasubramanian R, Mulders TMT *et al.* 1999 Oral progestogen combined with testosterone as a potential male contraceptive: additive effects between desogestrel and testosterone enanthate in suppression of spermatogenesis, pituitary-testicular axis and lipid metabolism. *Journal of Clinical Endocrinology and Metabolism* **84**, 112-122.

Yuzpe AA, Lancee WJ 1977 Ethinyl estradiol and dl-norgestrel as a postcoital contraceptive. *Fertility and Sterility* **28**(9), 932-936.

Yuzpe AA, Smith RP, Rademaker AW 1982 A multicenter clinical investigation employing ethinyl estradiol combined with dl-norgestrel as a postcoital contraceptive agent. *Fertility and Sterility* **37**(4), 508-513.

Zhang GY, Gu YQ, Wang XH *et al.* 1999 A clinical trial of injectable testosterone undecanoate as a potential male contraceptive in normal Chinese men. *Journal of Clinical Endocrinology and Metabolism* **84**, 3642-3647.