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CONTRACEPTIVE RESEARCH AND DEVELOPMENT DURING THE FIFTY YEARS OF INDEPENDENCE IN INDIA: ACHIEVEMENTS AND DESIRED GOAL

The Family Welfare Programme of India is to be complimented for substantially reducing the burden of reproductive ill-health of people during the last fifty years. Marked reduction in the infant and maternal mortality rates, decrease in the total fertility rate and increase in life expectancy for both men and women are testimonies to the achievements of the Programme. However, in spite of these achievements we are far away from the desired goals. The population of India has increased by over 600 million people since independence. Moreover, there is a visible large inbuilt momentum for continued growth of the population over the next several decades as over 45% of the women in India today are in the reproductive age group of 15-44 years. At the present growth rate of a little over 2%, the population will cross the one billion mark by the turn of the century. The coming years are thus very crucial for the survival of the people of India. The actions taken now to improve the reproductive health (RH) of people and particularly to control population growth will determine the quality of life in the years to come.

Numerous factors have contributed to the increase in population. Some of these are low age at marriage; unmet needs for contraception including poor access to health facilities; low status of women; low female literacy; perceiving children as assets for old age and not taking risk due to high infant mortality. Low contraceptive prevalence was probably the most killing factor responsible for high population growth and this in turn had a bearing on other components of RH such as high incidence of unwanted pregnancies and induced abortions, high infant and maternal mortality and increasing incidence of sexually transmitted diseases (STDs).

The Programme of Action of the International Conference on Population and Development (ICPD) held in Cairo in 1994 has acknowledged the advances made in developing a greater range of safe and effective modern contraceptive technologies and has also emphasized that many people, particularly men, still cannot find a family planning method that suits their needs. The ICPD has emphasized the need for a wider range of safe and effective methods.

Indian scientists have played a commendable role in the development of contraceptive technologies over the last five decades. The Indian Council of Medical Research (ICMR) and some other national agencies including the Department of Biotechnology, Department of Science and Technology and Council of Scientific and Industrial Research have provided enormous technical and financial inputs for the success of research programmes in these areas.

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This article is a tribute to the Indian scientists for their endeavours during the post independence era to develop contraceptive technologies to improve the RH of people. The article also addresses some of the desired changes in the expression and perception of needs for fertility regulating technologies, especially in relation to the new concepts of RH expressed at the ICPD and the Fourth World Conference on Women held in Beijing.

ACHIEVEMENTS

The research contributions by Indian scientists have led to evaluating and improving the safety, efficacy and acceptability of a number of contraceptive methods, and the development of new methods of fertility regulation. In addition, the studies elucidating the intricate mechanisms regulating fertility and the new hypothesis proposed by them have provided the fundamental base for the development of contraceptive technologies.

EVALUATION OF THE SAFETY AND EFFICACY OF CONTRACEPTIVE METHODS

The ICMR through a series of multicentric clinical trials and many scientists at their own initiative have carried out a number of studies evaluating newer contraceptive methods for their safety, efficacy, side effects and continuation rates. The information derived from such studies on the Indian population suggests that a number of contraceptives, in particular the use of oral pills and copper (Cu)-bearing intrauterine devices (IUDs), are safe, effective and reversible in preventing pregnancy. Some of the copper IUDs, such as CuT 220C and CuT 380A, are effective for as long as 12 years after insertion, thereby suggesting that the couples need not resort to terminal methods to control their fertility. Improved counselling and better quality of services are essential to improve the acceptance of the available methods and their continued use.

Vasectomy and its Long-term Sequelae

Vasectomy is used by approximately 40 million men world-wide as the preferred method of fertility regulation[1]. In India almost 2% men of reproductive age rely on vasectomy for fertility regulation. It is highly effective and has a low complication rate. However, there have been sporadic reports about possible development of cardiovascular sequelae and an increased risk of prostate and testicular cancer among vasectomized men. Studies carried out under the aegis of the ICMR have shown that vasectomy had no adverse effects on the cardiovascular system[2]. Similarly, a review by the ICMR has concluded that there was no consensus about an increased risk of prostate cancer among vasectomized men[3]. The overall morbidity and mortality rates due to cancer in vasectomized men are equal to or lower than those of community-matched controls. Regarding the association between vasectomy and testicular cancer, follow up of a study funded by the WHO in Denmark involving some 65,000 men who had had vasectomy demonstrated that there was no such association[1]. These observations are quite reassuring to dispel any fear which vasectomized men or those thinking of opting for this approach for fertility regulation might have.

Oral Contraceptives

Oral contraceptives (OCs) containing estrogen and progestin were introduced over 35 years ago. During this period the content of these steroids in OCs has been considerably reduced to curtail the associated side effects without compromising the contraceptive efficacy[4]. The two most widely used OCs contain either a combination of ethinyl estradiol and levonorgestrel or norethisterone (COC) or only levonorgestrel (minipills). More recently OCs containing newer progestins such as norgestimate, gestodene or desogestrel have been developed which help to further reduce the side effects due to the intrinsic androgenic activity of levonorgestrel or norethisterone.

Indian scientists have undertaken a number of studies evaluating the contraceptive safety and efficacy of available preparations. Multicentre studies carried out by the ICMR have shown that OCs are generally safe and highly effective in preventing pregnancy [5,6]. Some of these studies have shown that the progestogen-only contraceptives have an advantage over the combination pills in that they can be used safely by lactating women and by those in whom the use of estrogens is contraindicated. However, the incidence of breakthrough bleeding and method failure rate was slightly more in the minipill users compared to the COC. Studies on the long-term follow up of infants and children exposed for short or long periods to low dose progestins in infancy through their mother's milk did not show any obvious adverse effects on the infants' or children's anthropometric measurements or major systems [7]. However, subtle effects that could go unnoticed cannot be ruled out [8].

In addition to evaluating some of the oral contraceptives, the Central Drug Research Institute, Lucknow, has

developed a nonsteroidal antiestrogen centchroman [3,4-trans-2,2-dimethyl-3-phenyl-4-p-(β-pyrrolidinoethoxy)phenyl-7-methoxychroman], the postcoital or weekly use of which provides acceptable pregnancy protection. Centchroman is being marketed in India as a weekly contraceptive. A dose of 30 mg administered biweekly for the first three months and thereafter at weekly intervals to 377 women volunteers, covered for 3,932 months of use, provided excellent pregnancy protection. No drug related side effects were observed or reported[9]. Babies born to user-failures presented normal milestones. The contraceptive effect was readily reversible and subsequent pregnancies were normal.

In addition to providing contraceptive protection, the use of OCs also provides protection against some of the life threatening diseases and conditions that impair the quality of life. Their use has been shown to be associated with decrease in the incidence of epithelial ovarian cancer, endometrial cancer, pelvic inflammatory disease, ectopic pregnancy, benign breast disease, iron deficiency anaemia and formation of functional ovarian cysts[10,11].

However, there are some concerns and controversies about the long-term effects of the OCs on the development of neoplasia and on the cardiovascular system. A number of studies have found no overall association between OC use and the risk of breast cancer [12,13]. However, some[14] have reported a weak association between long-term use of OCs and breast cancer in young women in general who had early menarche and those who have used the combination pill for long periods of time. The WHO supported multinational case-control study found that women who had ever used OCs had an overall relative risk of 1.15 of developing breast cancer compared with women who had never used OCs[14]. This issue of the possible association of breast cancer with OC use is still controversial and can possibly be resolved by further research in this area. However, considering that the risk of breast cancer in these age groups is low and that such cancers represent a very small proportion of all breast cancers, the association if real is not of significant public health importance. Similarly, it is still not resolved whether the use of OCs, particularly the third generation OCs, have any association with increased incidence of venous thromboembolism, myocardial infarction or stroke[15-17]. It is, however, very clear that if women with risk factors for coronary heart disease are excluded from taking OCs, the incidence of myocardial infarction in healthy women who are taking the pill is not increased.

In spite of the fact that the OCs are quite safe and effective, less than 2% of the Indian women use oral pills to prevent a pregnancy. The issue of compliance deserves closer attention by family planning care providers. Proper counselling and providing balanced information on significant contraceptive and noncontraceptive benefits/risks associated with OCs and services should help improve compliance.

Long-acting Methods

Indian scientists have also made significant contributions to the development of contraceptives which once administered provide pregnancy protection for a long time. Such injectables include subdermal silastic implants, and intramuscular depot preparations containing either only-progestogen or estrogen-progestogen preparations.

Silastic implants

After evaluating silastic implants of varying length, wall thickness, the amount of progestin contained in them and the release rate, Srivastava and associates identified an implant (Implant D) which released norethindrone acetate at an average release rate of 128 μg/day and calculated functional life of 10 months[18]. Administration of these implants to 876 women, who were followed up for 3,975 woman-months, 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[19]. The cumulative removal rate, for medical and personal reasons, at the end of 8 months was 7.5%. These studies revealed that development of slow-releasing devices was an attractive option for long-term contraception.

The ICMR has also evaluated levonorgestrel-releasing Norplant^{R}, consisting of six capsules, and Norplant II, consisting of two covered rods which were developed by the Population Council, New York[20]. No method failure was reported by the 172 women who had used these devices for a period of up to 2 years. 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. In another phase III multicentre clinical trial Norplant^{R}-II was evaluated over a 5-year of use. A total of 1,466 women were observed for 52,849 woman-months. The cumulative method failure rate was 0.8 per 100 users and continuation rate at 5 years was 42.1%[21].

Over the years, clinical studies with Norplant^{R} have involved 55,000 women, the device has been registered in 60 countries and the method has been used by some 6 million women world-wide[22]. The cumulative pregnancy rate at the end of 5 years is approximately one per 100

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women. Ectopic pregnancy rates are correspondingly low, 0.3 per 1,000 woman-years. The major advantage of this method is its long-term effectiveness. However, by the end of 5 years, almost 25% of the Norplant[R] users had requested for its removal because of bleeding problems and another 15% for medical problems including headache and weight gain. Difficult removal of the implant is another associated problem of implant use. In addition to the levonorgestrel releasing implants, implants releasing 3-keto-desogestrel, nomegestrel or nestorone are being developed in an endeavour to further reduce the incidence of side effects and the number of implants to be inserted in a woman's body.

The use of subdermal implants form a good option for fertility regulation for programmes which have adequate service facilities including counselling and provision for training for the providers.

Progestogen-only injectables

A three-monthly injectable depot-medroxyprogesterone acetate (DMPA) has been approved for use as a contraceptive in over 100 countries where an estimated 10 million women have used this method. DMPA is highly effective in preventing pregnancy. In India, studies have been undertaken to assess its utility in the family planning programme. In a study in which 138 women participated for a total of 907 woman-months no pregnancy occurred[23]. However, the discontinuation rates due to severe menstrual disturbances were very high. Almost 32% of women discontinued after the first injection and another 38.8% before receiving the third dose.

Similar observations were made in a multicentre study conducted by the World Health Organization (WHO) in 13 countries[24]. A total of 1,587 women were observed for 20,550 woman-months over a 2 year period in which only 3 pregnancies occurred. The discontinuation rate in the 13 participating countries 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.

A recent survey of first users of DMPA from the USA reported a continuation rate of 28.6% at one year of use[25]. It seems that women who have wider choice of alternative contraception do not prefer to continue using DMPA. The Ministry of Health and Family Welfare, Government of India has not yet approved DMPA for the National Family Planning Programme but has approved its use by private physicians.

Norethisterone enanthate (NET-OEN, 200 mg) given at two or three-monthly interval has also been extensively evaluated for its efficacy and side effects in multicentre studies conducted by the ICMR[26,27]. The method is as effective as DMPA. The discontinuation rates for bleeding disturbances and due to other medical and personal reasons were very high in NET-OEN users and seemed comparable to those with the use of DMPA.

Estrogen-progestogen combination

To overcome the problems of irregular bleeding observed with the progestogen-only injectables, combined estrogen-progestogen preparations have been developed. Several dose finding studies have been carried out in India to determine the optimum dose of the two steroids in the combination regimen[28]. The two preparations which have undergone extensive clinical evaluation are Cyclofem (25 mg DMPA and 5 mg estradiol cypionate) and Mesigyna (50 mg NET-OEN and 5 mg estradiol valerate)[29]. A phase III randomized clinical trial, on 849 subjects observed for 7,817 woman-months, comparing Mesigyna given at monthly or two monthly intervals showed that the pregnancy rates with one monthly injections (0.2 per 100 users) were less than with the two monthly injections (1.1 per 100 users)[26]. Moreover, the subjects using the monthly preparation had a better bleeding pattern.

Phase III clinical trials carried out by the WHO and other agencies in some 9,793 women for 1,02,058 woman-months of use have also confirmed the high contraceptive efficacy of Cyclofem and Mesigyna[29]. More than 65% of women had predictable regular cycles. Discontinuation due to bleeding related problems were less than half of those seen with progestogen only injectable. Both Cyclofem and Mesigyna are thus safe and effective contraceptives. With proper counselling and service delivery it should be possible to add these combination regimens to the existing range of contraceptive methods.

Vaginal rings

The use of a vaginal ring releasing small quantities of contraceptive steroids offers an attractive method of contraception. The device is long-acting, under user's control and is not limited by the constraints of daily administration or coitus related such as the use of condom. Silastic rings impregnated with either combination of estrogen and progestins or only progestins have undergone extensive evaluation. However, menstrual disturbances, vaginal irritation and lesions in some cases have so far hampered the widespread use of vaginal rings.

In a large multicentre study carried out by the WHO on 1005 women the rate of intrauterine pregnancy in levonorgestrel-releasing contraceptive ring was 4.5 per 100 women. The discontinuation rate at one year was 66%. Since the vaginal lesions and irritation was thought to be due to the texture of the silastic ring, the WHO is considering the possible development of a new vaginal ring with higher dose of levonorgestrel [30].

Vaginal ring releasing levonorgestrel has also been evaluated in India. Menstrual irregularity (36%), vaginal irritation or increased vaginal discharge (23%) and expulsion (6%) were the most common reasons for discontinuation[31]. Since most women find this method more suitable for their contraceptive needs, efforts to develop more safe, effective and acceptable rings need to be pursued.

Intrauterine devices

A number of studies have been conducted in India to develop new intrauterine devices (IUDs), to evaluate the contraceptive efficacy of available IUDs and to improve their utilization. Soonawala's CuY and Merchant's CuR are two devices developed by Indian scientists during 1970s. CuT 200 which is offered in the National Family Planning Programme has in particular been extensively investigated for its efficacy and side effects. A multicentre study initiated in early 1970s on 4,357 women, observed over 32,709 woman-months, showed high contraceptive efficacy of the device. The discontinuation rate at the end of two years due to expulsion and medical reasons were 9.4 and 15%, respectively. Almost 22% of the women had the device removed for non-medical reasons[32]. The discontinuation rates due to pregnancy and medical reasons including bleeding disorders and pain were less than those observed with the Lippes loop[33].

In a more recent study, CuT 200 was evaluated in comparison to CuT 220C, CuT 380Ag and a levonorgestrel releasing device [34]. In a multicentre study 1905 women were randomly allocated to one of these four types of IUDs and observed for 45,683 woman-months of use. While no method failure was reported with the levonorgestrel IUD, the cumulative failure rate per 100 users, at 36 months of use, was least with CuT 200C (0.3) as compared to CuT 380Ag (1.0) or CuT 220C (1.6). Continuation rates were significantly lower with the levonorgestrel IUD as compared to the other devices, which were primarily due to higher menstrual disturbances and amenorrhoea. The risk of expulsion ranged between 8.3 to 10.6 per 100 users and was comparable for the four devices.

WHO sponsored clinical research in multicentric, randomized studies have shown that CuT 220C and CuT 380A are effective for at least 12 years of use [35]. The cumulative 12-year intrauterine pregnancy rate per 100 women, with CuT 380A was less (1.9 ± 0.5) as compared to the CuT 220C (7.0 ± 0.6). However, the overall continuation rate at all intervals since insertion was higher with the CuT 220C device, mainly due to higher removal rates for nonmedical reasons with the CuT 380A.

These studies suggest that IUDs provide a reversible non-surgical alternative to sterilization for women requiring very long-term pregnancy protection. However, its use must be properly counselled and the device carefully applied.

Development of New Methods of Fertility Regulation

Approaches for Male Fertility Regulation

Hormonal methods

Testosterone which is essential for the maintenance of spermatogenesis and libido when given in pharmacological doses has inhibitory effects on gonadotrophin secretion and consequently on spermatogenesis. These observations led Reddy and Rao in 1972 to evaluate the effects of long-term treatment with testosterone propionate on spermatogenesis in adult men[36]. Daily intramuscular treatment of men, aged 23-38 years, with testosterone propionate (25 mg/day) resulted in complete suppression of spermatogenesis by 60 days. The libido and potency of these men were not affected. The inhibitory effects on spermatogenesis were reversed within 150 days of the stoppage of treatment. This study demonstrated the feasibility of a hormonal method for fertility regulation in normal men.

The lead established by the Indian scientists was taken up by many research centres in the world to develop male hormonal methods of fertility control. The major emphasis of the research programme was to develop more potent androgens so that the need for daily administration of the drug could be avoided. Using a relatively longer acting androgen, testosterone enanthate, the WHO has completed two clinical multicentric trials and has confirmed the contraceptive potential of androgens in men[37,38]. A total of 670 adult men from 9 countries volunteered for the two studies. Weekly administration of 200 mg testosterone enanthate caused azoospermia in 425 men and oligospermia in another 81. The 506 men started relying only on testosterone enanthate as a contraceptive after the treatment had induced either azoospermia

or oligospermia in them. Only five pregnancies occurred in the partners of these men. The overall pregnancy rate in the two studies was 1.2 per 100 person years which was superior to that achieved with condoms or the withdrawal method. The fertility or sperm production was restored within 7 months after the treatment was stopped. High level of acceptability was found in both the recipients and their partners in spite of the need for weekly injections.

In addition, studies are on to evaluate androgen in combination with progestogen as a male contraceptive[39]. In the combination strategy, progestogen is to primarily block gonadotrophin release and consequently steroidogenesis whereas low doses of androgens are to maintain libido. Studies have shown that oligospermia and azoospermia are achieved much faster and in more number of subjects using a combination regimen as compared to androgens alone. The combination regimen may be preferred over the androgen only regimen as it may reduce the potential for lipid, behavioural and prostate changes that could arise from the continued exposure to androgen alone.

These studies supported the idea that androgens either alone or in combination with progestins could be used as male contraceptives. However, availability of a longer acting preparation will be a distinct improvement and more attractive. Studies carried out with testosterone buciclate have shown that a single injection can provide sustained levels of testosterone for 3-4 months[40,41]. Alternatively there is a need to develop formulations and delivery systems such as slow-release biodegradable implant; testosterone incorporated into sustained-release delivery systems such as the biodegradable copolymer microspheres; and long-acting testosterone esters which on hydrolysis release the biologically active form of testosterone in the body which can help obviate the need for frequent systemic administration.

Vas occlusion

Vasectomy is highly effective and has a low complication rate but its more widespread acceptability is affected by the need for a surgical intervention; and that the procedure must be considered permanent as reversal is difficult and the success rate, as determined by subsequent fertility, is low. Although the advent of no-scalpel vasectomy has considerably reduced these concerns, and the success rates of vasovasectomy are improving, an approach is needed that is easier to perform and more predictably reversible if a greater number of men and couples are to find this type of method attractive.

Guha and associates have shown that injection of styrene maleic anhydride (SMA, 60 mg) in a solvent system of dimethylsulphoxide into the vas deferens induces complete azoospermia[42]. The phase I clinical trial and continuing follow up of the subjects over a period of seven years have demonstrated that the procedure does not lead to any clinical complications in the urogenital system and other parts of the body. In the phase II study, 12 adult healthy men were administered the drug and followed up for a period of one year. These volunteers and their wives did not use any other form of contraception during the study period. Regular monthly semen examination showed azoospermia in all 12 men. The treatment was safe and provided pregnancy protection during the one year study period. The results of recent preliminary studies carried out in non-human primates and men have shown that the process can be reversed by flushing out the SMA plug into the urethra[43]. Hopefully, vas occlusion using SMA will develop into an acceptable method of male contraception.

More recently, liquid silicone is also being tried to form cured-in-place plugs following injection in the vas. However, the results of the initial studies carried out in Indonesia and China have shown high frequency of vas rupture following percutaneous intravasal injection of silicone[44] and the studies carried out in the Netherlands have shown poor occlusion rate as evidenced by a relatively high number of sperm in the ejaculate compared to vasectomy cases[1]. These studies need to be extended to determine the optimum volume and pressure characteristics needed to achieve complete vas occlusion without causing any damage to the vas.

Immunological methods

The antigenic nature of hormones, spermatozoa, secretory products of accessory glands and tissues of the reproductive system have been utilized to target them for contraception by using actively or passively induced antibodies to these substances. Rao and associates at the Institute for Research in Reproduction (IRR), Mumbai, showed that antibodies to spermatozoa could block fertility. These investigators proposed in early 1960s that the presence of autoantibodies to spermatozoa in men or iso-antibodies in some women could be the cause of infertility[45]. These authors further demonstrated that the buffalo seminal plasma contained at least 16 antigens, and spermatozoa at least 7, of which 4 were common to seminal plasma. These pioneering observations by the

Indian scientists have provided leads to develop a sperm vaccine based on identification of suitable surface-expressed epitopes that are sperm-specific, adequately immunogenic and involved in fertilization.

Sperm-surface antigens

The IRR scientists have identified a 80 kDa protein on the sperm surface using circulating antisperm antibodies from infertile women as probes[46]. The preliminary studies show that active immunization with this protein results in infertility in both male and female rats. This protein has been sequenced and studies are being extended to determine the N-terminal or internal fragment of the native 80 kDa protein, immunization against which might have contraceptive potential.

Scientists at IRR have also generated a panel of monoclonal antibodies (MAb) to identify sperm membrane antigens which may play a role in sperm function[47]. One of the MAbs, D_2G_4 was found to react with the 26 kDa protein present on the acrosomal region of mouse and human spermatozoa. This 26 kDa antigen is also present in the cauda epididymis and is regulated by androgens. The antibodies directed to the 26 kDa protein had antifertility effects in both male and female mice[48]. These studies suggest that sperm maturation antigens are particularly suitable for immunocontraception as in the male the antibodies inhibit post testicular modulation and are not expected to interfere with testicular function. The gene encoding the 26 kDa epididymal protein has been cloned using a monkey epididymal cDNA library and is being sequenced. Working on similar approaches, Shaha and Seshadri at the National Institute of Immunology (NII), New Delhi, have identified two proteins of 94-96 kDa and 40 kDa on the sperm surface, the antibodies against which blocked sperm-oocyte interaction in rodents[49].

FSH vaccine

Another immunological approach being developed by Indian scientists is based on the bioneutralization of follicle stimulating hormone (FSH). FSH has specific receptors on the Sertoli cell membrane and blockade of FSH inhibits spermatogenesis without affecting testosterone biosynthesis. Moudgal and colleagues at the Indian Institute of Science, Bangalore, have shown that immunization of bonnet monkeys with ovine FSH (oFSH) generates antibodies which disrupt spermatogenesis, leading to oligospermia and infertility[50].

A limited clinical trial carried out on 5 adult men showed that active immunization with oFSH produced antibodies which bound and neutralized bioactive human FSH. The antibody produced was specific for FSH and no significant changes in the values of related glycoprotein hormones (LH/testosterone and TSH/thyroxine) were recorded. Seminal plasma transferrin, a marker of Sertoli cell as well as of seminiferous tubular function, showed reduction (30-90%) following immunization with oFSH. Preclinical and clinical toxicology studies revealed that oFSH vaccine at the doses tested was free from toxicity. Adopting such an approach for male contraception appeared attractive, as it had no effect on serum testosterone and libido, the problem that besets other steroid-based male contraceptive procedures.

Inhibin and related peptides

Inhibin was initially thought to be a protein of testicular origin and having a specific function of inhibiting the secretion of FSH. However, over the years, a number of inhibin and inhibin-like substances have been identified with multiple effects. Some of the inhibins have also been suggested to be secreted by the prostate or other male accessory reproductive organs[51]. Sheth and colleagues from IRR have undertaken extensive work on the human seminal plasma inhibin (HSPI)[52]. Following isolation and purification the primary structure of HSPI was determined. Further, HSPI (10.4 kDa) was shown to be sperm-coating protein of prostatic origin having potential for immunocontraception. This prompted the group to further identify and synthesize sequence segments that might mimic the immunobiological activity of the native protein. The N-terminal 1-17 (R-17) and C-terminal 67-94 (R-28) sequences are two such peptides. Studies (IRR-unpublished observations) have shown that active immunization with R-17 induced infertility in male rats.

Approaches to Female Fertility Regulation

Clomiphene citrate

Clomiphene citrate, a non-steroidal agent, was shown in early 1960s to have gonadotrophin-suppressing, ovulation inhibiting and blastotoxic actions in rats[53]. These observations raised hopes of developing clomiphene citrate as a potential antifertility agent. However, subsequent studies by Roy and associates showed that clomiphene citrate had estrogenic and antiestrogenic actions which could be manifested at the same dose levels depending upon the hormonal milieu[54]. These investigations also showed that its antifertility effects were limited to laboratory animals and could not be confirmed in humans. In none of the

11 ovulatory women, who received clomiphene citrate in doses of 50 to 200 mg per day for varied duration ovulation was suppressed[55]. On the contrary, administration of clomiphene citrate induced ovulation in women. Clomiphene administration to women with inadequate luteal phase resulted in improvement in luteal phase. It is the result of these observations that the clomiphene is being widely used for induction of ovulation in patients desiring pregnancy and in several other clinical conditions.

Antiprogestins

Antiprogestins such as RU 486, ZK 98.299 and ZK 98.734, intercept progesterone action at the molecular level of receptor binding, and have the potential to terminate early pregnancy[56]. RU 486 which has undergone extensive clinical evaluation is commonly referred to as the "abortion pill" as its oral administration, followed 48 h later by a small dose of a prostaglandin analogue, terminates pregnancy in almost 95% of the women with an amenorrhoea of less than 63 days.

The studies carried out at IRR have shown that these antiprogestins have direct inhibitory effects on the endometrium as well as hypothalamo-hypophyseal axis and therefore have a potential for intercepting a wide range of progesterone-dependent reproductive processes[57]. Moreover, their effects on the endometrium and the gonadotrophs are dose-related, the endometrium being more sensitive than the gonadotrophs. Low doses of the drugs retard endometrial development and consequently block implantation without affecting ovulation or other menstrual cycle parameters[58]. These drugs have therefore shown potential for further development as a contraceptive where the drug could be taken either daily like a 'mini pill' or once-a-week throughout the menstrual cycle or just during the early luteal phase[59]. Antiprogestins have also shown potential for use as an emergency method of contraception. Studies carried out under the aegis of the WHO have shown that a dose of 10 mg RU 486 when taken within 72 hours of unprotected sex averts pregnancy in almost 80% of instances[30]. The major advantage of developing antiprogestins as contraceptive is that the need for simultaneous administration of estrogens would be obviated and their use is likely to decrease the risk of endometrial and breast cancer through their antiproliferative effects on target organs. Even when used as an emergency contraceptive method the side effects were much fewer compared to the Yuzpe regimen.

Gonadal peptides

Nandedkar *et al*[60] at IRR have identified some novel proteins in the human ovarian follicular fluid which have shown potential as fertility regulating agents. Extensive efforts on the purification and characterization have resulted in the isolation of a 4 kDa protein which when injected into rodents and non-human primates impairs fertility[61]. Studies on sequencing of this protein are being conducted to embark upon extensive preclinical and clinical evaluation of this protein for its antifertility effects.

Immunological methods

Rao and Shahani[62] from IRR had shown in 1961 that human chorionic gonadotrophin (hCG) can act as a true antigen and the antibodies against hCG can neutralise the parent molecule. Antiserum raised in a rabbit immunized with a mixture of hCG and Freund's adjuvant showed serological reactions, characteristic of an immune serum containing specific antibodies. These results provided evidence that protein hormones mixed with adjuvants and injected systemically can elicit serologically active antibodies in the blood which can neutralise the parent molecule. These observations have given impetus to the concept of developing immunocontraceptives.

hCG vaccine

Indian scientists have developed a hCG vaccine which has undergone phase II clinical evaluation[63]. A vaccine consisting of a heterospecies dimer of the β subunit of hCG associated noncovalently with the α subunit of ovine LH and conjugated to tetanus and diphtheria toxoids as carriers when injected to 148 women induced antibodies of high avidity against hCG. In 80% of the women, the antibody titre was more than 50 ng/ml; with only one pregnancy occurring in this group. Some of these women had completed up to 30 menstrual cycles of continuous exposure to the risk of pregnancy. On the other hand, in women in whom the antibody titre was less than 50 ng/ml, 26 pregnancies occurred. The antibody response declined with time, fertility was regained when the titres fell to less than 35 ng/ml. This study presents evidence of the feasibility of a vaccine for control of human fertility.

In this respect the work carried out by Indian scientists to develop a contraceptive vaccine is at the most advanced stage as compared to laboratories in other parts of the world engaged in similar studies.

WHO is also developing a synthetic peptide-based hCG immunocontraceptive[64,65]. It is envisaged that a further 5-7 years of clinical testing and product improvement will be required before a first-generation product will be available. A second-generation, totally synthetic, bioengineered product is also under development by the WHO and could become available within a similar or a slightly more extended time-frame.

Some vaccines originally developed for fertility control are also being evaluated for treatment of hormone-dependent cancers[66]. Recombinant hCG vaccine is in clinical trial in Mexico in lung cancer patients carrying a type of tumour that secretes hCG and its subunits. Similarly, LHRH vaccine is approved for trials in prostate carcinoma patients.

Zona pellucida antigens

The zona pellucida has generated considerable interest as a target for developing immunocontraceptive vaccine. The advantage of this approach would be of blocking pregnancy by acting at the pre-fertilization stage. In this direction, studies carried out by Gupta and coworkers at the NII have centred on delineating the epitopes recognised by MAbs generated against porcine ZP3α and ZP3β[67]. The MAbs against these antigens delayed trypsin-mediated zona lysis and also inhibited the binding of ZP3 to sperm membrane vesicle. It is hoped that the leads taken by Indian scientists in this direction will help in the development of a new effective contraceptive vaccine.

Riboflavin carrier protein

Scientists at the Indian Institute of Science and the IRR have isolated riboflavin carrier protein, a novel estrogen-dependent protein, from the hen's egg white[68]. Immunization against this protein has shown antifertility effects in laboratory animals and non-human primates[69-71]. Scientists at IRR have also identified some epitopes with potential antifertility effects. A synthetic peptide, based upon this epitope, was shown to have antifertility effects in rodents[71].

Herbal Preparations

Indian scientists have identified a number of plants that possess antifertility effects. The ICMR had published a special report on "Plants with antifertility activity" way back in 1966 emphasing the need to explore the antifertility potential of herbal preparations[72-73]. The Central Drug Research Institute, Lucknow has screened about 3,300 plant materials for antifertility activity of which some 67 have shown potential[74]. The plants which have demonstrated interesting antifertility activity in clinical trials include *Hibiscus rosa-sinensis* and *Embelia ribes*. The extract of red petals of the plant *Rudrapushpaka*, collected between October and December, when given orally from day 7 to day 22 of the menstrual cycle prevented pregnancy in all the 22 women[75]. *Embelia ribes* is being used in combination with *Piper longum* and borax as a contraceptive by practitioners of the traditional systems of medicine. When given in high doses for ten days in a cycle, *Embelia ribes* prevented pregnancy in 95% of the women observed for 2,051 cycles over 4 years[76]. In addition, there are a large number of other plants, such as seeds of *Daucus carota, Butea monosperma* and *Sapindus trifoliatis*, which have demonstrated antifertility effects in rodents[77] and there are some, such as *Vicoa indica* known as *banjhauri*, which are being used by people in rural areas at their own initiative and risk to prevent pregnancy[78]. The groundwork done by the Indian scientists in screening a large number of plants with antifertility effects and in identifying the few which need further testing has thus become extremely valuable. However, research in this area has not received continued support.

Immunodiagnostics

Scientists at IRR were the first in the world to develop a simple enzyme-linked immunosorbent assay (ELISA) for the detection of estrone-glucuronide and pregnanediol glucuronide[79,80]. The assay methods for steroid hormones are of considerable diagnostic value in reproductive endocrinology. Similarly, they were the first to develop a pregnancy detection test based on ELISA technology[81]. This test allows detection of pregnancy within 30-35 days from the last menstrual period. The scientists at IRR have also done considerable work on the early pregnancy factor (EPF) which has been observed to be a promising biomarker of pregnancy, and allows detection of pregnancy even before the missed period or 48 hour after fertilization[82]. This method also has immense clinical value in assessing pregnancy wastage and in assisted reproductive technologies where it can be used for detection of fertilization.

DESIRED GOAL

The desired goal of contraceptive research and development should be to empower couples to control their fertility by choice rather than by chance. More and

more people should therefore be provided with a greater range of safe, effective and affordable methods of fertility regulation. They should also be provided with information about the use of contraceptives and services to manage the possible side effects and contraceptive failure, if any. This will enable the couples to have a satisfying and safe sex life, the capacity to reproduce and the freedom to decide, if, when and how often to do so – the essential ingredients of good RH. Fertility regulation in turn will also have bearing on other aspects of RH. The timely use of appropriate contraceptive technologies will help prevent unwanted pregnancy and its consequences, STDs, infertility, and will ensure infant survival and safe motherhood.

Research Needs

New research on developing safe and effective methods of fertility regulation must be guided by the user's needs and perspectives and after assessing the feasibility of product development and service delivery. The prevailing RH indicators should help identify the conditions or problems responsible for creating an unnecessary burden on the RH and decide on the research agenda to address those unresolved problems.

In our country, the infant and maternal mortality rates are still very high. The infant mortalilty rate is approximately 74 per 1,000 live births[83] which is almost ten times of that in many developed countries. Similarly, in India, 1 in 57 women has the chance of dying from complications of pregnancy, childbirth or unsafe abortion during her life time as compared to 1 in more than 17,000 in some of the developed countries[84]. At the prevailing maternal mortality rate of 437 deaths per 100,000 live births more than 100,000 women in India die every year from causes related to pregnancy and child birth[83]. It is estimated that 15,000-20,000 abortion-related deaths occur annually among married, multiparous women in India. Similarly, the incidence of reproductive tract infections (RTIs) and STDs is very high[85,86]. Almost 20% of the eligible couples who do not want children or want to space their children are not using any method of contraception[83]. Moreover, in south-east Asia only 57% of eligible couples have access to contraception at an affordable price as compared to 90% in east Asia.

The above mentioned RH indicators point to the need of integrating technology development with provision of services. Expanding family planning services is an important strategy for reducing the population growth rate, spacing the children and consequently decreasing the infant and maternal mortality rates and reducing the incidences of RTIs and STDs. High priority should be given to the development of male methods of fertility regulation; emergency contraception; and vaginal methods that provide dual protection against pregnancy and STDs. In addition, there is a need to promote basic research to understand the reproductive processes which may eventually lead to the development of newer treatments and technologies.

Expanding family planning options

Male Methods

In spite of the fact that a number of methods have been developed to allow women to control her fertility, the options available to men are rather limited. The male reproductive system, particularly the process of gametogenesis, maturation of spermatozoa and the sperm-egg interaction, is so complex that it has not so far been possible to find an effective intervention that can be converted into a product. Reversible hormonal method has shown promising results but still needs to be developed into a viable product. Antifertility vaccine directed against FSH has entered clinical trial and basic research is being continued on vaccines directed against specific molecules on the spermatozoa or the epididymal secretions. Development of a reversible male method which will help control fertility without affecting the potency will enrich the field of contraceptive research and development. The approaches targeting maturation of spermatozoa in the epididymis or sperm-egg interaction, without interfering with sperm production or secretion of testosterone, may be more acceptable to men.

In addition to the development of male methods of fertility regulation, it is essential to formulate strategies to increase male participation and responsibility in reproductive health. It will help to improve acceptance of available male methods and eventually the wellbeing of the entire family. Some of the ongoing studies at IRR show that lack of initiative, misconceptions about family planning methods, wives and family members objection, fear of surgery in case of vasectomy, lack of knowledge about the methods and poor quality of services contribute to low acceptance of male methods[87]. Further research needs to be undertaken to study the attitude and sexual behaviour of men about fertility regulation, and the factors inhibiting their role and participation in reproductive health so that appropriate intervention studies could be planned to enhance their involvement and responsibility.

Emergency Contraception

Currently available emergency contraceptive methods when used shortly after unprotected coitus can prevent 75% or even more pregnancies[88]. Unfortunately, however, these methods have not been used to their full potential. Research needs to be directed to assess the reasons why these methods are not available to or used by the potential users. This also necessitates research on the risk taking behaviour of people, determinants and consequences of induced abortion including its effects on subsequent fertility, reproductive and mental health and contraceptive practices.

In addition, more biomedical research is needed to overcome the limitations of the most commonly used emergency contraceptives (estrogen-progestin combination, levonorgestrel or danazol) such as: (i) effective only when started within 48 or 72 hours after unprotected intercourse; (ii) two doses must be taken; (iii) relatively high incidence of nausea and vomiting; and (iv) prevents only about 75% of unplanned pregnancies that would have occurred otherwise. Research should be aimed to increase the window of effectiveness of the available methods of emergency contraception, and to increase their contraceptive efficacy to almost 100%. The development of better methods for emergency contraception is therefore a challenging task requiring high priority.

Barrier Methods

The incidences of STDs including HIV/AIDS are gradually increasing in India. It has necessitated development of methods that not only protect against pregnancy but also against STDs. Moreover, increasing emphasis is being placed upon the interrelationship between methods of fertility regulation and STD infection. Areas that need increased attention include barrier methods, both male and female, for fertility control and the prevention of STDs including HIV/AIDS. The interim results of studies supported by the WHO suggest that promoting condom use among couples for dual protection against pregnancy and STDs may be more successful than for prevention of STDs alone.

CONCLUSIONS

The contributions of Indian scientists over the past 50 years have enriched the field of contraceptive research and product development. Some of their contributions were targeted towards the evaluation and improvement of the safety, efficacy and acceptability of promising methods of contraception so that they could be incorporated in the National Family Planning Programme; the development of newer methods of fertility regulation for both men and women; and understanding of the reproductive processes and proposing new hypothesis which may lead to the development of newer technologies. Achievements in these areas have helped in improving the RH of the people and have made us more optimistic for further development of newer contraceptive technologies. It is time that we review our research activities and orient ourselves to meet new challenges resulting from the paradigm shift from a narrow focus on family planning and population control to the broader, holistic concept of RH. Contraceptive research should be viewed in relation to the overall health, social and service context and should have the involvement of potential users in determining the research needs and priorities. Moreover, high priority contraceptive research should be decided after assessing the feasibility of product development and service deliveries.

Author's Note

A sincere and unbiased attempt has been made in this article to acknowledge all those efforts which have contributed substantially to contraceptive development. In view of the large body of data available on this subject, omission of any other significant contribution from this article is inadvertent.

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ICMR NEWS

The following meetings of various technical groups/ committees of the Council were held :

Meetings of the Scientific Advisory Committees :

Institute for Research in Medical Statistics, Chennai	September 28-29, 1998
ICMR Genetic Research Centre, Mumbai	October 7, 1998
Institute for Research in Reproduction, Mumbai	October 8-9, 1998
Regional Medical Research Centre for Tribals, Jabalpur	October 12-13, 1998
National Institute of Virology, Pune	October 15-16, 1998

Meetings of the Expert Group/Technical Advisory Group/Sub-Group and other meetings:

Expert Group on *Argemone mexicana* toxicity	September 19, 1998 (at New Delhi)
Technical Advisory Group on Pharmacology and Toxicology including Traditional Medicine	September 22-23, 1998 (at New Delhi)
Sub-Group on Hepatitis	September 25, 1998 (at New Delhi)
Meeting of the Principal Investigators of the district nutrition project	October 14-15, 1998 (at New Delhi)

Participation of ICMR Scientists in Scientific Events:

Dr. Neeru Singh, Dy. Director, Malaria Research Centre (MRC), Delhi, participated in the II European Congress on Tropical Medicine at Liverpool (September 14-18, 1998).

Dr. A. Roy Chowdhury, Dy. Director, Regional Occupational Health Centre, Calcutta, participated in the X International Symposium on Biological Monitoring in Occupational and Environmental Health at Seoul (September 23-25, 1998).

Dr. A.K. Jain, Senior Research Officer, Institute of Pathology, New Delhi, participated in the V conference of the International Society for Trace Element Research in Humans at Lyon (September 26-30, 1998).

Dr. S.K. Subbarao, Dy. Director (Sr.Grade), MRC, Delhi, participated in the V meeting of the WHO Committee on Molecular Entomology at Geneva (September 27-28, 1998).

Dr. Aruna Dewan, Dy. Director, National Institute of Occupational Health, Ahmedabad, participated in the meeting of the Expert Group on Women and Health– Mainstreaming the Gender Perspective into the Health Sector at Tunis (September 28 to October 2, 1998).

Dr. Vasantha Thavaraj, Asstt. Director, All India Institute of Medical Sciences, New Delhi, participated in the International Conference of the Society of Paediatric Oncology at Yokohama (October 4-8, 1998).

Dr. N.K. Ganguly, Director-General, ICMR, co-chaired the XII meeting of the Joint Working Group of the Indo-US Vaccine Action Programme at Washington D.C. Dr. D.A. Gadkari, Director, National Institute of Virology, Pune and Dr. P.R. Narayanan, Director, Tuberculosis Research Centre, Chennai, also participated in the meeting.

Dr. U.M. Donde, Dy. Director, Institute for Research in Reproduction (IRR), Mumbai, participated in the VIII Asia-Pacific Congress of Clinical Biochemistry at Kuala Lampur (October 11-16, 1998).

Dr. H.S. Juneja, Director, IRR, Mumbai, participated in the regional symposium on Inter-regional Cooperation on Reproductive Health Research : Asia and Pacific at Shanghai (October 12-13, 1998).

Appointments :

Dr. S.K. Subbarao took over as the Director of the Malaria Research Centre, Delhi w.e.f. October 9, 1998.

Honours/Awards :

Dr. G.B. Nair, Dy. Director, National Institute of Cholera and Enteric Diseases, Calcutta, has been awarded the 1998 Shanti Swarup Bhatnagar Prize in Medical Science by the Council of Scientific and Industrial Research for his outstanding work in characterizing a novel toxin in *Vibrio cholerae* and identifying and chacracterizing a new serogroup 0139 causing a cholera pandemic.

Dr. Kalyan Banerjee, former Director of the National Institute of Virology, Pune and Dr. N.K. Ganguly, Director-General, ICMR, have been awarded the Om Prakash Bhasin Awards for Health and Medical Sciences for the years 1996 and 1997 respectively.

ICMR AIDED SYMPOSIA/SEMINARS/WORKSHOPS/COURSES/CONFERENCES

Symposium/Seminar/Workshop/ Course/Conference	Date & Place	Contact Address
Symposium on Alzheimer's Disease and Neurocognitive Disorders	October 3-4, 1998; (at Delhi)	Col. D.S. Goel, Senior Advisor (Psychiatry), Base Hospital, Delhi Cantt-110010.
International Symposium on Temporomandibular Joint Disorders and Chronic Orofacial Pain	October 30-31, 1998; (at Mangalore)	Prof. P.K. Dayal, Organising Secretary of the Symposium, KMC College of Dental Surgery, Mangalore-575001.
Symposium on Current Trends in Autoimmune Diseases Immunology	October 30-31, 1998; (at Lucknow)	Prof. S. Naik, Department of Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow-226014.
XXXI Annual Conference of the Indian Pharmacological Society	December 17-20, 1998; (at Lucknow)	Dr. V.N. Puri, Organisng Secretary of the Conference, Division of Pharmacology, Central Drug Research Institute, Lucknow-226001.

COUNCIL'S TRAINING PROGRAMMES FOR 1998-99

Leprosy

At the Central JALMA Institute for Leprosy, Agra:

- Multidrug Therapy Orientation Course in Leprosy for Medical Officers (October 26-November 6; and December 7-18, 1998).

Reproductive Biology

At the Institute for Research in Reproduction, Mumbai:

- Workshop on Andrology for Clinicians (November 16-30, 1998)

Nutrition

At the National Institute of Nutrition, Hyderabad:

- Postgraduate Certificate Course in Nutrition (December 1, 1998-February 28, 1999).

Occupational Health

At the National Institute of Occupational Health, Ahmedabad:

- Training Course on Environmental Hygiene Practice (November 16-20, 1998).

Biomedical Statistics

At the Institute for Research in Medical Statistics, Chennai:

- Basic Course in Statistics for Medical Officers (November 30-December 6, 1998).

Haematology

At the Institute of Immunohaematology, Mumbai:

- Training Course in Advanced Haematology and Immunohaematology (September 21-October 9, 1998).

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