

Current status of fertility control methods in India

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Approximately 48.2% of couples of 15 to 49 years of age practice family planning methods in India. Female sterilization accounts for 34.2%, with male sterilization declining from 3.4% in 1992–93 to 1.9% in 1998–99. Use of the condom increased to 3.1% from 2.4%. There is an urgent need for research to develop new contraceptive modalities especially for men and also for women and to make existing methods more safe, affordable and acceptable. Current efforts in India to develop a male contraceptive are mainly directed towards (i) development of antispermatogenic agents to suppress sperm production, (ii) prevention of sperm maturation, (iii) prevention of sperm transport through vas deferens or rendering these sperm infertile and (iv) prevention of sperm deposition. Research work in the field of prevention of sperm transport through vas deferens has made significant advances. Styrene maleic anhydride (SMA) disturbed the electrical charge of spermatozoa leading to acrosome rupture and consequent loss in fertilizing ability of sperm. A multicentre phase-III clinical trial using SMA is continuing and it is hoped that the SMA approach would be available in the near future as an indigenously developed injectable intra-vasal male contraceptive.

The safety and efficacy of available oral contraceptives were evaluated. An indigenously developed oral contraceptive 'Centchorman', which is a nonsteroidal, weakly estrogenic but potently antiestrogenic, was found to be safe and effective and is now being marketed in India since 1991 as a 'once a week' pill. Cyclofem and Mesigyna have been recommended as injectable contraceptives with proper counselling and service delivery by Indian studies. It has been recommended that these injectable contraceptives be added to the existing range of contraceptive methods available in the National Family Planning Programme. Based on the Indian studies CuT 200 was also recommended. Studies have indicated the advantage of intrauterine devices (IUD); they are long acting, relatively easily removed and fertility returns rapidly after their removal. Recent studies have recommended CuT 200 for use up to 5 years. The combination of some plant products i.e. *Embelia ribes*, Borax and *Piper longum* has been found to be safe and effective as a female contraceptive and the results of phase-I clinical trials are encouraging.

Research work is going on in the country in various areas with special reference to hormonal contraceptive – a three monthly injectable contraceptive, immuno-contraceptives, antiprogesterins, etc.

Keywords. Epididymis; estrogen; luteinizing hormone; ovary; progesterone; sperm; testis; testosterone; uterus

Abbreviations used: CPA, cyproterone acetate; DHT, dihydrotestosterone; FSH, follicle stimulating hormone; GnRH, gonadotropin releasing hormone; GST, glutathione S-transferase; hCG, human chorionic gonadotropin; IUD, intrauterine device; LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone; LNG, levonorgestrel; LNG-B, LNG-butanoate; NET-EN, norethisterone enanthate; RCP, riboflavin-carrier protein; SMA, styrene maleic anhydride; TE, testosterone enanthate; VTE, venous thromboembolism.

1. Introduction

The first five-year development plan initiated in 1951 in India recognized the need for population stabilization as an essential prerequisite for sustaining a good quality of life and a National Family Planning Programme was launched in 1952. The objective of this programme was “reducing birth rate to the extent necessary to stabilize the population at a level consistent with requirement of national economy”. Successive five-year plans provided the required framework on which policy decisions were taken and funding allocated. The results of the 1961 census, which showed a rapid growth in population, prompted the government to form the Department of Family Planning. The Family Planning Programme was renamed as Family Welfare Programme in 1979 and family planning services were integrated with those of Maternal and Child Health and Nutrition. A major achievement of the Family Welfare Programme is the increase in couple protection rate (CPR) from 10.45% in 1970–71 to 45.4% in 1997. The National Family Health Survey (NFHS 1998–99) showed that there is a large unmet need for contraception, which is 11% for birth spacing methods and 8.5% for terminal methods. The predicted massive increase in population in the 15–59 age group from 500 million to 800 million, based on population projections for 1996–2016 by the Technical Committee on Population Projections, underlines the urgent need to provide adequate contraceptive options for both men and women. Enhancement of men’s participation in Family Welfare Programmes is recognized now as important in controlling the population growth. Currently, more than 97% of sterilizations done are female sterilizations and there is a very urgent need to popularize vasectomy and provide access to safe vasectomy services in both rural and urban India.

The National Family Health Survey of 1998–99 indicated a contraceptive prevalence of 48.2% (NFHS 1998–99), with female sterilization accounting for 34.2% while male sterilization declined from 3.4% in the 1992–93 survey to 1.9% in 1998–99. Condom use recorded only a marginal increase to 3.1%, compared to 2.4% in 1992–93. Use of oral contraceptive pills by women increased marginally to 2.1% in 1998–99. These data call for research efforts to develop new contraceptive modalities for men and women as also to make existing methods more safe, affordable and acceptable.

2. Male contraceptive options

Current research in India to develop a male contraceptive is directed mainly towards: (i) development of anti-spermatogenic agents to suppress sperm production,

(ii) prevention of sperm maturation, (iii) prevention of sperm transport through vas deferens (or rendering these sperm infertile) and (iv) prevention of sperm deposition.

2.1 Agents for suppression of spermatogenesis

The first clinical trial to use androgens for male contraception was carried out in India in 1972 by Reddy and Rao (1972) who succeeded in inducing uniform azoospermia in men by daily injections of testosterone propionate. Subsequent studies using a longer-acting androgen, testosterone enanthate (TE) was unable to induce uniform azoospermia (Rajalakshmi 1994).

The pharmacokinetics of TE indicates the need for frequent injections to maintain adequate testosterone levels in circulation (Bajaj and Madan 1983; Rajalakshmi and Ramakrishnan 1989). This resulted in spurts of supraphysiological androgen levels, which were reported as one of the unpleasant side effects of androgen use in clinical trials. The levels of dihydrotestosterone (DHT) and estradiol levels were elevated in these studies. It was felt that such elevation in androgen and estrogen levels might affect various target organs, when used for male contraception. The impact of these fluctuating high hormone levels on testis, prostate, liver, pancreas and on lipid profiles were evaluated in a long-term study in rhesus monkeys kept at controlled dietary conditions by Rajalakshmi and colleagues at the All India Institute of Medical Sciences (AIIMS), New Delhi (Udayakumar *et al* 1998; Tyagi *et al* 1999a, b, c). In this study, adult rhesus monkeys were injected with TE once in 14 days for 32–33 months. The treatment increased serum testosterone levels to a supraphysiological range within 1–3 days after injection followed by a decrease until the next injection. However, nocturnal levels of testosterone were suppressed; testosterone bioavailability studies showed a change in metabolism of testosterone by the liver favouring the formation of androsterone, instead of androstenedione (Tyagi *et al* 1999a). Long-term TE injections also decreased HDL-cholesterol levels and increased the LDL/HDL-cholesterol ratio (Tyagi *et al* 1999b). Thus, long-term androgen administration caused a major shift in blood lipoprotein fractions, which is known to act as a risk factor for ischemic heart disease.

In addition to the change in lipoprotein fractions, prolonged TE administration also increased liver transaminase levels (Tyagi *et al* 1999b). While glucose tolerance was not affected in these animals, serum hypoinsulinemia occurred and was attributed to an improvement in tissue sensitivity to the glucoregulatory effects of insulin (Tyagi *et al* 1999c). These studies carried out in India demonstrated the need for a critical evaluation of the effects of androgen use on

prostate, liver, cardiovascular and other target organ functions, before the drug could be used for male contraception. Major studies have not been done to assess the effects of androgen administration on testicular functions in Indian men, except for that of Bajaj and Madan (1983).

The ability of an androgen-alone modality to induce and maintain azoospermia was evaluated in a multicentre contraceptive efficacy study carried out by WHO, using weekly injections of 200 mg of TE, as a prototype androgen. The results showed that the cumulative life-table to achieve azoospermia was only 64.5% (WHO 1990). The inability of an androgen-alone regimen to induce and maintain uniform azoospermia was evident even when androgen with prolonged duration of action like testosterone buciclate (TB) was used (Kinger *et al* 1995). TB, injected (80 mg at 4 sites) twice at 90-day intervals to adult bonnet monkeys, suppressed testicular and epididymal functions. The animals showed reduction in testicular volume and sperm count (azoospermia was not attained) and suppression in sperm motility and gel penetrability while serum testosterone levels were maintained within physiological limits (Kinger *et al* 1995). The inability of TB to induce azoospermia was likely to be due to its pharmacokinetic profile. TB, when administered to short-term castrated rhesus monkeys exhibited a pharmacokinetic profile, which was superior to that induced by TE (Rajalakshmi and Ramakrishnan 1989; Rajalakshmi and Bajaj 1999). A single injection of 40 mg of TE to castrated monkeys elevated serum testosterone, DHT and estradiol levels to supraphysiological range within 3 days after injection. But, a similar dose of TB increased serum testosterone gradually to reach peak values by day 14 after injection; these levels were within the physiological range. Testosterone levels were maintained within the normal range until day 136. Circulating levels of DHT and estradiol were also elevated but maintained at the normal range. These studies clearly indicated the need for caution in using relatively short-acting androgens like TE for male contraception.

Since testosterone and its esters undergo aromatization and resultant estradiol production may evoke unwanted side effects like gynaecomastia and behavioural changes, studies were done at All India Institute of Medical Sciences, New Delhi to evaluate the ability of non-aromatizable androgens like DHT and androstanediol to suppress spermatogenesis. In rhesus monkeys treated with these androgens, spermatogenesis was arrested to the spermatid stage in some tubules while adjacent tubules showed qualitative maintenance. The ejaculated spermatozoa were immotile but some of the animals failed to ejaculate semen (Ramakrishnan *et al* 1989, 1990) indicating that non-aromatizable androgens may not support ejaculatory response.

The contraceptive potential of STS-557 was demonstrated in bonnet monkeys at National Institute of Health and Family Welfare, New Delhi; but androgen supplementation was needed to offset decrease in androgen levels (Sharma and Das 1992).

Studies carried out at the Population Council, New York, USA have shown that a potent synthetic non-17 α -alkylated androgen like 7 α -methyl 19 nor-testosterone (MENT) undergoes aromatization but does not undergo 5 α -reduction and can be delivered subdermally (Sundaram *et al* 1993). Preliminary studies conducted at the Indian Institute of Science, Bangalore have shown that MENT is a promising androgen for use in male contraception (Sriraman and Rao 2001).

2.2 Combination regimens

Use of steroidal agents like progestogen or antiandrogens, while suppressing spermatogenesis to varying degrees, also induced androgen deficiency due to their gonadotropin-suppressing activity, thus requiring external androgen supplementation. In progestogen–androgen combination regimes, smaller doses of androgens are needed, compared to androgen-only modality, since androgen potentiates the antispermatogenic activity of the progestogen, which acts as the primary antispermatogenic agent in the regimen. Effective suppression of spermatogenesis could be achieved only by use of a potent and long-acting progestogen like depot medroxyprogesterone acetate (Patanelli 1978; Meriggiola *et al* 1999). It would be worthwhile to initiate studies in India to evaluate the effectiveness of progestogen–androgen regimes to suppress spermatogenesis in Indian men, since this would make available a viable contraceptive option for use in family planning programmes in India.

Levonorgestrel (LNG) is a potent gonadotropin inhibitor. Extensive preclinical studies in bonnet monkeys showed that the long-acting ester of LNG, LNG butanoate (LNG-B), when combined with a long-acting androgen (TB), was effective in suppressing spermatogenesis to azoospermia or severe oligozoospermia (Rajalakshmi *et al* 2000). The dose of TB used maintained circulating androgen levels in the physiological range. These studies also established the inherent androgenic activity of LNG-B, demonstrated by ventral prostate assay.

Cyproterone acetate (CPA), in addition to its potent antiandrogenic activity also acts as a progestogen. Phase-I clinical trials conducted in India (Roy and Chatterjee 1979) and in other centres outside India established the ability of CPA to suppress spermatogenesis effectively. Significant androgen deficiency was noted in these subjects indicating need for external androgen supplementation. Lohiya and associates at Jaipur using CPA and TE in langur monkeys showed spermatogenic suppression

ranging from severe oligozoospermia to azoospermia (Lohiya and Sharma 1983; Lohiya *et al* 1987). The only study from India reporting uniform suppression of spermatogenesis using CPA and an androgen was by Sharma *et al* (2001) who used a low dose of CPA (5 mg/day, i.m) and 40 mg of TB once in 60 days in bonnet monkeys. This regimen did not evoke any adverse effects on liver function or lipid profile. CPA is in extensive clinical use for the treatment of hyperandrogenism, acne and hirsutism. The absence of any reports on its teratogenicity and carcinogenicity coupled with lack of adverse effects on liver function parameters (Lohiya and Sharma 1983; Sharma *et al* 2001) are encouraging. This study also underlined the need to titrate the dose of androgen in combination modalities since Sharma *et al* (2001) reported that spermatogenesis was restimulated, when the dose of TB was increased to 80 mg/60 days.

Non-steroidal antispermatogenic agents tested extensively for arresting spermatogenesis include gonadotropin releasing hormone (GnRH) agonists and antagonists. Use of these agents also requires androgen supplementation concurrently. But, even superactive GnRH agonists are less effective than steroidal agents in suppressing fertility. Studies conducted by Kumar *et al* (1986) using daily administration of GnRH agonist, D-Trp⁶-Pro⁹-NET-luteinizing hormone releasing hormone (LHRH), either by injection or by nasal route to rhesus monkeys for 90 days did not induce azoospermia and suppressed androgen levels; with increase in duration of administration, animals did not ejaculate semen. But Lohiya *et al* (1991) were able to induce uniform azoospermia in langur monkeys treated with LHRH agonist Leuprolide and TE.

In contrast to the early generation of GnRH antagonists, antagonists which are currently available have a higher potency. However, there existed a disagreement regarding the timing of androgen administration in combination with GnRH antagonist, which could successfully induce azoospermia (Weinbauer *et al* 1988 1989; Bremner *et al* 1991). This controversy was addressed to by Rajalakshmi *et al* (1995) by administering a potent GnRH "Nal-Lys" antagonist (Antide) in which testosterone (TB) substitution was given either simultaneously or delayed by 45 days after starting the antagonist treatment. Simultaneous administration of the antagonist and TB induced azoospermia in all treated bonnet monkeys albeit at different times, whereas delayed injection of TB restimulated spermatogenesis. However, the high cost of GnRH analogues precludes their extensive use in developing countries even in clinical trials.

2.3 Follicle-stimulating hormone suppression

While a role for follicle-stimulating hormone (FSH) in the maintenance of spermatogenesis was well known, details

of its site of action were shown by Suresh *et al* (1995). These studies carried out at the Indian Institute of Science, Bangalore showed that FSH deprivation by immunoneutralization significantly reduced the proliferation of spermatogonial cells and a marked inhibition in the transformation of spermatogonia to primary spermatocytes. Moudgal *et al* (1997) showed that immunizing bonnet monkeys with recombinant FSH receptor protein affected testicular function and fertility. But, occurrence of spermatogenesis and significant fertility has been reported in gonadotrophin-deficient mice (Singh *et al* 1995), in the FSH-*b* knockout model (Kumar *et al* 1997) and in men homozygous for an inactivating mutation of the FSH receptor (Tapanainen *et al* 1997). This indicates that FSH suppression may not be a viable option for the development of a male contraceptive vaccine. Preliminary clinical trials conducted in India using o-FSH vaccine did not suppress sperm counts to any significant extent but also caused hyperprolactinaemia in many volunteers (M Rajalakshmi, unpublished results). A newer generation of vaccines may yet provide better results.

2.4 Inhibition of sperm maturation

With the development of new andrology techniques like subzonal insemination of sperm and intracytoplasmic sperm injection, the relevance of the epididymis in sperm maturation has come under increasing doubt. A role for epididymis in sperm maturation was established in non-human primates and in humans at the All India Institute of Medical Sciences. These studies evaluated changes in sperm motility and its hormonal dependence (Rajalakshmi *et al* 1989; Kaur *et al* 1990, 1992), changes in sperm ultrastructure and reorganization of lipid bilayer (Sivashanmugam and Rajalakshmi 1997) and changes in lectin binding to sperm (Navaneetham *et al* 1996a, b). As an extension of the above studies, sperm surface proteins undergoing maturational changes were identified (Kaur *et al* 1992; Navaneetham 1993). These studies clearly showed the occurrence of modification in sperm surface epididymal glycoproteins during maturation.

Monoclonal antibodies, D₂G₄ and D₇G₃, were raised against distinct regions of human sperm by Hegde *et al* (1994). Of these, D₂G₄ mAb reacted with spermatozoa and antigens present in cauda epididymis; the antigens identified were androgen-dependant glycoproteins (Hegde *et al* 1994). Evaluation of its antifertility effect showed inhibition of fertilization in mouse *in vitro*. Shaha *et al* (1988) used hyperimmune rabbit serum against whole human sperm to identify a 40 kDa antigen on human sperm acrosome and tail; the antibody against this cross-reacted with a 24 kDa antigen in rat testicular cytosol. Active immunization with the 24 kDa molecule rendered rabbits with high antibody titers infertile. This antigen is

identical to glutathione S-transferase (GST) (Aravinda *et al* 1995) which is a family of multifunctional proteins. Since GST occurs in multiple forms in a single tissue or cell type and is involved in detoxification, the likelihood of it being developed as an antifertility male vaccine appears remote.

Thus, gamete-based vaccines are still at a very early stage of development and it is unlikely that a vaccine will be available in the near future to provide an immunological approach for regulation of male fertility.

2.5 Prevention of sperm transport

This is essentially a vas deferens based approach. Vasectomy has been in use since many decades as a terminal method to prevent sperm transport; intra- and extra-vasal non-occlusive methods have been developed in India. The recent National Family Health Survey indicated a decline in the percentage of men undergoing vasectomy from 3.4% in 1992–93 to 1.9% in 1998–99. Steps need to be undertaken to increase the acceptance of vasectomy. Since vasectomy is perceived as a terminal method, its acceptance rate may increase if centres are identified to undertake recanalization of the vas in subjects who desire of another child.

Two major approaches have been attempted in India to prevent sperm transport through the vas deferens. These are: (i) use of intravasal copper by Kapur and colleagues at the All India Institute of Medical Sciences, and (ii) injection of a non-sclerosing agent, styrene maleic anhydride (SMA) into the vas by Guha and colleagues at the Indian Institute of Technology, New Delhi.

The insertion of intravasal copper wire rendered rats infertile by decapitation of spermatozoa (Ahsan *et al* 1980). But, the effectiveness of the method declined with time (Kapur *et al* 1984) and further studies to improve the method were not carried out. Injection of SMA into the vasal lumen provided partial occlusion. This resulted in the decrease in the number of sperm passing through the vas deferens. Further, SMA disturbed the electrical charge of spermatozoa leading to acrosome rupture and consequent loss in fertilizing ability of sperm (Guha *et al* 1993, 1997; Guha 1999). Flushing out SMA restored fertility in langur monkeys (Lohiya *et al* 1998). SMA can be used as a spacing method in male langur monkeys; the application of a combination of mechanical and electrical methods reverses occlusion (Lohiya *et al* 2000b). A multicentre phase-III clinical trial using SMA is ongoing and the SMA approach may shortly become available as an indigenously developed injectable intra-vasal male contraceptive.

2.6 Prevention of sperm deposition

Barrier methods like use of condoms have dual effectiveness, viz. prevention of sperm deposition in the female tract and prevention of transmission of STDs and HIV. The contraceptive prevalence of condom in India is an insignificant 3.1% (NFHS 1998–99). Recently, scientists and experts agreed that to increase use of condoms four major issues needed to be addressed: (i) changing norms about sexual behaviour and condom use, (ii) assuring effective use, (iii) providing greater access to condoms, and (iv) changing restrictive policies concerning condoms.

2.7 Use of plant products for male contraception

The use of plant products to regulate male and female fertility in India is of ancient origin. But, in spite of numerous studies, no plant product with confirmed contraceptive efficacy (of non-steroidal nature) but devoid of toxicity has emerged so far. Based on the antifertility response evoked by neem oil, polyherbal neem in a cream preparation showed contraceptive efficacy on intravaginal application and its safety was shown in monkeys (Garg *et al* 1993). Neem oil acted as a spermicidal agent and inhibited sperm motility (Riar *et al* 1990; Sharma *et al* 1996).

Several plant products have been tested for their antifertility activity at the University of Rajasthan. Lohiya *et al* (1990) showed that the hypokalemic effects of gossypol acetic acid could be reversed by concurrent use of potassium chloride. Chinoy *et al* (1984) showed the antifertility effects of crude extracts of *Carica papaya* seeds. Using crude aqueous and chloroform extracts of *C. papaya* seeds, sterile matings were recorded in rodents by Lohiya and Goyal (1992) and Lohiya *et al* (1999). The extracts immobilized human sperm *in vitro*, in a dose-dependent manner (Lohiya *et al* 2000a). These authors have suggested that a combination of *C. papaya* extracts and other spermicides may have better applicability.

3. Female contraceptive options

Currently, the following contraceptive methods are available for women worldwide: (i) oral contraceptive pills, (ii) injectable contraceptives, (iii) contraceptive implants, (iv) intrauterine devices, (v) contraceptive vaginal ring, (vi) barrier methods, and (vii) natural family planning methods. Indian scientists have made significant contributions during the last five decades in the evaluation and improvement of the safety, efficacy and acceptability of a number of contraceptive methods.

3.1 Oral contraceptives

Oral contraceptives (OCs) allow effective and convenient family planning for women and couples worldwide, and have revolutionized the reproductive lives of millions of women since their introduction in the 1960s. The first OC, which was a combination of mestranol and norethynodrel, was made available in May 1960, in the USA. Combined OCs inhibit ovulation by inhibiting gonadotrophin secretion and abolishing nocturnal luteinizing hormone (LH) surge while the progestogen component renders the cervical mucus relatively impenetrable to sperm and also reduces the receptivity of the endometrium to implantation (Williams and Stancel 1996). Combined OCs are very effective in preventing pregnancy when used correctly with less than one pregnancy per 100 users in the first year of use. Combined OCs are available currently as monophasic, biphasic and triphasic preparations. The sequential combined OC regimens available currently include estrogen alone for a short interval – usually one week – followed by a combination of estrogen and progestogen (Wharton and Blackburn 1988; Kleinman 1990).

The doses of estrogen and progestogen in the combined OCs, which are available today, have decreased by at least three-fold (Piper and Kennedy 1987). In addition, the chemical composition of the two steroids used in combined OCs has also changed. Nausea, headache, vomiting and other side effects like thromboembolic disease were noticed in the high estrogen group (Thorogood and Villard-Mackintosh 1993). These findings resulted in the development of lower dose pills in the 1970s and 1980s, with the eventual phasing out of those which contained more than 50 µg of estrogen. The dose of progestogen has also decreased over time, and many different types have been developed. These lower-dose combined OCs were found to be as effective as high-dose pills in preventing pregnancy but had fewer side effects (Wharton and Blackburn 1988). The two most widely used OCs contain either a combination of ethinyl estradiol and levonorgestrel or norethisterone. More recently, OCs containing newer progestogens such as norgestimate, gestodene or desogestrel have been developed, which help to reduce further the side effects.

Indian scientists have evaluated the safety and efficacy of available OCs. Multicentric studies conducted by the Indian Council of Medical Research (ICMR), New Delhi showed that OCs are safe generally and are highly effective in preventing pregnancy (ICMR 1992, 1994b). Progestogen-only OCs have an advantage over the combination pills since they can be used safely by lactating women and by those in whom the use of estrogen is contraindicated, though the incidence of bleeding and method failure rate were slightly more in the former group. The exposure of infants and children to low-dose

progestogens during infancy through the mother's milk for varying periods did not adversely affect their anthropometric measurements or major body systems (Toddywalla *et al* 1995); however, occurrence of subtle effects cannot be ruled out (Toddywalla *et al* 1994).

The Central Drug Research Institute (CDRI), Lucknow has developed a nonsteroidal, weakly estrogenic but potent antiestrogenic compound, Centchroman [3,4-trans-2,2-dimethyl-3-phenyl-4-p-(*b*-pyrrolidinoethoxy)phenyl-7-methoxy chroman], for postcoital contraception. The contraceptive action of Centchroman is by disrupting the balance of estrogen and progesterone necessary to prepare the uterus for implantation. Centchroman is reported to accelerate ovum transport also. The resulting asynchrony between uterine receptivity and ovum transport prevents implantation of the fertilized egg (Kamboj *et al* 1992). Excellent pregnancy protection without any drug related side effects was seen when 30 µg of Centchroman was administered biweekly for the first three months and thereafter at weekly intervals to 377 women covering 3,932 cycles of use (Nityanand *et al* 1994). The babies born to user failures showed normal milestones. The contraceptive effect of Centchroman was easily reversible and subsequent pregnancies were normal. The drug "Centchroman" is being marketed in India since 1991 as a 'once-a-week' pill.

A comparative study of the metabolic effects of two-combined OCs indicated that both OC regimens increased HDL-cholesterol (Sadik *et al* 1985). Joshi (1984) reported that adverse effects of OCs on carbohydrate metabolism should be viewed in the context of age, obesity, a history of impaired glucose tolerance and concurrent occurrence of worm infestation. Barsiwala *et al* (1976) and Joshi (1984) also reported that use of OCs altered the levels of hormones other than insulin, such as an increase in growth hormone and prolactin. Indian scientists have also reported that combination regimens did not alter routine liver function parameters (Mehta *et al* 1981; Bamji *et al* 1981). Altered levels of vitamins both in blood and tissues (Joshi 1984), especially thiamin (Bamji 1978), tryptophan (Ahmed *et al* 1975) and vitamin C levels (Kalesh *et al* 1971) and altered level of zinc and copper were also reported (Prasad *et al* 1975; Donde *et al* 1980). The metabolic effects of contraceptive steroids has been reviewed extensively by Bajaj *et al* (1987).

3.1a Health benefits and risks of OC's: OCs provide not only protection against pregnancy but also have beneficial effects on the life threatening diseases and conditions that impair the quality of life. OC use is associated with decrease in the incidence of ovarian epithelial cancer, endometrial cancer, pelvic inflammatory disease, ectopic pregnancy, benign breast disease, iron deficiency anemia and formation of functional ovarian

cysts (CDC 1983a, b). However, there are controversies regarding the safety of long-term use of OCs, particularly on the development of neoplasia, effects on the cardiovascular system and stroke. The possible role of OCs in the development of breast cancer has been debated for over three decades. In 1996, the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) published an analysis of the pooled epidemiological evidence from 54 studies in 25 countries (CGHFBC 1996a, b). The data indicated that overall, women currently taking OCs or who have stopped its use within the past 10 years were more likely to be diagnosed with localized breast cancer than nonusers. The data further revealed that the risk was greatest for current users. The duration of OC use did not affect risk of breast cancer. The finding that modest additional risk is greatest during OC use and eventually disappears after a woman stops OC use has important public health implications (Westhoff 1996). Because most women use OCs when they are young, and breast cancer is extremely rare at young age, the number of breast cancer cases attributable to OC use would be quite small. It has also been reported that number of additional cases would be smaller in developing countries, where breast cancer is not very common (CGHFBC 1996a). However, these issues have not yet been resolved and further research is required. Recent studies have suggested that there is no increased risk of myocardial infarction among users of third-generation OCs with no other risk factors (Jick *et al* 1996; Lewis *et al* 1996, 1997). Studies with low-dose OCs in the 1980s and 1990s suggested that the overall risk of stroke was less than what was reported in earlier studies (Thorogood 1998). The multicentre WHO study which is the largest case-control study of stroke and OCs, found an overall relative risk of ischemic stroke of about 3 among OC users. Current OC users who did not smoke, and did not have high blood pressure were at 1.5 times greater risk than non-users. In contrast, OC users who smoked faced a higher risk (Poulter *et al* 1996). But this study reported conflicting findings on the relationship between dosage and ischemic stroke risk. For haemorrhagic stroke, the WHO study found a slightly increased risk among OC users in general and the difference was statistically significant in developing countries (WHO 1996, 1997).

Thromboembolism is an obstruction of a blood vessel by a blood clot. The most common thromboembolic disorder in OC users is known as venous thromboembolism (VTE), or deep vein thrombosis, which involves clots that form in veins deep in the leg. A WHO multicentric study, conducted from 1989 to 1993 (Poulter *et al* 1996), and three smaller studies in the mid-1990s (Bloemenkamp *et al* 1995; Jick *et al* 1995; Spitzer *et al* 1996) found that modern low-dose OCs pose less risk of thromboembolism than indicated by earlier studies that

involved mostly first generation pills. In a new case-control study, the risk of VTE was reported to be about three times greater among users of second-generation OCs than among women not using OCs, and about six times greater among users of third-generation OCs containing desogestrel and gestodene (Farley *et al* 1997). Major multicentre studies to evaluate the safety of OC use and contraindications regarding its use, have not been carried out in India possibly due to low prevalence of OC use. Further, the psychosocial reasons for the low compliance of OC use in India deserves closer attention by family planning advisors and care providers.

3.2 Injectable contraceptives

3.2a Progestogen-only injectable: The development of injectable progestogen-only contraceptives resulted from a growing understanding of steroid hormones and the research that eventually led to the development of combined oral contraceptives. Progestogens that have been used so far in "progestogen-only" contraceptives are chloromadinone acetate, desogestrel, ethynodiol diacetate, levonorgestrel, lynoestrenol, medroxyprogesterone acetate, norethisterone, norethisterone acetate, norethisterone enanthate, norgestrel, norgestrienone and progesterone. Of these, norethisterone enanthate and medroxyprogesterone acetate are available worldwide as progestogen-only injectable contraceptives and their formulation has remained unchanged since their development in the late 1960s and early 1950s respectively (WHO 1999).

Progestogen-only contraceptives prevent ovulation (Lande 1995) by inhibiting gonadotrophin secretion, as in OCs (Kleinman 1990).

Norethisterone enanthate (NET-EN) is a long-chain ester of norethisterone. It is commonly used as a 200 µg dose, given every eight weeks or two-months, although in some programmes it is given on a two-month schedule for the first six-months and every three months, thereafter (Lande 1995). NET-EN (200 µg), given at two or three-monthly intervals, has been evaluated extensively for its efficacy and side effects in multicentre studies conducted by the Indian Council of Medical Research (ICMR 1990; Datey *et al* 1995). The method is effective; but the discontinuation rate for bleeding disturbances and due to other medical and personal reasons is very high. A pre-programme introductory study carried out in B and C type post-partum centres and primary health centres of the country have revealed that this method could be an additional choice in the programme and should be made available under medical supervision at those urban family welfare centres where adequate facilities for screening, counseling and follow-up care are available.

Depot medroxyprogesterone acetate (DMPA) is administered as an aqueous microcrystalline suspension at a dose

of 150 µg once in 90 days (Lande 1995). DMPA is highly effective in preventing pregnancy. In an Indian study, carried out to assess usefulness of DMPA in the National Family Planning Programme, 138 women participated for a total of 907 women-months; no pregnancy occurred (Mukherjee *et al* 1980). But the discontinuation rate due to severe menstrual disturbances were very high. Approximately, 32% of women discontinued after the first injection and another 38.8% discontinued before receiving the third dose. Similar observations were reported by WHO in a multicentric study conducted in 13 countries (WHO 1983). While 1,587 women participated for 20,550 women-months over a two-year period, only 3 pregnancies occurred. The discontinuation rate ranged between 33.3 to 75.0 and 49.5 to 91.3 per 100 women at one and two years of use respectively. The major reasons for discontinuation were menstrual irregularities, weight gain, and headache. DMPA has been approved for use as a contraceptive in over 100 countries where an estimated 10 million women have used this method. The Drug Controller-General of India, after reviewing available global data on safety and efficacy of DMPA, has recommended its use for marketing, but only when prescribed by a gynecologist.

3.2b Estrogen-progestogen combination injectable: Irregular bleeding is a major disadvantage in the use of progestogen-only injectable contraceptive. To overcome this problem, combined estrogen-progestogen injectable contraceptive preparations were developed and evaluated in several dose-finding studies worldwide, including in India (ICMR 1985). Two preparations which have undergone extensive clinical evaluation are 25 µg DMPA plus 5 µg estradiol cypionate (Cyclofem) and 50 µg NET-EN and 5 µg estradiol valerate (Mesigyna) (WHO 1993). ICMR (1990) conducted a randomized phase-III clinical trial in 849 subjects for 7,817 woman-months, comparing the efficacy of Mesigyna given at monthly or at two-monthly intervals. The results showed that the pregnancy rate with one-monthly injections (0.2 per 100 users) was less than with two-monthly injections (1.1 per 100 users). In addition, subjects using monthly preparations reported a better bleeding pattern. The high contraceptive efficacy of Cyclofem and Mesigyna has been confirmed by WHO and other agencies in phase-III clinical trials which were carried out in 9,793 women for 1,02,058 women-months of use (WHO 1993). More than 65% of women showed predictable regular cycles. Discontinuation due to abnormal bleeding pattern was less than half as seen with progestogen-only injectable contraceptive. As both Cyclofem and Mesigyna have been recommended as safe and effective injectable contraceptives, with proper counselling and service delivery, it should be possible to add these combination regimens to the existing range of contra-

ceptive methods available in Family Planning Programme. ICMR is planning to initiate clinical evaluation of Cyclofem shortly.

3.3 Contraceptive implants

Subdermal implants releasing progestogen slowly over a long period of time provide long-term, reversible contraception. The prototype, Norplant[®], consists of six silicone rubber (silastic) capsules, 2.4 mm in diameter and 3.4 cm long, which are inserted under the skin of the forearm or upper arm and provide contraception for five years.

Subdermal implants inhibit ovulation through suppression of LH and FSH and exert progestogenic effects on the cervical mucus and the endometrium (Kleinman 1990; McCauley and Geller 1992). Indian scientists conducted safety and efficacy studies using different kinds of implants. Implant D which was identified by Srivastava *et al* (1973) used norethindrone acetate with an average release rate of 128 µg/day and a calculated functional life of 10 months. Bhatnagar *et al* (1975) administered implant D in 876 women for 3,975 women-months of use and showed high contraceptive efficacy. The pregnancy rates at 7 and 8 months of use were 2.3 and 3.9 per 100 woman months, respectively. The cumulative removal rate for medical and personal reasons was 7.5% at the end of 8 months. These data suggested that development of slow-releasing devices was an attractive option for long-term contraception. Norplant[®], consisting of six capsules and Norplant[®]-II, consisting of two-covered rods and containing levonorgestrel developed by the Population Council, New York, USA, were evaluated by ICMR (1986) in 172 women who used these devices for up to 2 years and did not show method failure. The continuation rates with both devices were similar and were 80 and 65 per 100 users at the end of the first and second years of use, respectively. Norplant[®]-II was preferred, as it was easier to insert two rods as compared to the six rods in Norplant[®]. ICMR conducted a multicentre phase-III clinical trial with Norplant[®]-II and evaluated them for over 5 years of use (ICMR 1993). A total of 1,466 women were observed for 52,849 women months. The cumulative method failure rate was 0.8 per 100 user and continuation rate at 5 years was 42.1% (ICMR 1993). In a recent ICMR study informed contraceptive choice was evaluated by the method mix approach. A total of 8,077 women were given a balanced presentation of all available contraceptive methods. The data showed that the Norplant[®] was the first choice in 35% of women (Baveja *et al* 2000).

Norplant[®] is registered in 60 countries and has been used by about 6 million women worldwide (Fraser *et al* 1998). The cumulative pregnancy rate at the end of 5

years is approximately one per 100 women. Ectopic pregnancy rate is correspondingly low, 0.3 per 1,000 women-years. One of the major advantages of Norplant[®] is its long-term effectiveness. At the end of 5 years, almost 25% of the Norplant[®] users had requested its removal because of bleeding problems and another 15% for medical problems including headache and weight gain. Difficulties in removing the implant are also another problem associated with Norplant[®]. Like the injectable progestogen-only contraceptives, progestogen implants also cause amenorrhea or frequent or irregular bleeding in most users and are more costly than many other methods (McCauley and Geller 1992).

To reduce the incidence of side effects and the number of implants to be inserted, new implants releasing 3-keto-desogestrel, reformulated Norplant[®]-II and Implanon (single rod) have been developed. Clinical trials to evaluate their safety, efficacy and acceptability need to be carried out in order to explore the possibilities of their possible introduction in the Family Planning Programme of the country.

3.4 Intrauterine devices

The practice of inserting an object into the uterus to prevent pregnancy has a long history. Many of the issues that relate to the safety and effectiveness of IUD's which are in use today were of concern when the first "modern" IUD was introduced earlier in this century. IUD's are available in all the organized national family planning programmes in most parts of the world. Currently, IUD's are used by some 130 million women worldwide (WHO 2000). From a programmatic perspective, the most important research relating to IUD's is comparison of the efficacy and safety of the various types of available IUD's. For many years, the Lippes loop was the device most widely used by family planning programmes worldwide (Baker 1983). But, in attempts to diminish side effects like pain and bleeding which can lead to discontinuation, a number of new IUD's have been introduced.

During the early 1970s, several IUDs were evaluated for their efficacy, safety and acceptability and included CuT 200, CuT 220C, CuT 380A, CuY and Cu7. Indian scientists also developed two IUD's i.e. Soonawala's CuY and Merchant's CuR during 1970s. Based on the results of the clinical trials under taken by ICMR (Tejuja *et al* 1974), CuT 200 was recommended for inclusion in the National Family Welfare Programme in 1975. In a multi-centre comparative study, 1,905 women were randomly allocated one of the four IUD's i.e. CuT 200, CuT 220, CuT 380Ag, and a levonorgestrel (LNG) releasing device, and observed for 45,683 women-months of use. Method failure was not observed with the LNG-IUD; the cumu-

lative failure rate per 100 users was minimum in CuT 200C (0.3) users in comparison to CuT 380 Ag (1.0) or CuT 220C (1.6) users, at 36 months of use. On the other hand, the continuation rates were significantly lower with the LNG-IUD, in comparison to the other devices. The risk of expulsion was comparable for the four devices and ranged between 8.3 to 16.6 per 100 users (ICMR 1989). These studies indicate the advantage of IUD's since they are long acting, relatively easily removed and fertility returns rapidly after their removal. In another study, ICMR evaluated the performance of CuT 200 and CuT 380A and found them satisfactory in terms of efficacy and continuation rate up to 5 year of use. CuT 200 was recommended for use up to 5 year of duration in the National Family Welfare Programmes (Kambo *et al* 1998).

The main reasons for discontinuation of use of IUD are the side effects (pain and bleeding) and expulsion of the device. These side effects are due to the relative size of the frame of the IUD and its shape. To avoid these problems, WHO compared a "frameless" IUD with TCu 380A and tested it in over 2000 women. The interim data after seven years of use showed that the expulsion rates with the frameless IUD were no better than with the CuT 380A, and indeed were worse after the first year of use. The study was terminated in 1997 and since then an improved version of the frameless device has been developed but has not been studied yet in comparative trials (WHO 2000).

3.5 Contraceptive vaginal ring

Women's health advocates have argued that women need contraceptive methods that are under the control of the user and are long-acting without any side effects. The contraceptive vaginal ring is the only form of long-acting contraceptive, which meets these requirements. The vaginal ring can also be worn continuously for a number of weeks, its use is not coital related, and fertility returns quickly after it is removed. Vaginal rings impregnated with either progestogen-only or a combination of estrogen and progestogens have undergone extensive evaluation. But, menstrual disturbances, lesions in some women and vaginal irritation have hampered the widespread use of vaginal rings so far. The main reasons for discontinuation of LNG-releasing vaginal rings, in India were menstrual irregularities (36%), vaginal irritation or increased vaginal discharge (23%) and expulsion (6%) (Buckshee *et al* 1990). The rate of intrauterine pregnancy in LNG-releasing contraceptive ring was reported to be 4.5% and discontinuation rate at one year of use in a WHO study conducted in 1,005 women (WHO 1998) was 66%. Since vaginal lesions and irritation were reported to be due to

the texture of the silastic ring, WHO planned to develop a more flexible, higher-dose vaginal ring which released 35 µg LNG per 24 h. However, no further work was carried out on this product due to difficulties in obtaining these rings at a reasonable cost (WHO 2000).

3.6 Barrier methods

Barrier methods are effective in preventing pregnancy as well as the transmission of sexually transmitted disease (STD). Since this method does not involve the introduction of hormones into the body, barrier methods are more acceptable and inexpensive making them an attractive-choice of contraception (Rosenberg *et al* 1995). But the acceptability of barrier methods like diaphragm by women in India was very low (ICMR 1996–97). Contraceptive vaginal pessary (such as 'Today') did not find acceptance in India due to high discontinuation rate and unplanned pregnancy (ICMR 1996–97).

3.7 Natural methods of family planning

Rhythm or calendar method is the most commonly used method of natural family planning worldwide. But scientific evaluation of a method for determining a woman's fertile period when abstinence should be practiced is lacking. Billing Ovulation Method was tested in India in a multicentric study. The study was carried out based on single index cervical mucus parameter and showed an encouraging use-effectiveness of the method indicating method failure as low 1.5 ± 0.3 and use-failure 15.9 ± 0.8 per 100 users at 21 months (ICMR 1996).

4. New methods of fertility regulation in female

It is well known that contraceptive needs change during a couple's reproductive life, because of changing cultural, religious and reproductive needs. In addition, many couples do not use modern methods for the fear of side effects. To meet the unmet needs of the couples a wider range of fertility regulation methods should be made available. Research is going on worldwide for the development of improved versions of existing technologies as well as the development of new methods.

5. Levonorgestrel butanoate – a three-monthly injectable contraceptive

Although DMPA has been used worldwide, amenorrhea, weight gain and delayed return of fertility on withdrawal of injections are associated with its use. Therefore,

scientists have been investigating alternative injectable contraceptives, which may offer significant clinical improvement over DMPA.

Among the large number of progestogens screened, LNG-butanoate (LNG-B) was found to be effective at a much lower dose than DMPA and hence would impose a lower body burden of synthetic steroid (WHO 2000). Animal and clinical studies conducted by WHO have focussed on achieving the clinically acceptable formulation (WHO 1998). Once a clinically acceptable formulation is developed, pharmacokinetic and tolerance studies in animal models as well as clinical trials in human will be carried out.

6. Immunocontraception

The contributions of Indian scientists towards the development of an immunocontraceptive for women are considerable. Foremost among this, is the contribution of Talwar and colleagues in the development of a vaccine for inducing anti-hCG antibodies. Phase-II trials using hetero species dimer-hCG vaccine showed high efficacy with one pregnancy in 1,224 cycles (Talwar *et al* 1997). A biodegradable system using microspheres for delivery of the vaccine has been reported (Singh *et al* 1995). Riboflavin-carrier protein (RCP) has been tested as antigen to suppress fertilization in animal models (Karande and Adiga 1991). Active immunization with denatured RCP reduced fertility of rats and monkeys markedly (Adiga *et al* 1997). Gupta and associates have used epitopes of zona pellucida glycoproteins to develop an immunocontraceptive. Infertility was induced in female bonnet monkeys by immunization with porcine zona pellucida glycoprotein-ZP3 and recovery was obtained when antibody titers declined (Gupta *et al* 1995; Kaul *et al* 1996). The successful development of any immunocontraceptive for women depends on obtaining uniform titers in subjects which can be maintained for prolonged duration and without cross reaction with non-target tissues.

7. Anti-progestogens

Anti-progestogen like lilopristone (ZK 98734), onapristone (ZK 98299) and mifepristone (RU 486) show potent anti-progestational and variable degrees of anti-glucocorticoid activities. Ghosh and associates at the All India Institute of Medical Sciences evaluated the ability of mifepristone to prevent pregnancy in rhesus monkeys. Their studies showed that, (i) mifepristone given during follicular phase did not prevent implantation (Ghosh *et al* 1997), (ii) complete pregnancy protection occurred when mifepristone was given as a low dose single adminis-

tration, during early luteal phase (Ghosh and Sengupta 1993). These investigations established that the anti-nidatory action of luteal phase mifepristone was related to changes in endometrial prostaglandin concentration during the implantation window (Nayak *et al* 1997), mediated through a multifactorial mechanism (Nayak *et al* 1998). These authors have emphasized the need for simple methods to detect ovulation, if mifepristone is to be used as a once-a-month, early luteal phase contraceptive. Scientists at the Institute for Research in Reproduction, Mumbai have studied the effects of onapristone (ZK 98299) on pregnancy and fetal outcome in bonnet monkeys (Puri *et al* 1990). These scientists also reported luteolysis and pregnancy failure due to the action of lilopristone (Puri *et al* 1992). These antiprogestogen have direct inhibitory effects on the endometrium as well as on the hypothalamo-hypophyseal axis and therefore have a potential for intercepting a wide range of progesterone-dependent reproductive processes.

Mifepristone (RU 486) has been used as an abortifacient but when administered alone its efficacy is lower than the available alternative method e.g. vacuum aspiration or prostaglandin therapy (Baird 1990). ICMR (1994a) carried out a dose-finding study with two different doses of mifepristone each, in combination with two doses of 9-methylene-PGE₂ gel for termination of pregnancy. Data indicated that 200 mg mifepristone followed by 5 mg, 9-methylene-PGE₂ gel was as effective as 600 mg mifepristone followed by 3 mg or 5 mg, 9-methylene PGE₂ gel without any serious side effects (ICMR 1994a). Recently, ICMR (2000) conducted a multicentre, randomized, comparative clinical trial with 200 mg mifepristone followed by either 5 mg meteneprost (9-methylene PGE₂ vaginal gel) or 600 µg oral misoprostol (PGE₁) for termination of pregnancy within 28 days of a missed period. The results indicated a success rate of 84.6% and 87.7% in groups I and II, respectively without any life threatening side effects. The results of these studies have indicated that medical methods of abortions offer a choice for termination of early pregnancy to the woman as their success rate and side effects are within the acceptable range. However, these methods require the requisite emergency backup facilities for surgical evaluation and blood transfusion in the clinics providing the services.

8. Use of plant products for female contraception

The Task Force on Plants for Fertility Regulation set up by the World Health Organization (WHO) identified approximately thirty plants demonstrating anti-implantational activities. None of these have reached the stage of clinical evaluation (Chaudhury 2001). However, three plants from

India have shown promise in their use in female contraception i.e. *Hibiscus rosa-sinensis* (Tewari 1974); *Vicoa indica* (Chaudhury 1985) and *Embelia ribes* (Joshi *et al* 1977). The combination of *Embelia ribes*, Borax and *Piper longum* have been tried in phase-I clinical trials at three centres in the country. The results of the trials are encouraging and it is expected that phase-II clinical trials will begin soon (Chaudhury 2001).

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