PREFACE

Fertility control has come to the forefront as a topic of global concern, with important medical, social and political considerations due to the population explosion. In the past 25 years two dramatic developments have occurred to bring the population problem into focus. The first and of foremost importance is the unprecedented population growth, and the second, very significant phenomenon has been the massive migration of populations from rural to urban areas, thus creating disproportionately intense population pressures for many cities and societies.

India being the second largest country in terms of world population, the problem of population control requires urgent attention. At present, some popular methods of fertility control employed on a world wide basis are, surgical sterilization, oral contraceptives, abortion, conventional contraceptives and IUDs, vaginal rings etc., but none of them are cent percent safe and devoid of harmful side effects. Hence, biologists are faced with a herculean task in the search of new contraceptive methods, which should be effective, simple, widely acceptable, cheap and safe.

Contraceptives containing synthetic steroid hormones have been marketed for women in most countries of the world over the past decades. The original products were oral
medications containing a synthetic estrogen and a synthetic progestogen (mestranol and norethynodrel). The single silastic implant for long term contraception in women is a highly acceptable method amongst both rural and urban populations. It has a life span of about seven months. For long term contraception, polylactic, polyglycolic and copolymers of lactic (L+) and Glycolic (G) are being used to fabricate biodegradable implants releasing contraceptive steroids. Other approaches for contraception are investigations on vaginal rings, vaginal barrier contraceptives, postcoital contraceptives, intrauterine devices with or without steroids, and copper devices, use of prostaglandins; vaginal, cervical and subdermal implants etc. Steroid receptors in the human uterus and their blocking with the use of progestins are being investigated to explore alternative approaches to female contraception.

Recently, immunological approach has opened up newer avenues to contraception, but in long term safety trials it failed. Since early seventies, the effectiveness of administering small doses of steroids by intranasal sprays to block ovulation was reported and further work is underway at present.

Voluminous work on female contraception has been carried out, but in males, on the contrary, there are limitations for applying contraceptive measures effectively. But recently,
research on male contraception has received a big boost and now medical experts are in search of, as never before, for a safe and effective oral contraceptive and other contraceptives for men. The CHINESE group of workers have discovered a male contraceptive pill "Contramol", which were found to be 100% effective and their effects were reversible. The results of the clinical trials have given new hope for development of the male pills. The pill "Contramol" contains gossypol, a chemical ingredient of the cotton plant, which is used mainly in the rubber and plastic industries. These results created quite a lot of excitement among scientists working on a male contraceptive, and gossypol is being currently investigated in various countries, including India.

Immunological approach to form antigen against sperm specific antibodies (SSA) also has opened new avenues for development of male vaccines. Two scientists named Alina Lopo and Víctor Vacquier of the University of California recently injected sperms from a marine animal, the sea urchin into rabbits, and derived antibodies against them by processing their blood. Strangely however the SSA reacted not only with sperms from sea urchins, but also spermatozoa from a large number of other animals, such as starfish, sea anemones, crabs, salmon and even rats. Subsequent tests proved that the SSA in fact, combines with a protein present on the sperm
of all the species investigated, and this protein appeared to be vital for the process of fertilization. Further research is required to find out whether such a protein exists also on human sperms. Various studies have been devoted to studying the specificity of antibodies produced by immunization against gonadotrophins. It is well known that LH and FSH are required for normal spermatogenesis. The active immunization against LH or FSH can suppress the functions of the testis and hamper with spermatogenesis, and thus a reduced fertility rate can be achieved. Similarly, various scientists have used LH or FSH antagonist or agonists for male contraception, but so far no successful events have been observed.

Vasectomy has emerged as a leading method of contraception. Two main advantages offered by this technique are (1) that it is a simple out-patient surgical procedure requiring one-time motivation of the patient and (2) that permanent sterilization is achieved. Vasectomy has an end point of azoospermia after 10 to 15 ejaculates and vasovasostomy currently opens up new avenues for reversibility of vasectomy. However, improvements in the surgical techniques of vasectomy are needed to ensure not only easy and quick reversibility but also normospermic condition.
In male contraception, the research deals with vasectomy, vasoligation, occluding the vas with sclerosing agents, development of copper alloy intra-vasal devices and chemical sterilizations. Numerous synthetic progestogens were discovered, differing not only in progestational potency, but also in secondary hormone properties viz., androgenicity, anti-androgenicity, estrogenicity, anti-estrogenicity, glucocorticoid properties etc. These synthetic progestogens are used to inhibit spermatogenesis and sperm maturation. The process of spermatogenesis and sperm maturation are under the control of hypothalamo-hypophyseal-gonadal axis. Biologist are trying to develop new contraceptives, which would impair spermatogenesis and sperm maturation such as various synthetic progestogens. Cyproterone acetate, a synthetic progestogen has effective antiandrogenic and antigonadotrophic effects, hence impaired spermatogenesis and circulating androgen levels, lead to altered sperm count, motility and infertility, but still the effects of cyproterone acetate remain controversial. The results of German group of workers and those of our country, on cyproterone acetate trials in men, are contradictory, so that the antifertility effects of cyproterone acetate in human beings remains a controversial issue.

Recently, emphasis has been focussed on the role of 'inhibin', which is produced by testis and which is under the
control of FSH. Inhibin seems to act on the pituitary by blocking the effect of injected LHRI on FSH in rats, hence hamper with spermatogenesis and cause male sterility.

At present, the research activities represent the largest concerted effort on plants as a source of fertility regulating agents. These might be semi-purified isolates, stabilized and standardized plant extracts, or pure chemical substances of defined structure. More emphasis is being paid on these studies for economic reasons in terms of self-reliance and on the grounds of the potentially greater acceptability of local products. This technique has advantage, as could be taken immediately after intercourse to prevent pregnancy, or once-a-month on a regular basis.

Nutritional deficiency also plays an important role in reproduction. Malnourished animals showed impaired fertility rate, hence precautions should be taken when effects of contraceptives are tested on undernourished human populations.

Currently, male contraceptive pills, cyproterone acetate, nasal spray, inhibin, immunological techniques and vasovasostomy are under clinical trials, whereas, prostaglandins, nutritional deficiency, antiandrogens, occluding vasal sclerosing agents and their reversibility, copper alloy-devices in vas deferens, scrotum and epididymis as well as plant extracts
are being studied as male contraceptive measures.

The present thesis embodies studies on the physiology of the testis, epididymis, seminal vesicle and ventral prostate of rats and guinea pigs, under normal and several experimental conditions with the use of several contraceptive techniques. Special emphasis has been laid in studying the changes in sperm motility, metabolism and morphology leading to infertility. A greater emphasis has also been given to investigate the metabolic role of ascorbic acid in physiology of mammalian epididymis and testis. It is known that the free radical of ascorbic acid, monodehydroascorbic acid (MDHA) is a powerful reductant, by virtue of possessing an unpaired electron. The beneficial role of ascorbic acid in restoration of status quo of reproductive tissues under several altered physiological conditions has led to the suggestion, that, ascorbic acid be administered for prophylactic treatment of volunteers during and after a particular contraceptive treatment, such as vasectomy, administration of cyproterone acetate and other contraceptive drugs. Such a measure does not affect the contraceptive efficacy of the treatment.

On the basis of extensive studies carried out from this laboratory, it has been reported that reproductive tissue metabolism is energized not only by high energy phosphate (∼P)
but also via the paramagnetic electron flow from MDHA, which has stronger reducing properties than ascorbic acid itself. It was observed that tissues having a high tempo of metabolic activity possessed correspondingly a higher turnover of ascorbic acid. Chapter I is introductory one which includes review of literature. In chapter II, the materials and methods used are described in details. In chapter III the results and observations are given, followed by chapter IV, wherein, the results obtained have been discussed with respect to the recent data in the particular field. Chapter V, presents the summary of the work done and chapter VI includes the over all conclusions which could be drawn from the work of the thesis, and also the possible future lines of work which could be undertaken. Lastly, the bibliography has been listed in chronological and alphabetic order.

The work included in the thesis reveals for the first time the physiological response of testis, epididymis and sex accessory glands during different contraceptive techniques, with more emphasis on the role of ascorbic acid, whose levels are enhanced following stress conditions. It is involved in many oxido-reduction reactions, via involvement of its free radical hence more energy yield occurs, which maintain the physiology of testis and integrity of epididymis and sex accessory glands, during and following contraceptive treatment,
without interference with the contraceptive purpose. The thesis work emphasises more on the prophylactic role of ascorbic acid during and after male contraception. As such, the present work is a significant contribution to the existing knowledge in understanding the metabolic role of ascorbic acid in testis, epididymis and sex accessory glands in rendering male contraceptive technique more efficacious.

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