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Review Article

NEW ADVANCES IN CONTRACEPTIVE METHODS

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ABSTRACT

The present review sheds some light on family planning methods and contraceptive dosage forms in use nowadays and new ones under investigation. First, the benefits of family planning for women, men, children, nation and the world are addressed. Then a complete survey about the methods of contraception in use nowadays viz: pills, IUD, vaginal rings, injectables, barriers, natural methods, spermicides, sterilization (female or male) and implants, was included. Additionally, this review emphasized on the future methods that are in different stages of research, development and registration. This stems on the fact that the development of new and improved methods of contraception for both women and men is a key component of the strategy to improve the quality of family planning programs. Of the new methods presented are: Immunocontraceptive methods for female and male, improved IUD's and new pills.

Keywords: Contraceptive Dosage Forms, Family Planning, Female Contraception, Male Contraception

INTRODUCTION

When the U.S. Food and Drug Administration approved it in 1960, the birth control pill was revolutionary. For the first time, couples could safely and reliably plan their families with the help of effective medication. Since then, major strides have been made in contraceptive research and development, and women of reproductive age have many more contraceptive options. Steady progress in the development of safe and reliable modern methods, from the first oral contraceptive pill to IUDs to vaginal rings, has created a wide landscape of choice for women who want to plan their families and space their pregnancies. When women have access to contraception appropriate to their needs, desires, and budgets, the potential benefits are many, including reduced maternal mortality and morbidity, improved infant and child health, and a reduced number of abortions. In addition to its health benefits, family planning allows families and communities to invest more in education and health care and helps reduce poverty. Yet there's still a long way to go. Today, 222 million women in the developing world wish to avoid pregnancy but are not using modern contraception. Reasons for this include lack of access, lack of methods that meet their needs, and fear of side effects. If the needs of these women are met, each year the world could avert another 54 million unintended pregnancies, 26 million abortions, more than 79,000 maternal deaths, and 1.1 million infant deaths¹. Singh

and Darroch¹ stated that achievement of the desired number and healthy timing of births has important benefits for women, families, and societies. To meet the unmet need for modern contraception, countries need to increase resources and improve access to contraceptive services. One group of researchers pursuing the development of new contraceptive methods is the Population Council's International Committee for Contraception Research (ICCR). This network of scientists from around the world was formed in 1970 to design new contraceptive technologies and to conduct clinical trials to test their safety, efficacy, and acceptability. In addition to facilitating research on contraception, the committee strengthens the research capacity of clinical centers in developed and developing countries².

Since the 1960s, family planning programs have helped everyone around the world, first of all the women, to improve their general health. Hence, the number of maternal deaths could fall by one-quarter. Also, many family planning methods have other health benefits, for example, some hormonal methods help prevent certain cancers. Recently, Havrilesky et al.³, found that significant duration-dependent reductions in ovarian cancer incidence in the general population are associated with oral contraceptive pills use. Also, these methods save the lives of children by helping women space births. It was reported that between 13-15 million children under age 5 die each year. If all children were born at least 2 years apart, 3 - 4 million of these deaths would

be avoided. Family planning also helps men and women care for their families. Men around the world say that planning their families helps them to provide a better life for their families. Additionally, family planning improves family well-being. Couples with fewer children are better able to provide them with enough food, clothing, housing, and schooling. For the nations: family planning helps nations develop. In countries where women are having far fewer children than their mothers did, people's economic situations are improving faster than in most other countries. If couples have fewer children in the future, the world's current population of 6.1 billion people will avoid doubling in less than 50 years. Future demands on natural resources such as water and fertile soil will be less. Everyone will have a better opportunity for a good life³.

The prevalence of contraceptive use is increasing world-wide, and in many countries more than 75% of couples use effective methods. Existing methods of contraception are not perfect, however, and their acceptability is limited by side effects and inconvenience. Therefore, effective contraception and contraceptive management are necessary to reduce the unintended pregnancy because safe and reliable family planning directly improves public health. In addition, promoting the use of contraceptive methods to prevent unwanted pregnancies is one of the most effective strategies to reduce abortion rates, maternal morbidity and mortality^{4,5}. For these reasons, a lot of efforts have been directed toward the development of highly effective methods of birth control. This resulted in the development of different kinds of contraception which are varying in their mechanism of action, side effects and compliance. An ideal contraceptive should have 100% efficacy, reliable, complete reversibility and a lack of on or off-target side effects. These properties imply a search for more targeted and less systemic methods⁶⁻⁹. Different approaches have been proposed for the development of new contraceptive methods; they included the transition from high dose to low dose combined oral contraceptive, from inert to copper intrauterine device, from oral to transdermal delivered contraceptive, from hormonal to non hormonal and from female to male contraceptive¹⁰⁻¹³.

At present more than 580 million couples worldwide employ family-planning methods and it is expected that future demand for contraceptive options will continue to increase. The World Health Organization (WHO) has designated the development of new and improved methods of contraception for men and women as a key component in the strategy to improve the quality of family-planning programs¹. The main objective of this review is to focus on the methods available now for contraception either for female or male. Then, this is followed by survey upon the future methods that are in different stages of research.

Female Contraceptives

Female contraceptives are divided into two categories: either hormonal or non hormonal methods. First, hormonal methods will be reviewed followed by non hormonal ones.

1- Hormonal female contraceptive methods:

Most of the female contraceptive methods involve hormone manipulation. This method uses exogenous hormones to "trick" the female body into thinking that it is pregnant which

prevents ovulation and eliminates opportunity for pregnancy¹⁴. Hormonal manipulation is effective method of preventing pregnancy and they are the most common method of birth control in the world. The most commonly used hormonal contraceptives are combined oral pills and progesterone only pills¹⁵.

1.1- Oral Contraceptive Pills (OCP)

Oral contraceptive pills are very popular, safe and effective method. They were first introduced in general clinical trials at 1960¹⁶. They have been used by millions of women worldwide. Oral pills are hormonal preparations that contain combinations of the hormones estrogen and progestin or progestin alone. Combination of estrogen and progestin prevents pregnancy by inhibiting the release of luteinizing hormone (LH) and follicular stimulating hormone (FSH) from the pituitary gland. LH and FSH play key roles in the development of the egg and preparation of the lining of the uterus for implantation of the embryo. There are different types of combination birth control pills that contain estrogen and progestin but the newest formulations of the pills contain combined oral contraceptive of ethinyl estradiol and drospirenone (DRSP). The later represents the newest generation of progestin used in oral contraceptive pills. This combination improved water retention symptoms and bleeding pattern in women. The combined (OCP) is claimed to have a variety of benefits, inducing a regular shedding of a thinner endometrium and inhibiting ovulation thus having the effect of treating menorrhagia and providing contraception¹⁷. The progesterone only pills contain progesterone with the major function of maintaining the viscosity of cervical mucus, making it difficult for the sperms to enter the uterus and fertilize the egg^{18,19}.

The interaction of oral contraceptives with many drugs was the subject of many research articles. The most significant interactions occur when drugs metabolized by the same liver enzyme of estrogens e.g. rifampin and griseofulvin. Rifampin accelerates the elimination of ethinyl estradiol and some progestin components, resulting in an increased risk of oral contraceptives failure. Rifampin also affects sex hormone-binding globulin (SHBG). Moreover, it is well-known that certain drugs, such as phenobarbital, phenytoin, and carbamazepine, interact with oral contraceptives and can increase the risk of contraceptive failure and pregnancy. These reactions can either reduce the effectiveness of the oral contraceptive or cause the body to metabolize the hormones in the oral contraceptive too quickly. However, relatively few reported cases of oral contraceptive failure in women who took antibiotics. Pharmacokinetic evidence demonstrates that plasma levels of oral contraceptive steroids are unchanged with the concomitant administration of antibiotics²⁰⁻²³. Many articles reported the interaction of oral contraceptive with different drugs, these drugs include anticonvulsant²⁴⁻²⁶, antibiotic²⁷, antifungal²⁸, antidepressant²⁹ and steroidal analgesic drugs³⁰.

1.2- Implants

Contraceptive implants consist of hormone-filled capsules that are inserted under the skin in a woman's upper arm by a minor surgical operation. Of the implants available now in the market: Norplant and Jadelle (5 years duration), Implanone (3

years duration) and finally Uniplant (One year implant)^{31,32}. Reversible long-term use is their most appealing feature for many users. They have the practical advantage of overcoming the risks of user failure and low continuation rates associated with other methods that require continuous attention or motivation. Disruption of menstruation, complications of insertion and removal, and infection at implant site, constitute the majority of adverse effects associated with contraceptive implants³¹. Implants interrupt fertility by thickening cervical mucus (mechanically preventing the sperm from accessing the ovum) and through hormonal effects that prevent ovulation in about half of menstrual cycles. They are safe and appropriate contraceptive methods for most women and adolescents³².

The levonorgestrel intrauterine system (Mirena) releases 20 mg/24 hr of levonorgestrel from a polymer cylinder mounted on a T-shaped frame and covered with a release rate-controlled membrane. Levonorgestrel, a highly potent progestin, can provide effective treatment when released in small, predictable, daily doses directly into the uterine cavity. It is approved for 5-years use. In four clinical studies with over 10,000 woman-years of use, the average Pearl Index was 0.1³³.

1.3- Injection

Injectable contraceptives are administered by deep intramuscular injection. Such type of injection contains a hormone which is released very slowly into the body. The main way by which the injection works is to stop ovaries releasing an egg, ovulation process, thickening of the cervical mucus to prevent sperm reaching an egg and thinning of the lining of the womb to prevent a fertilized egg implanting. It is a very effective and safe form of contraception³⁴.

Two types of injectable contraceptives are available in the market³⁵: A) Progestin-only injectable contraceptives injectables that include DMPA (depot medroxyprogesterone acetate) and NET-EN (norethindrone enanthate).

B) Combined injectable contraceptives that contain both a progestin and an estrogen hormone as examples Cyclofem™ (Lunelle) and Mesigyna.

1.4- Intrauterine device (IUD)

Intrauterine devices (IUDs) are small flexible T-shaped devices made of metal and/or plastic that fits inside the uterus to prevent pregnancy. They are the most common form of reversible contraceptive agents. Much of their popularity stems from their effectiveness combined with their long duration. Moreover, they are safe for the majority of women, highly effective and cost-effective when left in place as ongoing contraception. They combine the best features of hormonal contraceptives and IUDs^{36, 37}. Whenever clinically feasible, IUDs should be included in the range of emergency contraception options offered to patients after unprotected intercourse³⁸. There are two types of IUDs now available: copper-releasing; Cu T 380A (Nova T, Multiload 375) and levonorgestrel-releasing (Progestasert, LevoNova, Mirena). The latter one, levonorgestrel intrauterine system, has a cylindrical reservoir around the vertical stem contains a mixture of silicone and 52 mg of levonorgestrel, a progestin widely used in implants, oral contraceptives, and vaginal rings. Twenty five microgram of levonorgestrel is released every day³⁶.

The mechanism of action of IUDs indicates that both prefertilization and postfertilization effects are significant contributors to the clinical efficacy of all types of IUDs. Although prefertilization effects are more prominent for the copper IUD, both prefertilization and postfertilization mechanisms of action contribute significantly to the effectiveness of all types of intrauterine devices³⁷.

Recently, new IUD forms e.g. GyneFix, CuSafe and Fincoid 350 are introduced with fewer expulsions, higher continuation rates, lower failure rates and easy insertion-removal³⁸.

1.5- Vaginal Ring

Vaginal ring is a thin, small, transparent, flexible, doughnut-shaped plastic ring that is inserted in the vagina. It is a long-acting method of contraception that do not require daily interventions. It is one of the newest birth control methods available in the market. It is the product of years of research begun in the late 1970s. The hormones in the ring are released into the vagina and prevent pregnancy by keeping the ovaries from releasing eggs. The hormones also work by causing the cervical mucus to thicken, which blocks sperm from meeting with and fertilizing an egg³⁹. Because of its small size, more than four out of five women using the ring reported that they do not feel it. The ring is easily inserted in the vagina where it stays for 3 weeks. No interaction exists between concomitant use of the vaginal ring and other drugs. The use of a contraceptive vaginal ring does not alter the vaginal ecosystem and therefore does not substantially affect vaginal health. Recently, the ring has been intended as a microbicide delivery method for HIV prevention in african women⁴⁰. Smith et al⁴¹ have used oestradiol-releasing vaginal ring for treatment of postmenopausal urogenital atrophy. Multipurpose prevention technologies like vaginal rings and gels that contain a contraceptive steroid and an antiretroviral compound could offer women dual protection from pregnancy and HIV.

In a study by Roumen et al⁴², a total of six pregnancies were reported during treatment, giving it a Pearl Index of 0.65. The ring contains the same hormones, progestin and estrogen, found in most birth control pills. There are three types of vaginal rings available now in the market viz: progesterone ring (6 month method), nesterone-progestin ring (12-24 month method), and combination ring (4-12 month method). Nestorone™ (ST-1435, 16-methylene-17 α -acetoxy-19-nor-progesterone) is a versatile synthetic progestin that has a potent contraceptive action and devoid of certain properties exhibited by other progestins. It is not active orally because of rapid first pass metabolism. For that it is safe for lactating woman, since it is completely inactivated when it is transferred through the mother's milk to the infant⁴³. Being an excellent candidate progestin, S. M. Ahmed et al⁴⁴ conducted a series of research articles concerning Nestorone™ stability. For the same reason S. M. Ahmed^{45,46} studied its interaction with cyclodextrins as a step forward to be formulated as vaginal rings, implants and transdermals. The Population Council and the ICCR have successfully completed phase III trials on a contraceptive vaginal ring containing nestorone and ethinylestradiol that women can use for one year. Clinical trials of vaginal rings releasing 150 μ g of Nestorone™ and 15 μ g of ethinyl estradiol daily over the course of a year have been conducted. Millions of women have already used vaginal

ring for contraception. It causes less side effects because it avoids the first-pass effect through the liver; and fertility returns rapidly on removal. Since vaginal rings, or any other contraceptive dosage form, might contain a combination of more than one hormone, it is essential to prove absence of physical or chemical interaction between them. In this respect, the interaction of estradiol/progesterone during the preparation of vaginal rings was investigated by Saleh et al⁴⁷. It was found that such combination of hormones is compatible and no physical or chemical interaction was detected. The Population Council and ICCR are also studying ulipristal acetate, a selective progesterone receptor modulator (SPRM) that could be delivered as a female contraceptive via a vaginal ring. The principal contraceptive effect of SPRMs is the suppression of ovulation¹.

1.6- Transdermal contraceptive Patches

The transdermal contraceptive patches were developed to provide a similar reversible contraceptive action with a more convenient dosing schedule that would enhance patient compliance and achieve high contraceptive efficacy. The use of transdermal patches provides several advantages over pills. These advantages include; once weekly administration, a regimen that is more convenient to women than the once daily which lead to improving the efficacy by decreasing the degree to which it is dependent on user compliance. When necessary, the patches can be easily removed from the body which is difficult with other long acting delivery system such as implant or injections. The transdermal delivery of hormones eliminates variability in absorption due the physiological factors (such as stomach pH, GI motility, stomach emptying rate and GI transient time). In the mean time, the delivery of the drug into systemic circulation avoids the hepatic first pass metabolism experienced with orally administered hormones. The transdermal delivery of female hormones maintains constant drug concentration in the circulation by eliminating the peaks and troughs in serum level that occurs with oral administration¹⁰.

The patch is 20 cm² and consists of 3 layers, including a release liner to be removed for application, a medicated adhesive layer, and an outer polyester protective layer. The patch is applied to either the buttocks, upper outer arm, lower abdomen, or upper torso (excluding the breast). Each patch should be applied to a unique area, which could be near the site of the last patch. Users may bath and swim as usual, but should not apply oils, creams, or cosmetics on or around the patch area⁴⁸⁻⁵¹.

1.7- Transdermal contraceptive spray (MDTS®)

Acrux Co. in collaboration with the Population Council has successfully produced Nesterone TM MDTS metered dose transdermal spray. This agreement enables Acrux to progress toward commercialisation of a unique contraceptive spray, containing the new generation contraceptive drug Nestorone®. This product gives women a very attractive new option for contraception. It combines the unique technology with the know-how of one of the world's leading developers of reproductive health products, the Population Council. Many women preferred the ease and convenience of this method to swallowing pills, taking injections, or wearing patches. Nestorone®, which cannot be taken orally, is a fourth-

generation progestin contraceptive that has no androgenic hormonal effects, and a good safety profile. MDTS® is a small, hand-held, easy-to-use spray that is designed to provide an easy and convenient means to deliver a preset dose of a therapeutic drug via the skin. The spray applicator is placed gently against the forearm and an actuator button is pushed. A light spray containing a proprietary formulation of Nestorone® is quickly absorbed into the skin. Nestorone® is released into the blood stream on a sustained basis over 24 hours, providing a practical and convenient once-a-day dosing regimen. The spray is fast-drying, non-irritating, and invisible after application⁵².

2- Non Hormonal female contraceptive methods:

Non hormonal contraceptive agents or devices work either by preventing a man's sperm from joining a woman's egg or preventing the implantation of a fertilized egg into the lining of the womb. They are considered as alternative or additional methods for hormonal contraceptive methods. Non hormonal contraceptives include physical and chemical barriers. The physical barriers, such condom, diaphragm and cervical caps prevent pregnancy by blocking the entry of sperm into the upper genital tract. While the chemical barriers (spermicides) kill or inactivate the sperms⁹.

2.1- Female condoms

The female condom (Femidom) is a thin, soft polyurethane pouch, which is fitted inside the vagina before sex. It has an inner ring that goes into the upper part of the vagina, and an outer one, which should be visible⁵³. It is a relatively new product that is intended to serve a dual role of protecting against unwanted pregnancy and sexually transmitted infections (STIs)⁵⁴.

2.2- Diaphragm

The diaphragm is a reusable soft dome that fits inside the vagina to cover the cervix before intercourse. The dome is filled with gel that acts as a spermicide and microbicide. It can be inserted up to 2 hours before intercourse and should be left in for 6-8 hr following intercourse⁷.

2.3- Sponge

The vaginal contraceptive sponge is a non-prescription barrier contraceptive which was recently approved by the FDA. It is a cup-shaped white polyurethane sponge with a removal loop. The hydrophilic sponge is impregnated with spermicide. The user-inserted sponge can remain in place for multiple coital acts during a 24-hour period, and must remain in place for six hours after the last ejaculation for a maximum of 30 hours. It acts by spermicidal action, absorption of sperm and as a mechanical barrier. The advantages of sponge include spontaneity, convenience and against the two most common sexually transmitted pathogens, chlamydia and gonorrhea, which causes the most serious health problems for women. While the disadvantages include removal and retention problems. It is a viable barrier-method alternative that can protect against sexually transmitted infections⁵⁵. Michael et al⁵⁶ showed that, women using the sponge are protected was found to be less effective than the diaphragm in preventing pregnancy.

2.4- Vaginal Cap

The vaginal cap (cervical cap) is a small thimble-shaped non-latex rubber device that fits over the cervix, creating a physical

barrier that prevents sperm from entering the cervix and uterus. The cervical cap is effective as diaphragm in preventing the unwanted pregnancy^{57,58}.

2.5- The Essure (Micro-Insert)

It is one of the most recently introduced contraceptive vaginal insert. It is composed of stainless steel inner coil with super elastic outer coil and polyethylene (PET) fibers. It is designed to be easily placed in the uterine end of fallopian tube where its action is based on tubal occlusion by the fibers it contains. Grosdemouge et al stated that tubal sterilization with Essure micro-inserts is a reliable and reproducible method that requires a short period of training^{59,60}.

2.6- Contraceptive Vaccines

Vaccines work by producing an immune system response in a woman's body causing a woman's body to attack the embryo. A novel, slow-release formulations of vaccines offers the promise of providing six months or more protection against pregnancy following a single injection. The Population Council also conducted valuable long-term studies (5 years) in New York. The first-ever efficacy trials on a birth control vaccine established high efficacy (one pregnancy in 1224 cycles) of anti-hCG antibodies at and above 50 ng/mL titers. Fertility was regained in the immediate next cycle⁶¹.

3- Natural methods

3.1- Periodic abstinence

It is the limiting of sexual intercourse to safe days. This method is based on recent research that identifies more precisely when a woman is most likely to become pregnant. Woman may use one technique or a combination of techniques e.g. calendar, basal body temperature, symptothermal methods, to identify the start and end of that period couples can make use of the lactation period of the breastfeeding woman as a safe period as well. This method is called LAM (lactation amenorrhea method). It is only more recently, however, that the use of breastfeeding as a temporary family planning method has been documented and guidelines for its effective use have been developed. LAM is a very effective method if the following three criteria are met: (a) the woman is amenorrheic, (b) the woman is fully breastfeeding, and (c) the baby is less than six months old. It is a free method that has high contraceptive efficacy when followed perfectly. The failure rate increases directly by breaking the rules. This is inherently safe but has limited acceptability due to low reliability, inflexibility and interference in the spontaneity of love-making⁶².

3.2- Ex-vaginal ejaculation (The withdrawal method)

It was the major pre-industrial method of family planning largely responsible for the demographic transition from high to low birth rates in industrial nation states. Similar to periodic abstinence method, it is cost and device free method, has limited reliability and demanding requirement for self-control. While safe and reasonably effective for experienced users, interfering with the pleurability of coitus leads to a correspondingly high failure rate in practice. Whittaker⁶³ declared that the reasons for use of withdrawal method included inconvenience and dissatisfaction with hormonal contraceptives and condoms. Withdrawal was described as an expected alternative to condoms in both casual and long-term

relationships, and as a secondary, or backup, method with use of hormonal contraceptives or condoms.

Male contraceptives

Recently many researchers have focused on male contraception as a good way for men to share in the responsibility of family planning and to avoid the complications of female contraceptives. Male contraceptives are pharmaceuticals that are directed at interrupting processes like spermatogenesis, sperm transport or zona binding ability. Based on this, many male contraceptive methods have been developed and now available for clinical trials. Conception can be prevented by diverting or suppressing sperm output and/or inhibiting sperm fertilizing capacity⁶⁴.

1- Hormonal male contraceptives

1.1- Testosterone alone

Male hormonal contraceptives have the potential to be safe, easy to use, and reversible. Additionally, male hormonal contraceptive must reduce the number of fertile sperm in the ejaculate to levels that reliably prevent fertilization. Testosterone provides both gonadotropin suppression and androgen replacement making it an obvious first choice as a single agent for a reversible hormonal male contraceptive. Testosterone, when administered in slightly supra-physiologic doses, can function as a contraceptive agent by suppressing the secretion of the pituitary gonadotropins LH and FSH, which are essential for spermatogenesis, leading to decrease in the sperm count. The sperm count increase after cessation of testosterone administration⁶⁵.

Adverse effects due to testosterone administration as male hormonal contraceptive include asymptomatic polycythemia, weight gain and acne as well as changes in mood or sexual behavior. These are usually minor in severity, reversible upon cessation of treatment and of minimal clinical significance. Also, the long-term effects of exogenous androgens on the prostate also require monitoring since prostatic diseases are both age and androgen-dependent^{66,67}.

1.2- New potent synthetic androgen [MENT]

MENT (methyl nortestosterone acetate) is a powerful synthetic steroid that resembles testosterone in action although it is more potent. The Population Council and the ICCR are investigated contraceptive implants for men that deliver the hormone MENT. Preliminary studies in male volunteers show promising results and prove that it is more safe for the prostate. In a comparative studies, S. M. Ahmed⁶⁸ proved that MENT androgen shows higher permeability and transfer through synthetic membranes. For that it is more effective than testosterone and can be used in much lower doses.

1.3- Androgen combination regimens

The extent and rate of spermatogenic suppression was higher upon combining non-androgenic steroids (estrogens, progestins) with testosterone (for androgen replacement) than with androgen alone. This synergistic combination reduces the effective dose of steroid hormone and reduces the androgenic side effects⁶⁹⁻⁷¹.

1.4- Gonadotropin releasing hormone (GnRH) antagonists

Pure GnRH antagonists create and sustain immediate competitive blockade of GnRH receptors^{72, 73} and are highly effective in combination with testosterone at suppressing spermatogenesis. Early hydrophobic GnRH antagonists were

difficult to formulate and irritating, causing injection site mast cell histamine release. Newer more potent but less irritating GnRH antagonists produce rapid, reversible and complete inhibition of spermatogenesis when combined with testosterone. GnRH antagonists are more superior over GnRH agonists due to high effectiveness and immediate inhibition of gonadotropin secretion and thereby more effective depletion of intratesticular testosterone⁷⁴⁻⁷⁶.

1.5- LHRH agonist and antagonist

In a comparative study by Zhu and S. M. Ahmed⁷⁷ it was found that administration LHRH antagonist Azaline B causes more pronounced suppression of spermatogenesis than LHRH agonist, Histrelin. It was concluded that the use of each of them accompanied with continuous androgen supplementation represents a step forward in male contraception^{78,79}.

1.6- Follicular stimulating hormone (FSH) antagonists

Theoretically, FSH antagonist reduces spermatogenesis without inhibiting the endogenous testosterone secretion. The current status of hormonal contraception in men involves the principle of suppression of gonadotropins, LH, and FSH. This must be achieved as completely as possible to facilitate cessation of spermatogenesis and, thus, reach azoospermia⁸⁰.

2- Non Hormonal contraceptives for men

2.1-Condoms

Amongst the most commonly used form of contraception in men, condoms work as barrier devices which prevent the semen from entering the vagina. Condoms provide safe, cheap, widely available, user-controlled and reversible contraception with few side-effects. New types of condoms with improved tactile sensitivity were developed to enhance user acceptability. Additionally, condoms provide protection against a wide range of sexually transmitted diseases (STDs) such as HIV, syphilis, and gonorrhoea. The interference with sexuality is the main drawbacks which limits the use of condoms especially among stable couples⁸¹.

2.2-Vasectomy

The disruption of sperm transport in the vas deferens is an attractive option available for the regulation of male fertility. Vasectomy is looked upon as a permanent male contraception method, used for men having completed their family and fit for minor surgery. Vasectomy is a quick, simple, highly effective and convenient method of permanent sterilization^{82,83}. The procedure does not take very long, and involves the 'vas deferens' from both testicles being cut, clamped, or sealed in some other manner.

2.3- Vas Occlusion

Intravasal occlusion of vas deference with plug or medical grade silicone rubber (MSR) are claimed to induce reversible azoospermia without interrupting spermatogenesis⁸⁴. It is a nonsurgical, potentially reversible technique involving the injection of polymers in the vas deference that harden in-situ after injection to form occluding plugs which may be later removed to restore fertility⁸⁵. A hydrophilic gel, composed of styrene maleic anhydride in dimethyl sulfoxide, forms a charged spermicidal biopolymer when injected into the vas deferens, is stable and potentially removable⁸⁶.

2.4- Heating

It has long been known that even brief elevations of testicular temperature can profoundly suppress spermatogenesis^{87,88}

while sustained elevation may contribute to testicular pathology in cryptorchidism, varicocele and occupational male infertility⁸⁹. Clinical studies evaluating the potential for tight scrotal supports as a practical male contraceptive method^{90,91} showed a reversible decrease in sperm output but of inadequate magnitude for reliable contraception. Given the dubious acceptability and safety of heat-induced suppression of sperm output, the feasibility of a male contraceptive method based on testicular heating remains to be established. New thermal-based birth control methods are being tested in various countries, including hot packs and pads, for their safety and efficacy.

2.5- Ultrasound

Tsuruta et al⁹² have been reported the application of therapeutic ultrasound as a recent mean for reversible male sterilization. The non-invasive nature of ultrasound and its efficacy in reducing sperm count make therapeutic ultrasound a promising candidate for a male contraceptive. However, further studies must be conducted to confirm its efficacy in providing a contraceptive effect, to test the result of repeated use, to verify that the contraceptive effect is reversible and to demonstrate that there are no detrimental, long-term effects from using ultrasound as a method of male contraception.

2.6- Chemical Methods

Innovative non-hormonal mechanisms to inhibit sperm production and/or function constitute attractive targets for application as male contraceptive. For example, extracts of *Tripterygium wilfordii*, a traditional Chinese herbal medicine for rheumatoid arthritis and skin disorders, inhibit fertility and impair sperm output and function in rodents and men. Also, a polyphenolic yellow pigment identified in China, causes male infertility⁹³. Many authors^{94,95} reported that inhibition of vitamin A action inhibits the generation of mature sperm and male fertility. This finding was based on identification of the essential requirement of vitamin A in spermatogenesis. A recent promising drug lead was the recognition that an alkylated iminosugar drugs that inhibit glucosyltransferase, used therapeutically to reduce lysosomal glycosphingolipid accumulation in storage disorder type 1 (Gaucher's disease), miglustat, was a potent and reversible oral inhibitor of male mouse fertility but free from apparent systemic toxicity. Miglustat treatment produced structural malformation of sperm acrosome, head and mid-piece with consequential impaired motility although sperm retain the ability to fertilize oocytes in-vitro and produce normal offspring⁹⁶⁻⁹⁹.

2.7- Contraceptive Vaccines

Contraceptive vaccines may provide viable and valuable alternatives to the presently available methods of contraception. Recent advances in antigen definition and production have made the development of a contraceptive vaccine more attainable. Such a vaccine must evoke an immune response that blocks an indispensable step in the reproductive process. Vaccines are being developed that could interrupt fertility by inhibition of gonadotrophin release, the function of follicle-stimulating hormone or the effects of human chorionic gonadotrophin (hCG). Alternatively, they may prevent fertilization by interfering with the transport of spermatozoa or with sperm-zona pellucida binding. The most advanced prototype is a vaccine based on antibodies to beta

hCG. Such vaccines are being studied for clinical efficacy. Many hurdles remain in contraceptive vaccine development. Since the antigens are peptides or small proteins, the resultant immune response is usually moderate, and better adjuvant and delivery systems must be developed to enhance and maintain the immune response. Improvement of the mucosal immune response may be necessary for vaccines incorporating sperm antigens. Research on vaccines that control fertility has resulted in a fascinating base of scientific knowledge that, it is hoped, can be converted into products that will allow another option for individuals who wish to control their fertility^{100, 101}.

2.8. Adjudin compound

Adjudin [1-(2,4-chlorobenzyl)-1H-indazole-3-carbohydrazide, formerly known as AF-2364] is a nonhormonal drug that has been identified as having potent antispermatogenic effects *in vivo*.¹⁰²

CONCLUSION

Although there are so many methods available for contraception for female and male there is no single method meets the needs of every woman or man, and continued development of new contraception remains essential.

Towards this end, continued development of new contraceptive methods remains essential as until now no single method meets the needs of every woman and man

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