

Birth control: Contraceptive drugs/pills and methods in the last decades

BUHARI ALIYU, CHINEDU ONWUCHEKWA

Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria

ABSTRACT

Man had always tried to regulate births through various means involving the use of one or more actions such as medications, agents, sexual practices, or surgical procedures to prevent conception or pregnancy. The existing birth control methods include traditional and modern. The traditional methods are celibacy or sexual abstinence and withdrawal or coitus interruptus while the modern methods include male and female condoms, spermicide, contraceptives, sponge, diaphragm, pills, and vasectomy. Research has shown that hormonal approach to male contraception may be effective, reversible, and even safe. Efforts are ongoing to develop newer male contraceptives that will allow men to become full partners in the prevention of unintended pregnancy. This work reviews existing methods of birth control including current researches in birth control especially in the male.

Key words: Birth control; contraceptive; hormonal; pregnancy; sexual practices.

Introduction

Birth control involves one or more actions, devices, sexual practices, or medications to intentionally prevent or reduce the likelihood of pregnancy or childbirth.^[1,2] While contraception is the use of various devices, drugs, agents, sexual practices, or surgical procedures to prevent conception or pregnancy. In this present age, contraceptive use helps couples and individuals realize their basic right to decide freely and responsibly if and when they want to have a baby.^[2,3] When considering the global impact, a staggeringly large percentage of global pregnancies (40%) are unintended.^[4] This is in part due to the worldwide variation of access to healthcare and contraception, as well as the differing needs for contraceptives that are not met by the current market.

The growing use of contraceptive methods has resulted in not only improvements in health-related outcomes such

as reduced maternal mortality and infant mortality^[5,6] but also improvements in schooling and economic outcomes, especially for girls and women.^[7] Contraceptives are also prescribed for reasons unrelated to sexual activity such as in the treatment of acne or in regulating menstrual periods.^[8] At present, contraception methods available to men include condoms, withdrawal, spermicides, periodic abstinence (or rhythm) and vasectomy.^[1,9] Efforts are also ongoing to develop newer male contraceptives to allow men to become full partners in the prevention of unintended pregnancy. This work reviewed the existing methods of contraception and the current status of research into the development of novel approaches to male fertility control.

Address for correspondence: Dr. Buhari Aliyu, Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria.
E-mail: bayarko74@yahoo.com

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Types of Contraception

Traditional control methods involve the following

- a. Celibacy or sexual abstinence-This means avoiding penis-in-vagina intercourse to prevent pregnancy
- b. Withdrawal (coitus interruptus)-When the man is about to have an orgasm, he pulls his penis out of the vagina. The ejaculation occurs outside the vagina. The idea behind this method is that no sperm will be deposited in the vagina. This method is about 90% effective if used correctly. However, about one-third of the couples that uses this method experiences an accidental pregnancy within 12 months.^[2]

Modern birth control methods

This involves birth control methods used in the female and male.

In the female

- a. Female condom – It is made up of polyurethane having a flexible ring at each end. One end is secured behind the pubic bone to hold the condom in place, while the other ring stays outside the vagina.^[2,3]
- b. Spermicides – This is placed in the vagina before intercourse to create a chemical barrier.^[1,10] It may be used alone or in combination with a physical barrier
- c. Contraceptive sponge – The contraceptive sponge has a depression to hold it in place over the cervix. Foam is placed into the vagina using an applicator. The sponge acts as a barrier which stops the sperm from reaching the egg and also acts as a spermicide.^[3]
- d. Diaphragm – It is a rubber dome-shaped device placed over the cervix and fits into place behind the woman's pubic bone with a firm flexible ring that presses it against the vaginal walls.^[10] The diaphragm is a very effective contraceptive device when combined with a spermicide
- e. Cervical cap – The cervical cap is a thimble-shaped latex rubber barrier device fitted over the cervix and blocks sperm from entering the uterus through the external orifice of the uterus, called the os.^[1] The cap stays in place by suction
- f. The Lea contraceptive – Is a soft pliable cup-shaped bowl with a loop inserted into the vagina before intercourse and it prevents sperm from entering the cervix. For effectiveness, it must be used with a spermicide and left in place for 8 h^[3]
- g. The pill – Is a combined contraceptive pills having two hormones – an estrogen and progesterin that stops the release of egg (ovulation), and also make the lining of the uterus thinner^[12]
- h. Contraceptive patch – Is a transdermal patch applied to the skin that releases synthetic estrogen and progesterin hormones. The “Patch” is worn each week for 3 consecutive weeks, generally on the lower abdomen or buttocks. The fourth week is patch-free. Moreover, it has been shown to be as effective as a combined oral contraceptive pill
- i. Contraceptive vaginal ring (NuvaRing) – It is the trade name for a combined hormonal contraceptive vaginal ring manufactured by Organon. It's a flexible plastic (ethylene-vinyl acetate copolymer) ring that releases a low dose of a progesterin and an estrogen over 3 weeks. The NuvaRing is inserted into the vagina for a 3-week period, and then removed for one week, during which a menstrual period will be experienced^[12]
- j. Contraceptive injection (The Shot) – The brand name is Depo-Provera. Depot medroxyprogesterone acetate (DMPA) is a progesterin-only long-acting reversible hormonal contraceptive birth control drug injected every 3 months.^[1] It stops the woman from releasing an egg and provides other contraceptive effects
- k. Implants – Implanon (made by Organon International) is a rod with a core of progesterin (etonogestrel) inserted under the skin of the upper arm of a woman.^[13] The progesterin is released slowly and is effective for 3 years
- l. Emergency contraception (emergency postcoital contraception) – This refers to contraceptive measures that, if taken after sex, may prevent pregnancy. They are referred to as emergency contraceptives or the morning-after pill. These drugs prevent ovulation or fertilization and possible postfertilization implantation of a blastocyst (embryo). As an emergency contraceptive pill, it is different from medical abortion methods^[10,13]
- m. Intrauterine devices (IUD) – Also known as a coil. It is a small, flexible T-shaped device that is placed in the uterus by a physician. It stays in place throughout the time pregnancy is not desired and is used as a primary contraception method but may be used as emergency contraception.^[11,15] An IUD can last from 5 to 10 years depending on the type. As an emergency contraception, it is intended for occasional use when primary contraception means fails and acts before implantation.^[10] However, as the egg may have already been fertilized, some see this as a potential abortifacient i.e., a substance that induces abortion^[13]
- n. Tubal ligation – Is a permanent form of female sterilization. The fallopian tubes are severed and sealed (pinched shut) to prevent fertilization.^[13]

Male contraception

Given the nature of sperm production, a male contraceptive can work in any of the two ways, the hormonal methods (sperm production) or nonhormonal means such as physical barriers (preventing sperm from reaching the egg).

Nonhormonal Means Such as Physical Barriers

Male condom

This device is a mechanical barrier that looks like long, thin deflated balloons made of polyurethane or latex. It is placed over the penis before sexual intercourse begins and is used to prevent pregnancy by stopping sperm from entering the vagina.^[14] Apart from preventing pregnancy, they are also useful in protecting sexual partners from sexually transmitted infections including human immunodeficiency virus.^[14] Since 1920, most condoms have been made of latex rubber and are mostly free from adverse side effects. Improper or inconsistent usage of condoms, such as breakage, reduces marginally its contraceptive efficacy. Pregnancy rates for couples using condoms as their sole means of contraception approach 15%–20% per year.^[15] A drawback to condoms is their poor long-term compliance because they must be used. Apart from its being used 100% correctly during sexual encounters, other drawbacks includes the dislike of condoms by some men because they feel that condoms either diminish sexual pleasure or are difficult to used, and finally, some men and women develop allergic reactions such as skin irritation, and rarely, anaphylaxis to the latex.^[16,17] Condoms are by far the most commonly used male contraceptives; however, they are inelegant and contain usability barriers that make them an imperfect solution.^[18]

Vasectomy

This refers to surgical procedure designed to make a man sterile. The vas deferens (the tubes through which sperm pass) are cut or blocked.^[14] It is a safe, simple, outpatient surgery performed under local anesthesia in which the ductus deferens is severed and the ends ligated through a small scrotal incision. Vasectomy is highly effective with a failure rate of <1% and a low incidence of complications, so it appears to be safe regarding overall male health and^[19,20] other techniques, such as “no-scalpel technique”, are a single puncture made midline in the scrotal raphe with scissors, are assessed to be superior to older techniques.^[21,22] The drawbacks to vasectomy include a delay in the onset of azoospermia, pain, and rarely, an infection of the surgical site. Vasectomies are most appropriate for men who no longer wish to father children. Vasectomy reversal, a procedure termed vasovasostomy, has the potential to restore fertility with pregnancy rates varying from 30% to 70% depending on the length of time between vasectomy and the reversal procedure. In 20%–30% of men, vasovasostomy is unable to restore patency of the vas if more than 8 years have elapsed since the original vasectomy.^[23] As documented by imaging techniques, 20%–40% of men remain infertile despite restored patency of the vas possibly due to the presence of antisperm antibodies.^[24] Even though vasectomy is sometimes

reversible, the likelihood of an abundance of abnormal sperm is high, resulting in lower fertility. The higher rates of aneuploidy and diploidy in the sperm cells may increase the rate of birth defects.^[14]

Intra vas device

The intra vas device (IVD) is a set of tiny implants that block the flow of sperm. There are two IVD designs in clinical trials. One is a pair of soft, silicone plugs made by the Shepherd Medical Company in the United States. The other is a urethane tube lined with a tiny nylon sieve made by the Foshan Medical Company in China. Both of these designs were inspired by the 1980s work of Dr. Lourens Zaneveld, who showed in pilot studies that the IVD is a safe and effective method of male contraception. The US design of the device is made in several sizes and comes with a patented insertion tool.^[25]

Adjudin

Adjudin is a compound that functions as a contraceptive by disrupting the adhesion of spermatids to sertoli cells, causing premature spermiation and infertility.^[26,27] Administration of two doses of 50 mg/kg of adjudin (one dose per week) induced 100% infertility 5 weeks after treatment in adult rats with fertility rebounding by week 11. Due to the fact that there was some liver inflammation observed in a 29-day study of adjudin administration, researchers conjugated adjudin to an FSH β mutant specifically targeting it to sertoli cells, thereby significantly reducing the dose necessary for contraception. Unfortunately, the cost of this approach and the possibility of developing anti-follicle stimulating hormone (FSH) autoantibodies is a concern that needs to be addressed as the compound progresses to human studies.

Gamendazole

Gamendazole is an indazole carboxylic acid derived from lonidamine shown to reduce fertility in male rats without affecting testosterone levels in rats. It is a novel drug candidate for male contraception that works by impairing the function of the apical ectoplasmic specialization. All male rats who received a single oral dose of gamendazole at 6 mg/kg were infertile, but only 57% regained fertility.^[28]

Retinoic acid inhibition

Nutritional studies in rats and genetic studies in mice demonstrates a requirement for vitamin A and its metabolites at puberty for initiation of spermatogenesis and in adults for maintenance of spermatogenesis.^[29,30] In the seminiferous tubules, both germ and sertoli cells synthesize retinoic acid from retinal via aldehyde dehydrogenases. Retinoic acid binds one of several retinoic acid receptors (RARs), which regulate gene expression. It has been demonstrated that male RAR

knockout animals are sterile due to various problems in spermatogenesis.^[31,32] The blockade of retinoic acid function or synthesis has the potential to inhibit spermatogenesis and is an appealing approach to male non-hormonal contraceptive development.

BMS-189453

BMS-189453 is an orally active retinoic acid receptor antagonist. At daily oral doses of 15, 60, or 240 mg/kg for 1 month, BMS-189453 produced marked testicular degeneration in rats, but also led to increases in leukocyte counts, alkaline phosphatase and alanine aminotransferase levels.^[33] But in another study in mice, it was explored whether a lower dose of BMS-189453 might function as a contraceptive without the toxicity seen at higher doses.^[34] The study showed that the mice were completely sterile by 4 weeks after a dosing regimen of 5 mg/kg and by the end of treatment with a dose of 2.5 mg/kg for 4 weeks. Hematology and serum chemistry analysis were unaffected by BMS-189453 administration. This compound, or a more specific retinoic acid- α antagonists hold promise for non-hormonal contraception.^[35]

WIN 18,446

Over 50 years ago, the oral administration of WIN 18,446 was shown to safely, completely and reversibly inhibit spermatogenesis in many species including man.^[36,37] Histologic examination of testicular biopsies from men in these studies revealed a complete arrest of spermatogenesis, with an absence of forms beyond spermatogonia. Unfortunately, subjects taking WIN 18,446 experienced a “disulfiram reaction” consisting of nausea, vomiting, and palpitations and sweating, when they drank alcohol. Because of this, further development of WIN 18,446 was abandoned without an understanding of the mechanism by which it inhibited spermatogenesis.

Injectable plugs

Injected plugs were developed in China as a potential alternative to vasectomy. The concept is similar to the Intra Vas Device, except instead of implanting pre-formed plugs, the plugs are injected into the vasa deferentia in liquid form. The plugs then harden in place and block the flow of sperm. Two different types of injected plugs have been tested: medical-grade polyurethane (MPU) and medical-grade silicone rubber. Starting in the early 1980s, thousands of Chinese men chose MPU plugs as an alternative to vasectomy. Estimates of the number of men with plugs range from 13,500 to 300,000.^[38]

Medical-grade polyurethane plugs

MPU plugs have good results in large-scale clinical trials, with the largest group of 12,000 men showing 98% azoospermia.^[39]

Unfortunately it takes months for MPU plugs to reach this level of effectiveness, with a slow but steady ramping up over 18–24 months. A larger trial of 1064 men showed 68% azoospermia after 6 months, and 98% after 2 years.^[40] Ninety-eight percent azoospermia was the same rate achieved by no-scalpel vasectomy in that trial, proving MPU to be a very reliable form of contraception.

Hormonal Male Contraception

Due to the drawbacks of existing methods of male contraception, efforts have been made to develop a hormonally derived contraceptive analogous to estrogen/progesterone birth control pill for women. Surveys conducted in several countries suggest that such a hormonally derived male contraceptive administered by either daily pills or periodic injections would be welcomed by a large percentage of men and women,^[41] although there are ethnic differences in interpreting results of contraceptive trials. Most studies to date, however, demonstrate that some men sustain partial but incomplete reduction of their sperm counts, a condition called oligozoospermia.^[42]

Testosterone as contraceptive

This involves hormonal contraceptive regimens with longer acting injectable testosterone esters such as testosterone enanthate (TE) given by intramuscular injection on a weekly to fortnightly basis. Testosterone when administered in slightly higher physiologic doses, can function as a contraceptive by suppressing the secretion of pituitary gonadotropins, luteinizing hormone (LH), and FSH. Low levels of LH and FSH deprives the testis of the signals required for spermatogenesis, leading to markedly decreased sperm counts in most, but not in all men. The drawback to TE is that the high-dose requirement decreases serum high-density lipoprotein cholesterol, which could accelerate atherosclerosis.^[43,44] The testosterone ester, 7 α -methyl-19-nortestosterone which is more potent than testosterone^[45] and is not converted into dihydrotestosterone, the androgen implicated in prostatic hypertrophy, acne, and male-pattern baldness could be advantageous in the long-term safety and side effect profile of a hormonally derived male contraceptive.

Testosterone with progestins

The use of progestin synergistically with testosterone to block sperm production has been tested.^[46] Studies of testosterone and DMPA combinations shows that they do induce azoospermia. These combinations shows poor contraceptive efficacy. Other newer progestins compounds that has been studied are levonorgestrel,^[47,48] desogestrel^[49] and combination of testosterone and levonorgestrel.^[26]

Other Efforts in Male Contraceptives

There are a number of researchers working to describe the various chemical pathways required for spermatogenesis. Scientists' understanding of the molecular functioning of males' reproductive tracts is many years behind that of their understanding of females'.

Reversible Inhibition of Sperm under Guidance

RISUG is an acronym for Reversible Inhibition of Sperm under Guidance and is composed of styrene maleic anhydride complexed with the solvent dimethyl sulfoxide.^[49] RISUG has two contraceptive effects: partial blockage of the vasa deferentia and disruption of the sperm that pass through it. RISUG is an injectable compound that partially blocks the vasa deferentia, providing effective contraception for up to 10 years per dose. It is effective immediately, has few side effects, and has proven to be reversible in primate studies. This contraceptive has completed Phase I and II clinical trials in India.^[50] Sperm that are present in the ejaculate after RISUG has been administered have broken cell membranes.^[51] The membrane carries molecular keys that are needed to attach to an egg and packets of enzymes that are needed to dissolve the outer coating of an egg. Without those keys or enzymes, the sperm is functionally infertile. Researchers postulate that RISUG ruptures the membranes by stressing their ion exchange mechanisms.^[52]

Nifedipine

Nifedipine belongs to a class of drugs known as calcium channel blockers and is used as a high blood pressure (hypertension) and migraine medication. It also partially block the calcium channels within the cell membranes of sperm. This affects sperm function rather than production. A man taking nifedipine produces a normal amount of sperm, and the sperm appears functional when viewed through a microscope, but *in vitro* tests show that these sperm cannot fertilize an egg. Research shows that the sperm of men taking nifedipine have low levels of mannose lectin on the sperm cell membranes.^[53] Mannose lectin is a molecule critical for binding with an egg's zona pellucida. Nifedipine treatment prevent mannose lectins from moving to the surface of the cell membrane by stiffening the membrane with excess cholesterol.^[53,54]

Retinoic acid receptor antagonist (BMS-189 453)

In the 1980s, researchers at the pharmaceutical company, Bristol-Meyers Squibb developed a drug they designated BMS-189453 and is a pan-retinoic acid receptor antagonist. The drug binds to retinoic acid receptor and prevents it from picking up retinoic acid and affects all three known types of retinoic acid receptors, namely alpha (α), beta (β), and

gamma (γ). The unexpected side effect made researchers not to study the drug further. It remained on a shelf until a group of scientists at Columbia University came knocking in 2007. Researchers at Columbia University have now shown that this drug works as a reversible contraceptive in mice.^[34]

Neem extracts (*Azadirachta indica*)

Neem is a tree with many medicinally valuable parts. Various forms of neem have been studied as potential reversible male contraceptives. The injection of minute quantities of neem oil into the vas deferens has been successfully tested as an alternative to surgical vasectomy.^[55] Male mice and rats fed with fresh neem leaves crushed in water impregnated fewer female mice and had smaller average litter sizes.^[56] Studies of various forms of neem for male contraception in different types of mammals have reported no changes in libido or hormonal function.^[57] In addition, neem bark extract and neem seed oil caused arrest of spermatogenesis within 2 months, with a decrease in the number of Leydig cells that is responsible for the manufacturing of testosterone.^[58]

Papaya seed extracts (*Carica papaya*)

The contraceptive qualities of papaya seed extract have been known since the early 1970s. When crude extract of papaya seeds was fed to male rats, the quantity and quality of the sperm they produced deteriorated. At higher doses, this provided 100% effective contraception, but it also resulted in weight loss, possibly due to toxicity.^[59,60] Chloroform extract of papaya seeds tested in langur monkeys for 1 year, showed a steady decrease in sperm production with no evidence of toxicity. Once treatment stopped, full recovery occurred within 5 months.

Oleanolic acid

This plant compound is extracted from the flowers of a myrtle family tree, *Eugenia jambolana* studies of oleanolic acid in rats show that low, sustained doses result in reversible infertility.^[61] The studies reported no changes in body weight or libido. The compound alters the way sperm pass through the epididymis. Normally, immature spermatids are converted in the epididymis to fully functioning, motile sperm. The sperm of rats treated with oleanolic acid emerged from the epididymis with decreased forward motility. Rats treated for 30 days became infertile; the contraceptive effect was reversed 14 days after ending treatment.^[62]

Catsper genes

The cation channels of sperm also known as Catsper channels or CatSper are ion channels with four members (Catsper 1, 2, 3, and 4) that forms voltage-gated Ca^{2+} channels that seem to be specific to sperm. The Catsper genes encode a series of calcium ion exchange channels which occur

exclusively in the male reproductive tract. As sperm encounter the more alkaline environment of the female reproductive tract, Catsper channels become activated by the altered ion concentration. These channels are required for proper fertilization.^[63] Catsper 1 is found in the primary piece of sperm and helping in evoking Ca^{2+} entry and regulation of hyperactivation in sperm. Catsper 2 is responsible for the regulation of hyperactivation and is in the sperm tail while Catsper 3 and Catsper 4 are involved in motility of the hyperactivated sperm and are found in the testes and sperm. Although Catsper seems to play an important role in sperm function, Catspers 1–4 null mice have been found to have normal testicular histology, sperm counts, and morphology, which is indicative of normal progression of spermatogenesis.^[64]

Septin 4 gene

Septins are highly conserved in yeast, *Drosophila*, and mouse and belongs to a family of GTP binding proteins required for cellular functions such as membrane compartmentalization, vesicle trafficking, mitosis, and cytoskeletal remodeling. Two of the 14 family members (Septin 12 and 14) in the mammalian species are expressed in the testis.^[65] In the mouse, knockout of Septin 4 and Septin 12 leads to male sterility with distinctive sperm pathology i.e., defective annulus or bent neck.^[66] In humans, sperm with abnormal expression pattern of SEPT 4, 7, and 12 are more prevalent in infertile men.^[67] The gene Septin 4 encodes proteins that help sperm to form normal tails. A treated man would produce the normal number of sperm; however, their bent tails would render them incapable of fertilizing an egg.

Ouabain analogs

Na, K-ATPase $\alpha 4$ is a testis-specific plasma membrane Na^+ and K^+ transporter expressed in sperm flagellum, characterized by a high affinity for the cardiac glycoside, ouabain. Its selective inhibitor, such as ouabagenin analog 25, has been found to affect sperm membrane potential, intracellular Ca^{2+} , pH, hypermotility, and decrease sperm motility both *in vitro* and *in vivo*.^[67] In addition, deletion of Na, K-ATPase $\alpha 4$ in male mice also results in complete infertility, making it an attractive target for male contraception.^[67]

Conclusion

Additional contraceptives, especially those intended for men, are needed to check population growth and prevent undesired pregnancy. Existing male methods of contraception, including condoms and vasectomy, are effective but have limitations. Research has progressed slowly; however, the hormonal approach to male contraception is effective, reversible, and seems safe. Long-acting injections of testosterone

esters (e.g. testosterone undecanoate) may prove effective in combinations with long-acting progestins. Current research is focused on both improving the method and characteristics of androgen administration and finding combinations with progestins that optimize sperm count suppression in all populations while minimizing side effects.

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