Thesis

Contraceptives for men

A feasible alternative or still an illusion?

submitted by

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Graz, am 17.06.2023

Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, am 17.06.2023 Marie Eimer eh

I. Acknowledgment

Ich möchte an dieser Stelle die Gelegenheit nutzen, um Danke zu sagen. Die letzten sechs Jahre waren eine Zeit in der ich nicht nur die Grundkenntnisse des menschlichen Körpers und dessen Krankheitsbilder erlangt habe, ich habe auch sehr viel über mich selbst gelernt, Die Herausforderungen und Höhen und Tiefen im Studium, aber auch auf persönlicher Ebene haben mich dazu bewegt zu wachsen. Das war jedoch nur möglich durch meine Familie, die immer da war, wenn ich sie am meisten gebraucht habe. Ohne meine Anne würde das Ende dieser Arbeit vermutlich immer noch in den Sternen stehen. Ich möchte mich von Herzen bedanken bei meiner Grazer Familie Heli, Isa und Alex, die auch in Zeiten der Krisen mein Leben erhellt haben und besonders das letzte halbe Jahr Graz zu meinem zu Hause gemacht haben. Aber auch meine Freunde aus Deutschland, besonders Marie, hatten immer ein offenes Ohr für mich und haben in der Zeit zu Hause das Studium in weite Ferne rücken lassen und mir die Möglichkeit gegeben durchzuatmen.

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II. Table of Contents

III.List of Abbreviations

LGBTQA+	lesbian, gay, bisexual, transgender, queer or questioning, intersex, asexual, and more
GnRH	Gonadotrophin-releasing hormone
LH	Luteinizing hormone
FSH	Follicle-stimulating hormone
DHT	Dihydrotestosterone
CRH	Corticotropin-releasing hormone
ACTH	Adrenocorticotropic hormone
RAR	Retinoic acid receptor
DMAU	Dimethandrolone Undecanoate
HDL	High-density lipoprotein)
SHBG	Sex hormone binding globulin
11 β-MNTDC	11-β Methyl-19-Nortestosterone 17-beta-dodecylcarbonate
MENT	7α-methyl-19-nortestosterone
LDL	low-density lipoprotein
H2 GMZ	H2-Gamendazole (
GAPDHS	Glyceraldehyde 3-phosphate Dehydrogenase-S
HIPK 4	Homeodomain-interacting Protein Kinase 4
TSSK	Testis-specific serine kinases
MEIG 1	Meiosis-expressed Gen 1
PACRG	Parkin co-regulated gene
MDH1B	Malate dehydrogenase 1B
LDH-C4	Lactate Dehydrogenase C4
RISUG	Reversible inhibition of sperm under guidance

SMA	Styrene-maleic anhydride
DMSO	Dimethyl sulfoxide
FDA	Food and Drug Administration
HCA	Human Contraceptive Antibody
MPT	Multipurpose prevention technology
SEMG1	Semenogelin1
ATP1A4	Adenosine triphosphate 1A4
sAC10	Soluble Adenylyl Cyclase 10
Cat Sper1	Cation Channel of Sperm1
ABHD2	Abhydrolase Domain-containing Protein 2
BRDT	Bromodomain Testis-Specific Protein
CABYR	Calcium Binding Tyrosine Phosphorylation Regulated Protein
ANT4	Adenine Nucleotide Translocase 4
PPP3CC	Protein Phosphatase 3 Catalytic Subunit Gamma
PPP3R2	Protein Phosphatase 3 Regulatory Subunit B
PSA	Prostatic specific antigen

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Hintergrund:

Die jährlich 121 Millionen ungewollten Schwangerschaften bergen große gesundheitliche und sozioökonomische Risiken mit. Darüber hinaus stellt das unkontrollierte Bevölkerungswachstum eine große Belastung für unseren Planeten dar. Ziel dieser Arbeit ist es einen strukturierten und aktuellen Überblick über Kontrazeptiva für den Mann zu geben. Diese Arbeit bietet einen leicht verständlichen theoretischen Teil über das männliche Fortpflanzungssystem, der als Grundlage für das Verständnis der Wirkmechanismen und Nebenwirkungen der verschiedenen Substanzen dient.

Methoden:

Für diese Diplomarbeit wurde die Methode der Literaturstudie gewählt. Die Suche nach relevanter medizinischer Fachliteratur erfolgte über PubMed und Google Scholar. Die Website der Male Contraceptive Initiative, die Calliope The Contraceptive Pipeline Database und das Center for Male Contraceptive Research and Development dienten als Quellen für aktuelle, relevante Forschungsergebnisse zu den wichtigsten Substanzen.

Ergebnisse:

Diese Arbeit enthält die neuesten veröffentlichten wissenschaftlichen Ergebnisse zu vier hormonellen und 32 nicht-hormonellen Kontrazeptiva für den Mann sowie die aktuellen Zahlen zu ihrer Akzeptanz in der Gesellschaft. Neue Technologien haben es Forschern ermöglicht zahlreiche weitere Angriffspunkte für mögliche Kontrazeptiva zu identifizieren. Diese Arbeit beschränkt sich auf Informationen über die wichtigsten Substanzen und Angriffspunkte in der aktiven Entwicklung.

Schlussfolgerung und Diskussion:

Trotz vielversprechender Forschungsergebnisse stehen die Entwicklung und Einführung von Verhütungsmitteln für Männer vor vielen Hürden. Eine große Herausforderung sind soziale und kulturelle Normen in Bezug auf Geschlechterrollen und Verhütung. Es gibt auch Bedenken hinsichtlich möglicher Nebenwirkungen wie verminderter Libido, Stimmungsschwankungen und

Fruchtbarkeitsproblemen, die in der zukünftigen Forschung berücksichtigt werden müssen.

Zusammenfassend lässt sich sagen, dass Kontrazeptiva für den Mann das Potenzial haben, Einzelpersonen und Paaren mehr Möglichkeiten zur Verhütung ungewollter Schwangerschaften zu bieten. Auch wenn ihre Entwicklung und Verbreitung noch einige Herausforderungen mit sich bringt, sind die laufenden Forschungs- und Entwicklungsarbeiten vielversprechend für die Zukunft der Kontrazeptiva für den Mann.

VIII. Abstract in english

Background:

The 121 million unintended pregnancies pose significant health and socio-economic risks each year. In addition, uncontrolled population growth is a substantial burden on the planet. This paper aims to provide a structured and up-to-date overview of male contraception. This work offers an easy-to-understand theoretical part about the male reproductive system, which serves as a basis for understanding the mechanisms of action and side effects of the different substances.

Methods:

The method chosen for this thesis was a literature review. Relevant medical literature was searched using PubMed and Google Scholar. The Male Contraceptive Initiative website, Calliope, The Contraceptive Pipeline Database and the Center for Male Contraceptive Research and Development were used as sources of recent relevant Research on the main compounds.

Results:

This paper presents the most recently published scientific evidence on four hormonal and 32 non-hormonal male contraceptives and the latest figures on their acceptability in society. New technologies have enabled researchers to identify many more targets for potential contraceptives. This paper is limited to information on the essential compounds and targets in active development.

Conclusion and Discussion:

Despite promising Research, there are several challenges to the development and uptake of male contraceptives. Social and cultural norms around gender roles and contraception constitute a significant challenge. There are also concerns about potential side effects, such as reduced libido, mood changes and fertility problems, which may need to be addressed in future Research. In conclusion, male contraceptives have the potential to offer individuals and couples more options for preventing unwanted pregnancies. While there are some challenges to their development and uptake, ongoing Research and development are promising for the future of male contraception.

1 Introduction

Sex is a fundamental part of the social structure of all creatures. The instinct to reproduce is deeply rooted in human behaviour. Regular sexual activity has many benefits. It improves memory by reducing chronic stress and allows better blood pressure response to stress.[1,2] Many methods have been developed over the past millennia to provide these benefits without the consequences of unwanted pregnancy. These range from barrier methods (e.g. condoms, sponges, diaphragms) and hormonal contraception (e.g. pills, injections, patches, rings) to intrauterine devices and behavioural methods (e.g. basal temperature, cervical mucus).[3] These strategies mainly affect women's reproductive cycles.

Nevertheless, 121 million unplanned pregnancies occur every year. Of these, 74 million (61%) end in abortion. These figures are exceptionally high in regions with weak medical infrastructure, low levels of education and low-income households. These conditions are inadequate to ensure maternal and child care or safe abortion and put the health of both mother and child at risk.[4]

The main reason for these 121 million unplanned pregnancies is inadequate or inappropriate contraception. Confronting young families with the responsibility of a child too early can trap them in a vicious cycle. Early unwanted pregnancies prevent women from getting a good education, making them more likely to live in poverty. Expanding contraceptive services, especially in areas with high population growth, would give 257 million women more control over their family planning. Establishing stable structures by prioritising education and financial security is critical to combating poverty and economic inequality.[4]

Inequalities in contraceptive choices between men and women perpetuate the idea that having and caring for children is 'women's work'. Allowing men to participate in family planning could lead to a more equitable sharing of reproductive and domestic responsibilities. This solution would allow women and girls to increase their participation in education and employment outside the home. The responsibility for financial and family provisions would not rest solely on men's shoulders and incomes. Sharing this burden and giving men the opportunity to be more involved in childcare would build a shared and more stable concept of family care.[5]

The world's population is growing by 83 million a year, despite the Earth's limited resources. If men were allowed to control their reproductive behaviour actively, population growth would adapt to the available resources, stabilising this imbalance. So that every human being has sufficient access to water, food and energy to live a healthy and happy life.[6]

Familiarity with one's reproductive tract encourages regular consultation with health professionals and makes early detection of pathologies more likely. As testicular cancer is the most common tumour in young adults, followed by prostate cancer in middle age, regular consultation with a specialist would promote early detection of such diseases. Many men also suffer from ejaculation problems. An open approach to sexual health creates the space to find solutions while addressing individual reproductive needs.[7]

The LGBTQA+ community also has unique needs. Currently, 5% of United States young adults identify as transgender or non-binary.[8] The contraceptive options currently available are insufficient to ensure that future contraceptives meet the needs and preferences of all people, regardless of gender identity.

Health concerns, side effects and contraceptive failure are the main reasons for discontinuing contraceptive use. Declaring contraception as fundamental to the rights and well-being of adolescents and adults of all genders and providing access to sexual and reproductive health services would prevent two-thirds of unintended pregnancies.[9] An expanded choice of contraception and family planning would allow everyone to choose what is best for them as their reproductive intentions evolve. The aim should be to create options that are safe, reversible, affordable, free of side effects and easy to use.

This paper provides an accessible overview of the male hormonal and reproductive cycle, various influencing factors and their impact on behaviour and physical appearance. They are actively developing male contraceptive strategies, including mechanisms of action, side effects and reversibility, based on currently available scientific literature are presented.

This thesis uses the terms "male" and "female". These terms refer to biological sex. This sex is determined at fertilisation and is independent of gender identification.

2 Theoretical background[10–12]

2.1 The Puberty: The prerequisite for reproduction

To father a child, a male individual must go through puberty. During puberty, a human child's body matures into an adult capable of sexual reproduction. This process is triggered by a hormone called kisspeptin. This hormone activates the brain to initiate the hormonal reproductive cycle. The hormonal reproductive cycle is controlled by three structures: The hypothalamus, the pituitary gland and the testes. The hypothalamus and pituitary gland are located in the brain, while the testicles are in the scrotum. The testicles, also known as the gonads, begin to produce hormones necessary for physiological changes in the human body. These changes include the physical growth (i.e. increase in height and weight) of the human body and the growth of the primary sex organs (penis and testicles). The activation of the hormonal cycle also triggers the development of secondary sexual characteristics and behavioural changes (e.g. libido). Secondary sexual characteristics in men include the growth of facial and body hair, including armpit, abdominal, chest and pubic hair, enlargement of Adam's apple and deepening of the voice, increased height and heavier bone structure. The steroid hormone testosterone is mainly responsible for these changes.

The onset of puberty varies between genders and individuals and has changed over time. Nowadays, girls begin puberty at 10-11 and complete it at 16-17. For boys, puberty begins at 11-12 and ends at 16-17. After completing puberty, a person has the desire to have sexual relations and can reproduce sexually.

2.2 The male reproductive system

In order to understand the different ways contraception can be used by manipulating the male reproductive organs, the whole process from sperm production to fertilisation of the egg in the female reproductive tract is explained. The overall function of the male reproductive system is to create the optimal conditions for sperm to fertilise an egg so that a child can be conceived.

The anatomy of the male reproductive system consists of four main parts.

- Testicles -> The place where sperm are produced.
- Duct system -> A series of tubes that allow sperm to mature and be stored.
- Accessory glands -> Provide protective and nourishing fluids for the sperm.
- Penis

2.2.1 Different stops on the path of a sperm cell

The following picture shows the different organs where sperm cells are produced and afterwards transported through. The following text describes the processes that take place in each structure.

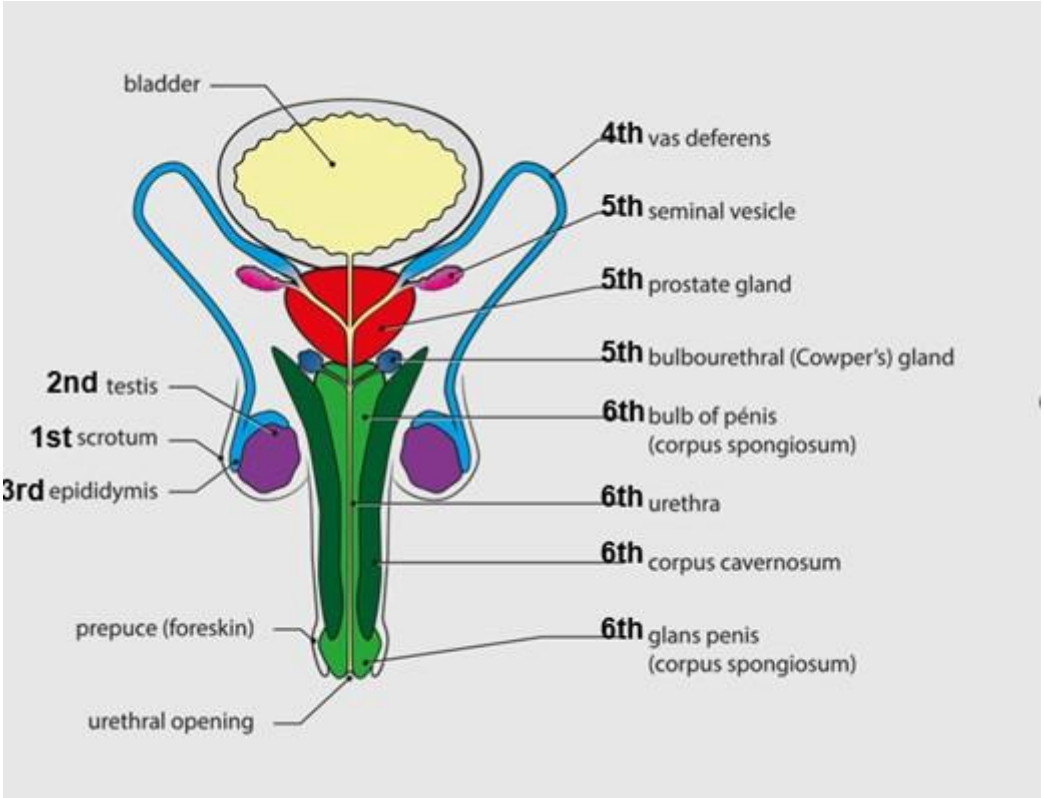

Figure 1: Stops in the path of a sperm cell, illustration has been modified, the permission to use has been obtained[13]

First stop: The scrotum

The scrotum and penis are the only male sexual organs visible outside. This skin bag is divided into two chambers by a central web called the raphe. The raphe is connected to the muscular septum, which separates the scrotum from the inside. The scrotum regulates temperature, as optimal conditions for sperm production are two °C below body temperature. The scrotum is connected to the body's trunk by a branch called the spermatic cord. The spermatic cord contains the vas deferens, arteries, veins and nerves. The cremaster muscle surrounds the spermatic cord. This muscle can change the position of the testicles in the scrotum by moving them closer or further away from the abdomen, depending on the ambient temperature. In cold temperatures and when the penis is erect, the cremaster muscle tenses and the testes move closer to the body's trunk. One testis is usually lower than the other to avoid compression in the event of an impact.

Second stop: The testicles

The testicles are paired egg-shaped organs that sit outside the abdominal cavity in the scrotum. After men reach puberty, the testicles produce and store millions of sperm cells. As part of the endocrine system, the testicles are also responsible for hormone production. Each testis contains a system of tubes with different compartments. The first compartment, where sperm production and maturation take place, is the seminiferous tubule. The sperm then travel through the seminiferous duct into the epididymis, which forms the second compartment. The vas deferens connect the tubular systems of the two testes.

Seminiferous tubules:

The production of sperm, also called spermatogenesis, occurs in the seminiferous tubules inside the testes. There are 800 seminiferous tubules in each testicle. These tightly coiled tubules can be divided into two types, the convoluted tubules and the straight tubules. The sperm cells are produced in the convoluted tubules and transported through the straight tubules into the short efferent duct and then to the epididymis.

Spermatogenesis:

As many male contraceptives interfere with sperm production, this process is explained in detail.

Early-stage germ cells (spermatogonia) divide by mitosis at the periphery of the seminiferous tubules. During mitosis, one cell becomes two cells of the same type. This process ensures a continuous supply of sperm cells and allows the production of 525 billion sperm cells in a lifetime.

Some spermatogonia start to differentiate and enter meiosis, the second stage of spermatogenesis. At this stage, they are called spermatocytes. During meiosis, the genes in the germ cells are recombined, and the number of chromosomes is halved. When a sperm meets an egg, they form a complete set of chromosomes.

In the final stage, the germ cells, now called spermatids, undergo extensive morphological changes. They acquire a tail and structures such as the acrosome. The acrosome is located on the head of the sperm and is composed of antigens and various enzymes that open the egg membrane to allow fertilisation.

During spermatogenesis, the developing germ cells migrate from the periphery of the seminiferous tubules to the interior, where the differentiated, motile spermatids are released into the lumina of the seminiferous tubules. From there, they travel through the straight tubules into the short efferent duct and then to the epididymis, where they acquire the ability to move forward and become fertile. The development of sperm takes about 74 days.

Special cells:

Two unique types of cells in the testes are essential for fertility and a healthy reproductive cycle.

Sertoli cells and the blood-testis barrier:

Sertoli cells form a tightly packed scaffold in the seminiferous tubules of the testes. This scaffold is also called the blood-testis barrier. This barrier separates the differentiating sperm cells from the general blood system by tight junctions. It allows the Sertoli cells to control the environment in the seminiferous tubules and create optimal conditions for spermatogenesis in a fluid with a unique chemical composition. As the general blood system does not supply the differentiating sperm, the Sertoli cells provide nutrients and stimulate the energy-providing differentiation process and immune modulation. Sometimes errors occur during cell division. Sertoli cells detect these and initiate DNA repair or phagocytic processes. Sertoli cells produce androgen-binding globulin to increase the testosterone concentration in the seminiferous tubules by a factor of 100-200 to stimulate spermatogenesis. When enough spermatocytes are produced, Sertoli cells produce the hormone inhibin to downregulate sperm production. During fetal development, Sertoli cells are also responsible for inhibiting the development of female sexual characteristics through a hormone called anti-Müllerian hormone.

Leydig cells:

Leydig cells are found in the connective tissue between the seminiferous tubules. These cells supply testosterone and other androgens to the testes and the rest of the body. After release, testosterone binds to an androgen-binding globulin and enters the bloodstream.

Third stop: Epididymis

Each testicle has a coiled epididymis. The epididymis is made up of three parts. The head is where newly formed sperm are stored until they are ready to mature. The body is a twisted tube that gives the sperm time and space to mature for about a week. The tail is connected to the vas deferens, which carry the sperm out of the body. This maturation process takes another 12 days.

Fourth stop: Vas deferens

The purpose of the vas deferens is to carry the ejaculated sperm from the epididymis. The right and left vas deferens form the connection between the two ductal systems of each testis. The vas deferens is 30 cm long and is protected by smooth muscle tissue. During ejaculation, the muscle tissue moves the sperm into the urethra with peristaltic movements. A well-established method of permanent contraception is vasectomy. In this procedure, the vas deferens are closed by tying or cutting/cauterising the vas deferens' ends so sperm cannot pass through.

Fifth stop: Accessory glands

The bulbourethral glands and seminal vesicles mix their secretions with the sperm during ejaculation.

Seminal vesicle:

The seminal vesicles are located at the junction of the vas deferens and the seminal canal. These paired tubular glands are located between the bladder and the rectum. Each vesicle contains a 3-5 cm long tube with several sacs. The seminal vesicles have many functions to support the sperm after it leaves the man's body. Because the vaginal environment is acidic, the seminal vesicles produce a fluid with a high alkaline pH. The seminal vesicle produces fructose to provide energy for the sperm in the female body. A protein called semenogelin prevents the sperm from capacitating prematurely. This protein is also produced in the seminal vesicle.

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Capacitation takes place in the female reproductive tract. It is a biochemical process that increases sperm motility and releases the surface molecules (acrosomes) on the head of the sperm from semenogelin, allowing the sperm to interact with the egg. This process is crucial before sperm can fertilise an egg and can take up to 10 hours. After capacitation, the sperm penetrates the egg membrane (zona pellucida) and fertilises the egg. The whole fertilisation process can take up to 24 hours.

Nowadays, this process can be initiated outside the human body. After this in vitro fertilisation, the fertilised egg is implanted in the woman's womb.

Prostate:

The prostate is a walnut-sized gland between a man's rectum and penis, just below the bladder. The urethra runs from the bladder to the penis, passing through the centre of the prostate. During ejaculation, the prostate secretes a milky fluid that nourishes and protects the sperm as it passes through the ejaculatory duct. The fluid contains enzymes (such as prostate-specific antigen), zinc and citric acid that help sperm live longer and move more efficiently. The prostate-specific antigen makes the thickened sperm more fluid, increasing the chances of successfully fertilising an egg.

Ejaculatory duct:

After the union of the two vas deferens, where the seminal fluids enter, the ejaculatory duct begins. Fluid from the prostate is added along the way. The ejaculatory duct flows into the urethra, where the ejaculate leaves the penis.

Bulbourethral glands/Cowper's glands:

These two small glands at the base of the penis secrete a fluid before ejaculation that prepares the male urethra for the passage of sperm. Because of the uric acid in the urine, the environment of the urethra needs to be neutralised before ejaculation. Approximately 4 ml of fluid is secreted during sexual arousal.

Sixth stop: Urethra and Penis

These two structures are the last destination before the sperm leaves the male body.

Urethra:

The urethra is the tube that connects the bladder to the urinary outlet. Men use the urethra to urinate and ejaculate. The 15-20 cm long tube passes through the prostate gland, so malignant or benign enlargement of the prostate gland often causes difficulty urinating. The urethra is often confused with the ureters. The ureters are muscular tubes that carry urine from the kidneys to the bladder.

Penis:

Like the scrotum, the penis is visible from the outside. Its function is to fertilise females or hermaphrodites (male biological sex but female secondary sex organs) during copulation or sexual intercourse, and it contains the urethra for urination. The penis develops from the same tissue as the female clitoris during human development. The stimulation causes the penis to stiffen and straighten, called an erection. The leading physical cause of an erection is the enlargement of the arteries that supply blood to the penis, causing the spongy tissue chambers in the penis to fill with blood.

2.3 The endocrine system

The structures described above are subject to a control programme. This control programme links the nervous system to the organs described above and is called the endocrine system. In order to induce reversible infertility, it is also possible to influence this system. Therefore, the basic mechanisms of this system will be explained.

2.3.1 Interactions between the nervous system and endocrine system

The nervous system perceives environmental changes through visual, thermal or olfactory stimuli. The hypothalamus interprets these signals. The hypothalamus is the interface between the nervous system and the endocrine system. It is located at the base of the brain near the optic chiasm, where the optic nerves cross and converge behind each eye. The hypothalamus coordinates all vital functions, including sleeping, regulating temperature, hydration and appetite, achieved through the endocrine system. The endocrine system consists of glands and tissues that produce hormones. These hormones can adjust organ function and behaviour to create optimal conditions for living and reproducing.

2.3.2 Hormones

The term hormone means 'to set in motion'. Hormones trigger a dynamic cascade of responses in specific target tissues. The cells of these tissues can be found anywhere in the body.

The mechanism by which hormones communicate with cells depends on the biochemical structure of the hormone. They can be divided into four groups: Protein/peptide hormones, steroid hormones, monoamine hormones and lipid-based hormones. In the context of reproduction, protein hormones and steroid hormones are the most common.

Protein hormones:

The building blocks of protein hormones are amino acids. Protein hormones are stored in vesicles in endocrine cells and released by exocytosis. During exocytosis, the vesicle membrane fuses with the cell membrane and the hormones are released into the extracellular space and the bloodstream. They are soluble in the blood and do not require a carrier protein. The protein hormones gonadotropin-releasing

hormone (GnRH), luteinising hormone (LH) and follicle-stimulating hormone (FSH) are essential in regulating the reproductive cycle.

Steroid hormones:

Steroid hormones are fat-soluble. This means they can easily pass through cell membranes and into the bloodstream. As they are not water-soluble, they require water-soluble carrier proteins. These carriers protect the steroid hormones from premature degradation and transport them to the target tissue. They can either interact with receptors on the cell membrane or diffuse into the cell and bind to cytoplasmic receptors, where they can alter protein biosynthesis.

All steroid hormones are produced from a precursor molecule, cholesterol, which is stored in lipid droplets in the cells of the producing hormone glands. Different steroid hormones are produced by reducing the carbon molecules of the basic building block, cholesterol.

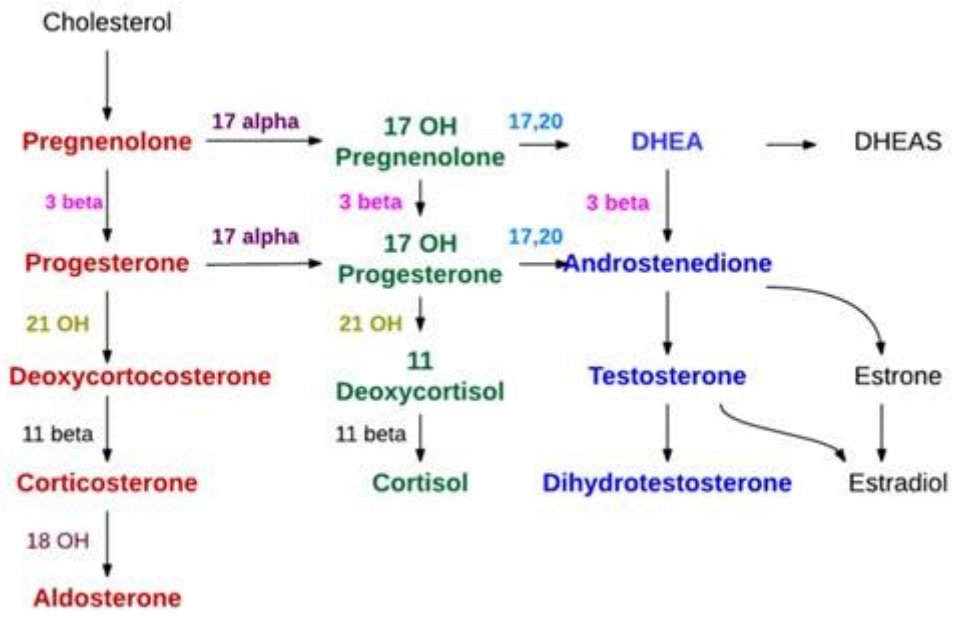


Table 1: Chart of steroid hormone building cascade, the permission to use has been obtained[14,15]

It is important to emphasise that men and women have androgens and oestrogens. The testes typically have more enzymes to produce androgens and fewer aromatising enzymes to convert testosterone into oestrogens. However, testosterone can be considered a prohormone that can be converted into Dihydrotestosterone (DHT) or oestrogen.

Hormones transmit their information through receptors. Binding affinity generally coincides with circulating hormone concentration. Receptor utilisation is a function of hormone concentration and depends on the receptor's affinity for the hormones. The number of receptors varies significantly in different target tissues and is one of the most critical determinants of specific cellular responses to hormones. The steroid hormone receptor belongs to a superfamily that includes vitamin D and retinoic acid receptors.

The number of receptors on the cell surface adapts to the hormone concentration. When the hormone concentration is low, more receptors are expressed (upregulation). When hormone levels are high, fewer receptors are expressed (downregulation).

2.3.3 Negative feedback regulation

The body has different mechanisms to regulate the different hormone secretions. The dominant principle is negative feedback regulation.

A set point is controlled either by down-regulating stimulatory pathways when the set point is exceeded or by up-regulating stimulatory pathways when the hormone level falls below this set point. The external environment influences the rhythms that occur and follow a pulsating pattern. This is why hormone concentrations change throughout the day, depending on internal and external factors.

This regulatory mechanism will now be explained as it applies to the reproductive cycle.

The first regulator of the male hormone system is the hypothalamus, with its pulsatile release of GnRH into the portal system. This pulse generation is a direct consequence of the intrinsic periodicity of GnRH and other neurons that synapse with GnRH neurons.

These neurons, which contain kisspeptin or excitatory or inhibitory neurotransmitters, form the link to the nervous system and can adapt the reproductive cycle to external conditions sensed by the eyes, ears, nose and temperature. The recently discovered hormone kisspeptin is responsible for initiating this hormonal cycle during puberty. It may have other functions that still need to be fully understood.

The portal system provides a vascular connection between the hypothalamus and the anterior pituitary. The anterior pituitary responds to GnRH's pulsatile and episodic release by secreting LH and FSH.

The pulsatile frequency of GnRH release is vital because interference with the nervous system will result in inadequate stimulation and may disrupt the entire cycle, leading to infertility. While the release of GnRH and LH is coupled, FSH pulses are less pronounced and are secreted constitutively.

LH's primary function is to stimulate testosterone production in the Leydig cells. As testosterone is released from the Leydig cells into the bloodstream, it acts on the receptors of the Sertoli cells and binds to sex hormone-binding globulin. High testosterone levels in the blood send a negative feedback signal to the hypothalamus to downregulate GnRH secretion.

In the adrenal cortex, adipose tissue and immature Sertoli cells, testosterone is converted to oestradiol by an enzyme called aromatase. In men, oestradiol is essential for modulating libido, erectile function, and spermatogenesis.

FSH interacts with testosterone to initiate and maintain spermatogenesis by activating Sertoli cells in the seminiferous tubules. This leads to the secretion of inhibin in the Sertoli cells, which acts as the primary endocrine negative feedback suppressor of FSH in the anterior pituitary.

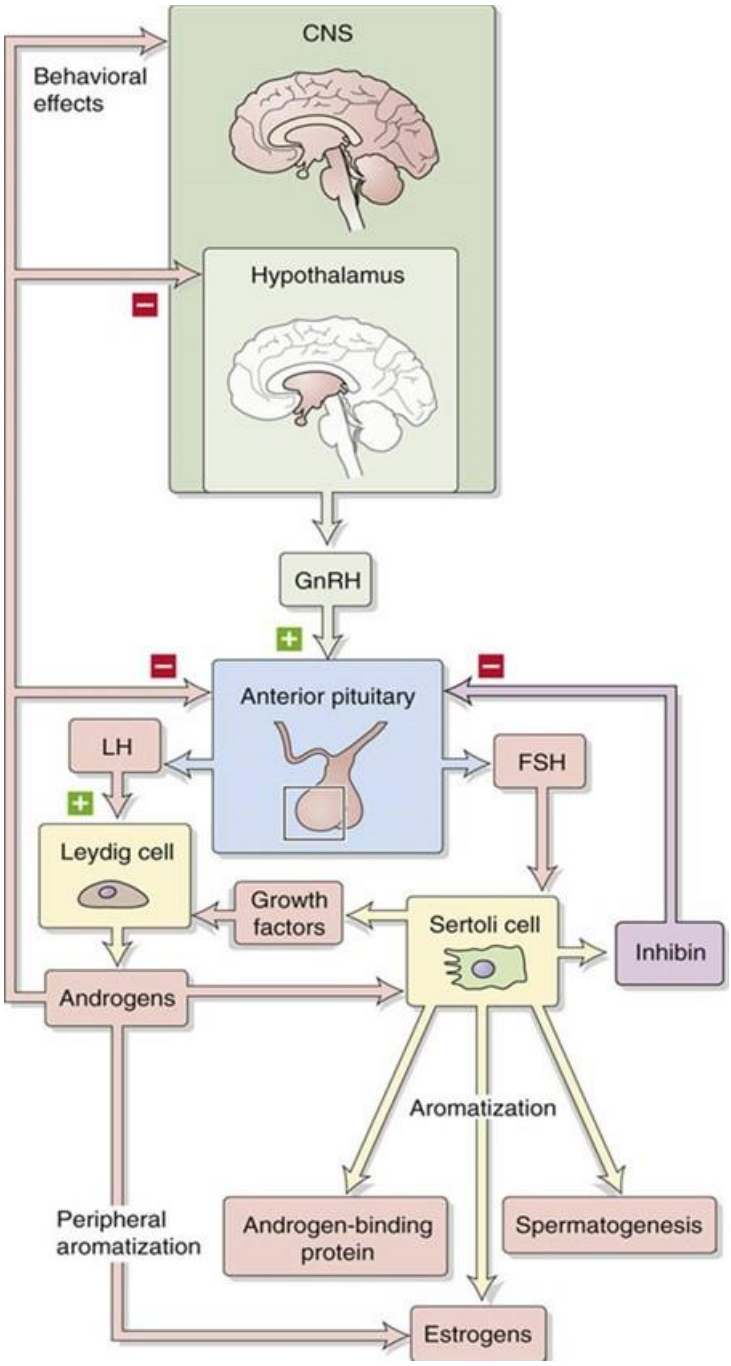


Chart 1: Hypothalamus-pituitary-testis axis, the permission to use has been obtained[10]

2.3.4 Testosterone

Testosterone levels in the blood are subject to circadian fluctuations. Testosterone levels are high in the morning and fall in the afternoon. Depending on age (19-39), the normal range for testosterone in sexually mature, non-obese men is between 264 and 916 ng/dL. In general, testosterone levels decrease with age.[16] Several medical groups consider a testosterone level of 350 ng/dl the minimum average level.[17] Testosterone levels also depend on the amount of sleep each night. Testosterone levels increase during sleep and decrease during waking hours. The highest levels of testosterone production occur during REM sleep. That period late in the sleep cycle helps replenish the body and mind. Because REM sleep occurs in the second half of sleep, it is crucial to get at least 7 hours of sleep.[18]

The testes mainly produce testosterone, but the adrenal glands also produce a small amount. LH controls the secretion of testosterone from the pituitary gland. Because testosterone is a steroid hormone, it is bound to transport molecules called sex hormone-binding globulin or albumin, produced by the liver. In its bound form, testosterone is not biologically active. When testosterone diffuses into the target cell, it is converted to DHT. DHT has a higher affinity for androgen receptors than testosterone. As the androgen receptor is intracellular, DHT can alter the transcription of genes and, thus, the biosynthesis products. Androgen receptors are located at multiple sites, so testosterone triggers many different anabolic functions in the body. The liver breaks down excess testosterone. Body fat contains the enzyme aromatase. This converts testosterone into oestrogen. This is why obese men become feminised.

Testosterone can also change people's behaviour. Testosterone levels increase during sexual arousal in both men and women, but to a greater extent in men.[19,20] The act of falling in love and fatherhood correlates with declining testosterone levels in men, which may be linked to the promotion of paternal care.[21]

Nutrients also affect testosterone. Men with vitamin A, D, and zinc deficiencies have lower testosterone levels.[22–24] A very high protein diet (>35% protein) also reduces total testosterone levels.[25]

Place of action	Description
Fetal state	Developmenr of primary sexual characteristics and sexual differentiation[26]
Early infancy	Masculinization of the brain by estrogen (aromatized testosterone)[27]
Puberty	Development of secondary sexual characteristics[28]
Reproduction	Spermatogenesis, Activation of accessorial sex glands (prostate, seminal vesicle)[29]
Central nervous system	Stimulation of libido, motivation, and potency[30]
Muscles	Building muscle mass through stimulation of protein biosynthesis[31]
Kidneys	Stimulation of production of erythrocytes (erythropoiesis) through increase of erythropoietin production[32]
Bone	After aromatization to oestrogen activation of osteoblasts[33]

Table 2: Overview of places of action of testosterone

2.3.5 Testosterone misuse and abuse

Testosterone can be used clinically in two modes: androgen replacement therapy and pharmacological androgen therapy.[34] However, most countries have an increasing prevalence of testosterone misuse and abuse. Testosterone misuse is when testosterone is prescribed for non-valid medical indications such as male infertility or sexual dysfunction (in men without pathological hypogonadism), but most commonly for anti-ageing. Androgen abuse is the non-prescription use of testosterone or a synthetic androgen unrelated to medical indications but for doping, bodybuilding, or other recreational, cosmetic, or occupational reasons.[35]

The chronic use of high doses of synthetic androgen is associated with adverse effects in several organ systems; however, there are still many gaps in the knowledge about the long-term consequences of this practice and how to deal with these patients. Healthcare professionals have a crucial role in combating this public health problem, recognising, and preventing the spread of androgen abuse.[36]

The side effects of testosterone abuse can be severe and harmful. In men, it can include reduced sperm count, infertility, shrunken testicles, erectile dysfunction, hair loss, breast development, increased risk of prostate cancer, severe acne, and stomach pain. In women, testosterone misuse can cause facial hair growth and body hair, loss of breasts and swelling of the clitoris.[37] When used in excessive doses, both testosterone and anabolic steroids cause harmful changes in cholesterol levels. In the long term, persistent use will increase the risk of cardiovascular disease and strokes.[38,39]

Healthcare professionals have a crucial role in combating this public health problem, recognising, and preventing the spread of androgen abuse. If testosterone therapy is necessary, healthcare professionals may prefer testosterone gel in the lowest effective dose as it results in reasonably stable testosterone levels, does not suppress gonadotropin levels as much as most injectables, is unpopular for misuse among testosterone users and can be quickly tapered in weeks or months.[40,41]

2.3.6 Environmental effects on reproductive function[10]

All living things exist in a dynamic balance. Any disturbance to this equilibrium requires energy to restore the original state. An individual's total available energy is divided among many competing needs. These needs must be balanced: growth, cell maintenance, immune function, reproduction, and thermogenesis. Understanding how external influences affect the internal state and hormonal cycle helps to understand how the body and environment are interrelated. It can also help in the decision-making process when choosing between hormonal and non-hormonal contraceptive methods.

All environmental changes cause stress to living things. Sources of stress are called stressors. These are non-specific factors (e.g., high temperatures or noise, inadequate food quality or lack of water, but also novel situations with a lack of control). The systems mediating stressors operate in complex down-regulation and up-regulation mechanisms. They are closely linked to psychological and genetic make-up, developmental history, social factors, and behavioural state. People perceive stressors differently, depending on their sense of control. The degree of control is crucial because those in control feel less vulnerable.

Another influencing factor is the extent to which an individual avoids the stimuli when given a choice. It is possible to develop coping strategies by getting used to the situation. Short periods of stress can have several adaptive effects, such as increased immediate energy availability, increased oxygen uptake and decreased blood flow to organ systems not required for movement, decreased pain perception, and improved sensory and memory functions. Short-term stress allows everyone to adapt to a changed environment. At the same time, it inhibits energy-intensive processes unrelated to immediate survival, such as digestion, growth, immune function, and reproduction. In the case of chronic stress, these functions are suppressed in the long term.

Looking at this process from an evolutionary perspective reveals that everybody's response to the environment competes with energetic demands. Thus, limited energy can compromise tissue renewal or immune function to support reproduction. Conversely, reproduction or immune function may be compromised when energy availability is significantly reduced.

This phenomenon is not unique to humans. Stress can also reduce milk production in cows and egg production in chickens.

The underlying mechanism is based on releasing corticotropin-releasing hormone (CRH) in the hypothalamus as a stress response. In addition, endogenous opioids are released to numb the sensation of pain. CRH and endogenous opioids can directly suppress the release of GnRH, leading to less secretion of LH and FSH and, thus, less testosterone production in the testes. Low testosterone levels can lead to low motivation and performance, both in sexual relationships and in everyday life. After releasing CRH, the pituitary gland secures adrenocorticotropin-releasing hormone (ACTH) into the bloodstream. ACTH stimulates the adrenal glands to produce cortisol.

Cortisol inhibits immune function and directly inhibits the secretion of GnRH and LH, which affects fertility. As cortisol is also a steroid hormone, the basic building block is cholesterol. Physiologically, cortisol production is only increased in the early morning. Chronic stress disrupts this system, and cortisol is generally elevated. The general increase in cortisol alters the concentration of oestradiol and testosterone because these hormones compete with cortisol for cholesterol. When cortisol levels are too high, there is no cholesterol left to make sex hormones. Cortisol also has a more direct effect on spermatogenesis. The testosterone-producing Leydig cells have cortisol receptors involved in cell growth, metabolism and energy use. In addition, the enzyme that neutralises cortisol in the testes is overwhelmed, and testosterone production is reduced. The resulting low testosterone levels cannot support spermatogenesis, so sperm count falls and stressed men become infertile.

Another factor that affects reproductive function is prolactin. Prolactin is released during stress, which increases the sensitivity of the harmful feedback mechanisms to testosterone in the hypothalamus. So the hypothalamus responds to already low levels of hormones with even less hormone production.

As sexual behaviour can occur at deficient testosterone levels, the effects of the chronic stress response can be better observed when trying to achieve a penile erection.

The parasympathetic nervous system, responsible for rest and digestion, and the sympathetic nervous system, responsible for fight or flight, must work closely together. The parasympathetic nervous system ensures that more blood flows into the penis and prevents blood from flowing out of the veins. As the penis fills with blood, it stiffens to allow insertion into the vagina. During copulation, the rest of the body must maintain a high sympathetic state, with increased heart rate, blood pressure and respiratory rate, so blood flows from the periphery to the central trunk.

The autonomic input to the genitals maintains its parasympathetic tone until sufficient stimulation occurs; at this point, the parasympathetic input is abruptly terminated. At the same time, the sympathetic input to the penis is activated, and ejaculation occurs.

This process is a delicate interaction of the nervous system, so any factor that alters the autonomic internal state can influence this response. Both stress and substances that alter the autonomic internal state, such as alcohol or drugs, can lead to dysfunctional copulation in humans. With stress, it becomes increasingly challenging to maintain parasympathetic activity in the penis, as the sympathetic nervous system works at a high level under stress. As the parasympathetic activity stops too quickly, the sympathetic input is too early and premature ejaculation occurs. Premature ejaculation has a prevalence of about 30% and is the most common sexual dysfunction in men.

One way men can delay ejaculation is to take deep breaths. Inflating the lungs triggers a volley of parasympathetic signals that delay the switch from parasympathetic to sympathetic input to the penis.

This tool does not only work during sexual activity. The breathing pattern is known as the physiological sigh (inhale twice and exhale once) causes the alveoli in the lungs to refill with air. During prolonged exertion, they collapse, causing oxygen levels to drop and carbon dioxide levels in the blood to rise. The physiological sigh has a direct effect on reducing stress and anxiety.[42,43]

3 Contraceptives for men

2.2 Acceptability and trust

Research suggests there is significant interest among men in using male contraceptives. A survey conducted by the Male Contraceptive Initiative in 2019 found that around 17 million men aged 18-44 in the United States are looking for a contraceptive method that fits their lifestyle and relationship. Reversibility and at least 99% effectiveness and protection against STIs are essential features of a new method. Men would also prefer a non-hormonal method, as the possible side effect of depression and reduced interest in sex are the biggest concerns about using a new method. [44]

Several factors, including cultural and social attitudes to gender roles and responsibilities, lack of education and awareness about the availability and effectiveness of male contraceptives, and the availability and accessibility of male contraceptive options, can influence the uptake of male contraceptives. These factors are remarkably variable in low- and middle-income countries with the greatest need. It is important to note that increasing education and awareness about male contraceptives, as well as making them more widely available and accessible, can help to increase the uptake and use of these methods. Better informed society and transparency about potential side effects would reduce social stigma and create realistic expectations about reproductive health and gender roles.[45]

The Malawi Male Motivation Project, a pilot project in sub-Saharan Africa, shows that contraceptive education programmes targeted at men can improve contraceptive uptake and communication about sexual health within couples, even among couples who have never used contraception. Modelling suggests that introducing novel, reversible male methods could significantly reduce unintended pregnancies by as much as 30-40%, particularly in areas where contraceptive uptake is currently low. Novel, cost-effective male contraceptives could have crucial global health and economic benefits that could reduce health inequalities over time.[46]

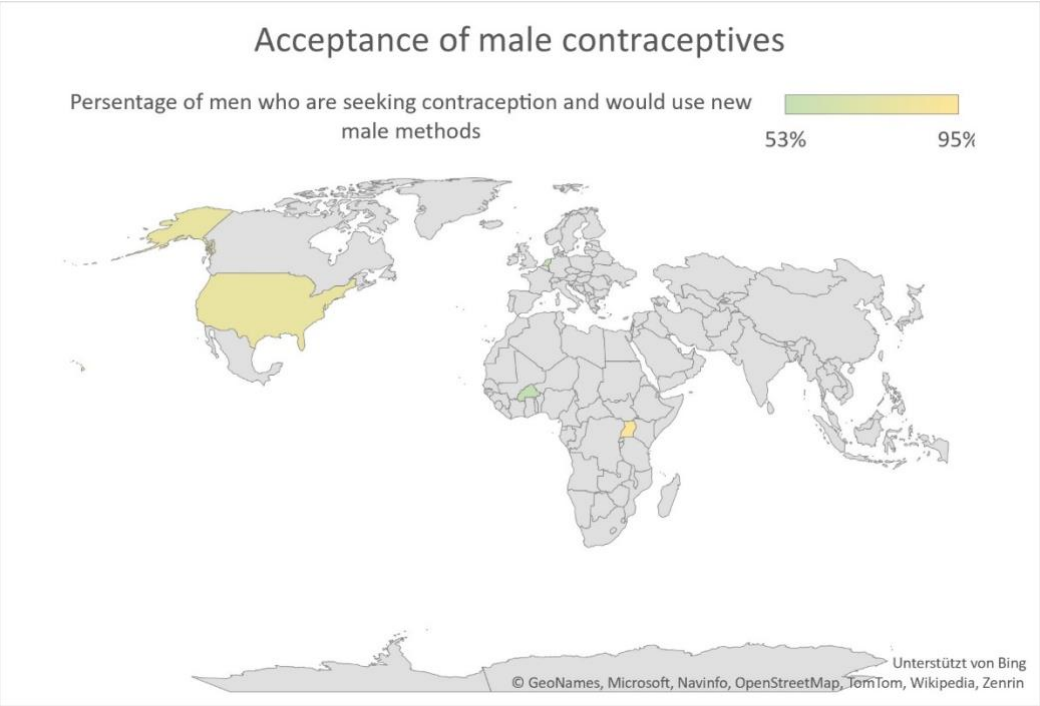


Figure 2: Male contraceptive uptake in the USA, Uganda, Burkina Faso and the Netherlands [47–49]

3.2 The concept of shared risk

The new risk-sharing model of male contraceptives refers to the idea that men and women should share responsibility for contraception rather than placing most of the responsibility on women. This model suggests that by providing men with effective and reliable contraceptive options and educating and encouraging them to take an active role in family planning, the overall burden of contraception can be more evenly shared between partners. The traditional model of contraception has focused primarily on women, with most contraceptive options targeted at them. As a result, women have borne a disproportionate share of the responsibility for preventing unintended pregnancy. This new shared risk model aims to shift the focus to men and their role in family planning by providing them with safe, effective, and accessible options to control their fertility. It also aims to empower men to take an active role in their reproductive health and to be more involved in family planning decisions. It is based on the idea that by giving men more control over their fertility, they will be more invested in preventing unintended pregnancy and more likely to use contraception consistently and effectively.[50]

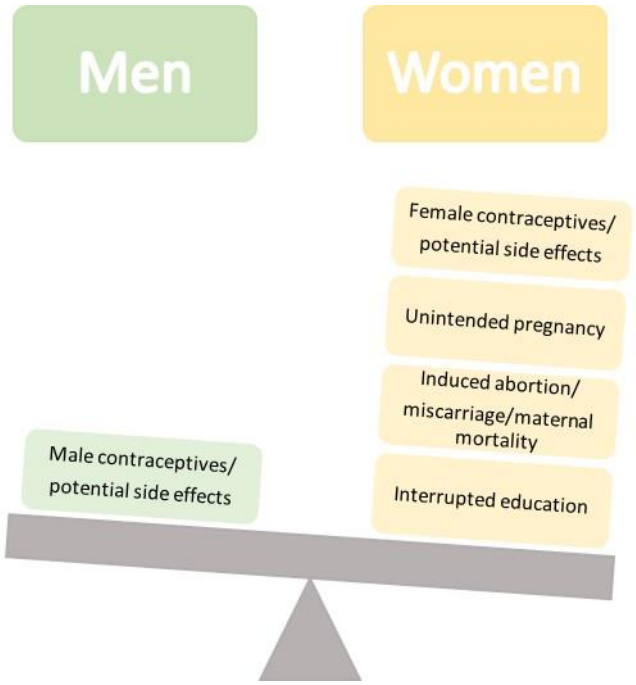


Figure 3: Model of shared risk [51]

3.3 Already available methods

Currently, the most widely used male contraceptive is the condom. *Condoms* are a barrier method that physically prevents sperm from fertilising an egg. According to a 2019 study, around 54.3% of sexually active students used a condom the last time they had sex.[52] The failure rate of condoms, when used correctly, is about 2%, but with typical use, the failure rate rises to 13%.[53] The advantages of condoms include high effectiveness when used correctly, easy accessibility and the added benefit of protection against sexually transmitted infections. However, the main disadvantage is that they may not be used consistently or correctly. In addition, their use interrupts sexual intercourse, which encourages inconsistent use.

Another option is a no-scalpel vasectomy. This type of vasectomy uses a small puncture in the scrotum to access the vas deferens rather than a traditional surgical incision. This method is less invasive and painful than a traditional vasectomy and usually requires fewer follow-up visits. The procedure is performed under local anaesthetic and takes about 15 to 30 minutes, during which the doctor uses a particular instrument to make a tiny puncture in the skin. The vas deferens are gently pulled through the puncture and cut, cauterised, or blocked with clips. It is associated with less pain, fewer complications, and faster recovery. Men with a no-scalpel vasectomy have less discomfort and swelling than those with a traditional vasectomy. There is also less risk of bleeding and bruising and a lower risk of infection. No-scalpel vasectomy is a permanent form of contraception with a high success rate of 99.85%. According to the World Health Organization, approximately 42 million men worldwide have undergone the procedure. The only significant long-term side effect is scrotal pain.[54] About 6% of men request a vasectomy reversal. The urologist can reattach the vas deferens (90-95% effectiveness) or create a bypass to the epididymal duct (65-70% effectiveness)[55]. If the vasectomy lasts more than five years, fibrosis develops in the seminiferous tubules and the likelihood of reversibility decreases.[56]

The withdrawal method, also known as the 'pull-out' method, is a contraceptive method in which the man withdraws his penis from the vagina before ejaculation. The idea behind this method is that by withdrawing before ejaculation, the man can prevent his sperm from encountering the woman's egg, thereby preventing

pregnancy. The withdrawal method is less effective than other methods of contraception because it relies on the man's ability to control his ejaculation and withdraw in time. Pre-ejaculatory fluid, or pre-cum, can contain viable sperm that can cause pregnancy. With a 20% failure rate, it is not a reliable method of contraception.[53]

3.4 The long road from research to drugs[57,58]

It is important to note that the drug development process can take many years and be complex and costly. In addition, not all drugs that enter clinical trials will be approved and made available on the market. As contraceptives are administered to healthy people, eliminating negative long-term consequences and side effects is a top priority. As these are often discovered in one of the last stages of development, some near-final methods have been discarded. The methods presented below can be categorised according to their stage of development, allowing us to predict when and if an alternative contraceptive will be available shortly.

The development of male contraceptives typically follows a multi-stage process, which includes the following stages.

- Discovery: This stage involves identifying potential targets for male contraceptives, such as hormones or enzymes involved in sperm production or function. Researchers may also investigate existing drugs that have potential contraceptive effects in men.
- Preclinical development: In this phase, researchers conduct laboratory and animal studies to evaluate the safety and efficacy of potential male contraceptive candidates. This includes testing for potential side effects, determining the appropriate dosage and assessing the drug's effectiveness in reducing sperm production or function.
- Clinical trials: Following preclinical development, the potential male contraceptive will enter clinical trials. The trials will be conducted in three phases. Phase 1 will involve a small number of healthy volunteers to assess the safety and side effects of the drug. Phase 2 will involve a larger group of volunteers to assess the drug's effectiveness and gather more information about its safety. Phase 3 will involve a large population of men and will be used to confirm the safety and efficacy of the drug.

- Approval and post-approval studies: If the drug is safe and effective in clinical trials, it is submitted to regulatory authorities for approval. Once approved, post-approval studies are conducted to monitor the drug's safety and effectiveness in the general population.
- Commercialisation: Once approved, the drug is manufactured and sold to the public.

3.5 Hormonal contraceptives for men

Hormonal contraceptives for women are the most widely used method of preventing pregnancy. Researchers have therefore tried to apply the same principle to the male hormone cycle. So far, however, no substance has proved successful.

3.5.1 Mechanism of action and reversibility

Hormonal contraceptives aim to suppress the hypothalamic-pituitary-gonadal axis and, thus, spermatogenesis. The substance used creates the illusion of enough sex hormones in the bloodstream. As a result, the hypothalamus suppresses the production of GnRH and does not activate the pituitary gland to secrete LH and FSH. So, there is less activation of the Leydig and Sertoli cells. Because the Sertoli cells do not care for the spermatocytes, they do not divide, and the number of sperm in the ejaculate falls. As the Leydig cells stop producing testosterone, the intratesticular testosterone concentration falls.

The cut-off point for sperm suppression with male contraceptives varies depending on the specific method and dosage. In general, most male hormonal contraceptives aim to reduce sperm concentration to less than 1 million sperm per millilitre of semen, which is considered the threshold for effective contraception.[59]

The contraceptive contains synthetic sex hormones, which, in addition to their inhibitory effect on the hypothalamus, ensure that extra testicular peripheral functions are maintained. This is particularly important to minimise the potential for side effects.

Hormonal contraceptives can be administered by injection, implant, tablet, or gel. The challenge is to find the correct dose and form to suppress spermatogenesis while providing all tissues with the right concentration of hormones.

When the user stops using a hormonal contraceptive, the hypothalamus-pituitary-testes axis takes over the task of hormone and sperm production and fertility is restored. However, this can take some time as the hormonal cycle needs to rebalance itself.

Initially, Research focused on testosterone-based substances. However, trials showed androgenic side effects such as acne, weight gain, mood changes, changes in libido, abnormal liver function tests and injection site discomfort. When a longer-

acting formulation was tried to reduce the frequency of injections, sperm rebounds occurred, a few pregnancies were observed, and side effects persisted. In addition, testosterone alone was sufficient and applicable for sperm suppression in East Asian men but less so in Caucasians. Combinations of progestins with androgens are sufficient to optimise sperm suppression efficacy and applicability in all ethnic groups. In addition, studies have shown that progestin combined with testosterone increases the rate and extent of suppression of FSH and LH release and may have additional direct inhibitory effects on the testes. It also allows physiological dosing of androgens, mainly eliminating hyper-androgenic side effects and minimising the time to suppress effective contraceptive thresholds.[60]

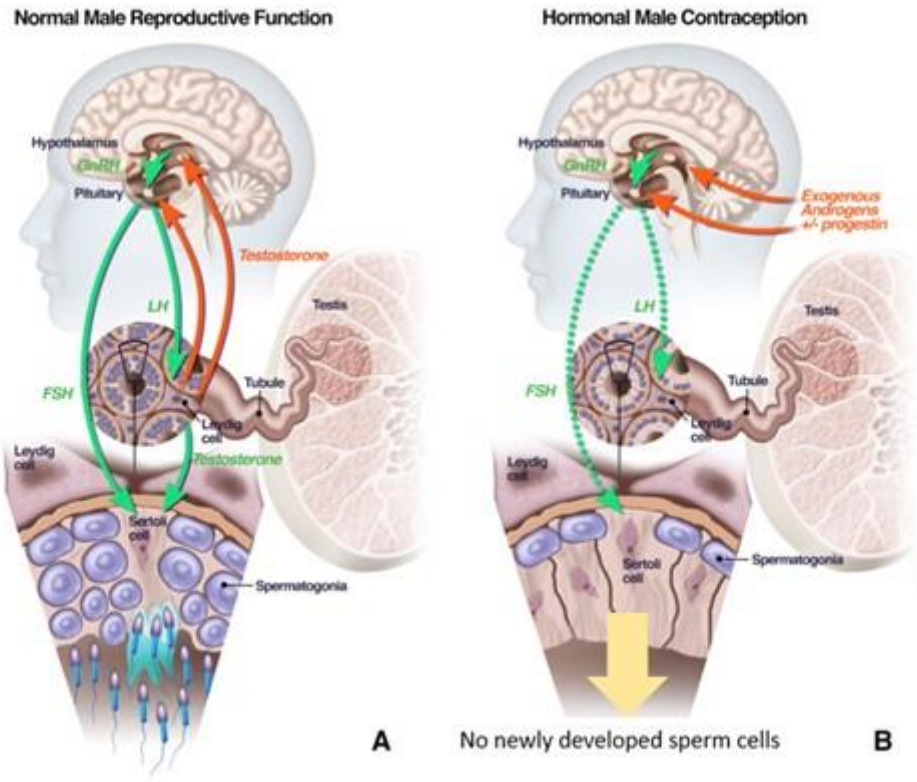


Figure 4: Mechanism of action of each hormonal male contraceptives, illustration has been modified, the permission to use has been obtained[61,62]

3.5.2 Substances

The following profiles provide an overview of hormonal contraceptives for men currently developing. The following parameters are described: The stage of development, the ingredients and the mechanism of action, the application, and the side effects. The hormonal contraceptives which are currently in development are:

1. Nestorone and Testosterone Gel

2. Dimethandrolone Undecanoate (DMAU)

3. 11-β Methyl-19-Nortestosterone 17-beta-dodecylcarbonate (11 β-MNTDC)

4. MENT Acetate Implant

1. Nestorone and Testosterone Gel[63–66]	
Development stage:	Clinical trial Phase IIb
Ingredients and mechanism of action:	Nestorone is a potent non-androgenic progestin that inhibits spermatogenesis and leads to reduced gonadotropin release in the hypothalamus through a negative feedback mechanism. Testosterone is an anabolic-androgenic steroid hormone that inhibits spermatogenesis and leads to reduced gonadotropin release in the hypothalamus through a negative feedback mechanism. It also maintains extratesticular androgenic functions.
Application:	The gel should be applied to the shoulders and upper arms once a day and is absorbed through the skin.
Side effects:	Previous studies have shown side effects such as depressed mood, changes in libido, mood swings, fatigue and irritability, and mild to moderate acne in some men. In this trial, however, the composition of the gel has been adjusted to provide physiological doses of androgens. The gel will contain a lower dose of testosterone, which may reduce hormone-related side effects such as acne, weight gain, oiliness or dryness of the skin, and mood changes. Another side effect is secondary exposure of Nestorone/testosterone contraceptive gel from the user to the partner, which can be prevented by showering or wearing a T-shirt.

2. Dimethandrolone Undecanoate (DMAU)[67–69]	
Development stage:	Clinical trial Phase I
Ingredients and mechanism of action:	DMAU is an experimental anabolic androgen and progestin. DMAU is converted into the active compound dimethandrolone. It acts as both an androgen receptor agonist and a progestin receptor agonist. Activation of the progestin receptor leads to inhibition of spermatogenesis, while activation of the testosterone receptor maintains sexual function, libido, and muscle mass. Activation of these steroid receptors leads to inhibition of gonadotropin release. DMAU has a strong binding and activating affinity for the androgen receptor, so lower doses are sufficient.
Application:	The compound can be taken daily as a powder in a capsule formulation with a high-fat meal to improve pharmacokinetics. It can also be administered as an intramuscular or subcutaneous injection every 2-6 months to avoid first-pass effect in the liver.
Side effects:	Weight gain of less than 5%, small increases in haematocrit, decrease in HDL (high-density lipoprotein) and SHBG (Sex hormone binding globulin) concentrations due to first-pass effect through the liver with oral administration (could be prevented by parenteral administration), slight decrease in adiponectin, decreased QTc time (measured variable in electrocardiogram interpretation) but still above threshold, and decreased libido were observed. All side effects were dose related and could be reduced by dose modulation. An increase in serum P1NP (Procollagen type I N-terminal propeptide) as a sign of increased bone resorption was observed, so monitoring of bone parameters is necessary. DMAU promotes a more androgenic body composition in rats.

3. 11-β Methyl-19-Nortestosterone 17-beta-dodecylcarbonate (11 β-MNTDC)[63,70]	
Development stage:	Clinical trial Phase I
Ingredients and mechanism of action:	11β-MNTDC is a selective androgen receptor modulator (SARM). It acts on both the androgen and progestin receptors. 11 β-MNTDC is a derivative of nandrolone. 11 β-MNTDC is converted by endogenous esterases. Nandrolone is a by-product of testosterone synthesis and has a higher bioactivity than testosterone. Activation of the progestin receptor leads to inhibition of spermatogenesis, whereas activation of the testosterone receptor maintains sexual function, libido and muscle mass. Activation of these steroid receptors leads to inhibition of gonadotropin release.
Application:	11β-MNTDC capsules are taken orally with food.
Side effects: Positive effects:	Increased weight, decreased HDL-C, decreased SHBG, increased LDL-C and increased haematocrit have been observed. 11β-MNTDC could stimulate endogenous myelin repair, which occurs in multiple sclerosis.[71] It also has the least hepatotoxic effects on the liver, making it a promising oral agent. 11β-MNTDC supports a more androgenic body composition

4. MENT (7α-methyl-19-nortestosterone) Acetate Implant[72–75]	
Development stage:	Clinical trial Phase II
Ingredients and mechanism of action:	7α-methyl-19-nortestosterone is a synthetic androgen. It binds to androgen receptors with greater affinity than testosterone and dihydrotestosterone. This higher bioactivity allows a reduced dose compared to testosterone. MENT leads to suppression of the endogenous hypothalamic-pituitary-testicular axis and therefore suppression of spermatogenesis due to reduced testosterone release in the Leydig cells. Due to its high potency, MENT fulfils all androgenic functions by supplying peripheral tissues.
Application:	As a subdermal implant for 1 year, releasing a dose of 1200 to 1600 µg per day.
Side effects:	An increase in haemoglobin and haematocrit, a decrease in HDL concentration, a decrease in cholesterol and an increase in blood pressure have been observed. Extrusion, pain, and androgen deficiency due to inadequate testosterone release from the implants were also reported. Participants also reported mood swings or personal reasons unrelated to the trial. As MENT is resistant to 5a-reduction, it has the potential advantage of not affecting hormone-sensitive prostate tissue.

3.5.3 Reversibility of hormonal male contraceptives

The exact time it takes for fertility to return after stopping a male hormonal contraceptive may vary depending on the individual, the specific method used and the duration of use.

With hormonal methods, such as a longer-acting testosterone preparation, full recovery of spermatogenesis is achieved by 12 months in 90% of men at any sperm threshold tested.[76]

3.5.4 Common side effects explained

Acne:

The sebaceous glands produce sebum to protect the skin from drying out. Androgens stimulate the sebaceous glands. When the sebaceous glands overproduce, they are more likely to become clogged and develop the comedones that are typical of acne.[77]

Weight gain:

Androgens are essential for maintaining lean body mass. Insufficient levels of androgens in the blood can lead to muscle loss and an increase in fat tissue.[78]

Increased haematocrit:

Androgens stimulate the production of blood cells in the bone marrow, resulting in an increased haematocrit.[79]

Influences on HDL, LDL (low-density lipoprotein), triglycerides and SHBG:

LDL is responsible for transporting cholesterol from the liver to the cells, while HDL transports excess cholesterol from the bloodstream back to the liver. If LDL levels are too high and HDL levels too low, the excess cholesterol will be deposited in the blood vessels, causing cardiovascular damage. In general, higher levels of endogenous testosterone are associated with higher levels of HDL and lower levels of cholesterol and triglycerides. There is a strong correlation between testosterone levels and SHBG levels. Low doses of androgens result in low levels of SHBG.[80] [81]

Effects on mood and libido:

Low testosterone levels are associated with depression and anxiety, while supraphysiological levels can lead to anger-hostility and verbal but not physical aggression. Testosterone also increases an individual's motivation and ability to gain and defend social status. Low levels of testosterone can therefore harm mood and sex drive.[82,83]

Hepatotoxicity:

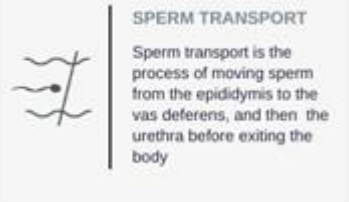
Androgens bind to intracellular androgenic steroid receptors, which translocate to the nucleus and bind to androgen response elements on DNA, inducing androgen-stimulated genes essential for cell growth and development. Unregulated growth stimulation of hepatocytes can lead to nodular regeneration and liver tumours.[84]

All these side effects are associated with supraphysiological or subphysiological doses. Treatment with testosterone in men with testosterone deficiency may benefit liver function and cardiovascular risk, highlighting the importance of finding the correct dose.[85] Particularly with oral administration, the first-pass effect plays a vital role in the actual availability of the substance in the bloodstream. After being absorbed in the intestine, the drug is transported via the portal vein to the liver, partially metabolised. The remaining part then reaches the target organs. The first-pass effect can be prevented by intravenous injection or implantation.[86]

3.6 Non-hormonal contraceptives

Non-hormonal contraceptives aim to prevent pregnancy without interfering with the hormonal cycle. As a result, these methods have fewer systemic side effects. There are four main ways of interrupting the sperm's journey from development to fertilisation.

Interruption of:	Substances, Target molecules
	1. YCT529 2. ALDH1a2 inhibitors 3. H2-Gamendazole (H2 GMZ) 4. Triptonide/ Tripterygium wilfordii 5. Glyceraldehyde 3-phosphate Dehydrogenase-S (GAPDHS) inhibitors 6. Homeodomain-interacting Protein Kinase 4(HIPK 4) 7. Testis-specific serine kinases (TSSK)1/2/3 and 6 inhibitors 8. RTI 4587 9. Meiosis-expressed Gene 1 (MEIG1)/Parkin co-regulated gene (PACRG) complex inhibitors 10. PACRG/DNALI 11. Malate dehydrogenase 1B(MDH1B) 12. Lactate Dehydrogenase C4 (LDH-C4)

	1. ADAM™ 2. (Smart) reversible inhibition of sperm under guidance (RISUG) 3. Vasalgel 4. Clean Sheets Pill 5. Tamsulosin
	1. Human Contraceptive Antibody (HCA) 2. Epididymal Peptidase Inhibitor/Eppin 3. Sodium, Potassium, ATPase α4 (ATP1A4)
	1. Soluble Adenylyl Cyclase 10 (sAC10)79,115,116 2. Cation Channel of Sperm1 (Cat Sper1)79,117,118 3. Abhydrolase Domain-containing Protein 2 (ABHD2) 4. Izumo 1 5. KCNU 6. ATPase Plasma Membrane Calcium Transporting 4 (ATP2B4) 7. Binding/Penetration Enzymes 8. Bromodomain Testis-Specific Protein (BRDT) 9. Calcium Binding Tyrosine Phosphorylation Regulated Protein (CABYR) 10. Adenine Nucleotide Translocase 4 (ANT4)

	11. Protein Phosphatase 3 Catalytic Subunit Gamma / Protein Phosphatase 3 Regulatory Subunit B (PPP3CC / PPP3R2) 12. CRISP1
ALTERNATIVE METHODS	1. Cryopreservation 2. Artificial Cryptorchidism

Table 3: Places of action of non-hormonal male contraceptives, illustration has been modified, the permission to use has been obtained[13]

3.6.1 Spermatogenesis inhibiting substances and targets

The onset of these methods takes 2-3 months because of the stored sperm cells in the epididymitis. These stored sperm cells can lead to unintended pregnancies when no additive contraceptive method is used in the first 2-3 months of substance application.

1. YCT529[87,88]	
Development stage:	Preclinical phase
Ingredients and mechanism of action:	YCT529 is a retinoic acid receptor alpha (RAR α) antagonist. Retinoic acid receptor alpha is an intranuclear receptor responsible for regulating gene expression during spermatogenesis. Inhibition of this receptor by YCT529 leads to altered protein expression and, later in development, to dysfunctional sperm cells that are unable to fertilise an egg. Only four weeks after the RAR-α gene was blocked in male mice, the mice were sterile.
Reversibilty	Fertility was fully restored four to six weeks after discontinuation of YCT529.
Application:	This substance is likely to be available as an oral pill.
Side effects:	Due to the specificity of YCT 529 for the RAR alpha receptor, no side effects were observed in mouse studies.

2. ALDH1a2 inhibitors[89,90]	
Development stage:	Preclinical phase
Ingredients and mechanism of action:	ALDH1A2 is an enzyme involved in the biosynthesis of retinoic acid in the testes. When this enzyme is inhibited, dysfunctional sperm are produced.
Application:	It is likely that the substance will be administered orally.
Side effects:	The mice showed no side effects during the trials.

3. H2-Gamendazole (H2 GMZ)[89,91]	
Development stage:	Preclinical phase
Ingredients and mechanism of action:	H2-gamendazole is a lonidamine derivate. H2-gamendazole induces a rapid increase in interleukin 1A in Sertoli cells, which causes disruption of the spermatid-Sertoli junction. This leads to the premature release of spermatids. These sperm can't fertilise an egg. Sertoli cells release less inhibin B. Reduced inhibin B is a marker of reduced spermatogenesis.[92] H2-gamendazole also binds and inhibits the activities of HSP90AB1 and EEF1A1. These two proteins are responsible for cell repair and protein synthesis and are essential for functional sperm production.
Side effects:	So far, no side effects have been observed.

4. Triptonide/ Tripterygium wilfordii[89,93–95]	
Development stage:	Preclinical phase
Ingredients and mechanism of action:	The diterpenoid triptonide from Tripterygium wilfordii (thunder god wine) exhibit unique bioactivities with potential uses as non-hormonal male contraceptives. The SPEM 1 gene controls the morphological maturation of spermatozoa. Triptonide blocks the interaction of SPEM1 with a protein called plakoglobin, disrupting the maturation process and preventing the sperm from moving forward.
Reversibility:	4-6 weeks after stopping Triptonide, fertility returns.
Application:	The substance may be administered as a single daily oral dose.
Side effects:	No evidence of systematic toxicity based on histological examination of vital organs in mice and haematological and serum biochemical analyses in monkeys. But its immunosuppressive effect may prevent its use as a contraceptive.

5. Glyceraldehyde 3-phosphate Dehydrogenase-S (GAPDHS) inhibitors[96]	
Development stage:	Discovery
Ingredients and mechanism of action:	To move forward, sperm cells need a supply of energy. GAPDHS is a specific enzyme that is part of the pathway that converts glucose into ATP. Sperm need ATP to move forward. If this pathway is inhibited, sperm can't move through the female reproductive tract.

6. Homeodomain-interacting Protein Kinase 4(HIPK 4)[89,97]	
Development stage:	Discovery
Ingredients and mechanism of action:	HIPK4 is mainly expressed in round and early elongating spermatids. This enzyme is essential for the development of a functional morphology in mature spermatozoa. Experiments have shown that HIPK4 mutant sperm have reduced oocyte binding capacity and are incompetent for in vitro fertilisation.

7. Testis-specific serine kinases (TSSK)1/2/3 and 6 inhibitors[89,98,99]	
Development stage:	Discovery
Ingredients and mechanism of action:	The role of kinases in the body is reversible protein phosphorylation. Phosphorylation is an important cellular process throughout the phylogeny, including cell growth, cell differentiation, cell cycle and cell migration. Testis-specific serine kinases are expressed in both germ cells and mature sperm, making it highly likely that they are critical for sperm differentiation and maturation. They have unique properties that increase the likelihood of finding specific small molecule inhibitors.

8. RTI 4587[89,100]	
Development stage:	Discovery
Ingredients and mechanism of action:	No side effects on ejaculatory function were observed. Issues of irreversibility in establishing efficacy in an animal model have prevented further development.
Side effects:	No side effects on ejaculatory function were observed. Issues of irreversibility in establishing efficacy in an animal model have prevented further development.

9. Meiosis-expressed Gene 1 (MEIG1)/Parkin co-regulated gene (PACRG) complex inhibitors[89,101,102]	
Development stage:	Discovery
Ingredients and mechanism of action:	The interaction of these two genes is necessary for the formation of flagella. The flagella allow the sperm to swim to the egg for fertilisation. Disruption of this interaction would result in impaired spermatogenesis and infertility.

10. PACRG/DNALI 1[89,103]	
Development stage:	Discovery
Ingredients and mechanism of action:	DNALI 1 encodes axonemal dyneins. These are large motor protein complexes that generate the movement of the flagella of sperm cells. This gene also interacts with PACRG for the maturation of the sperm tail. Disruption of this process would result in low sperm counts with abnormal sperm morphology, leading to infertility.

11. Malate dehydrogenase 1B(MDH1B)[89,104]	
Development stage:	Discovery
Ingredients and mechanism of action:	MDH1B is an enzyme that converts malate to oxalacetate. This reaction is necessary for the citric acid cycle. The citrate cycle is necessary for energy. Inhibition of this enzyme leads to reduced sperm motility and prevents sperm from fertilising an egg.

12. Lactate Dehydrogenase C4 (LDH-C4)[89,105]	
Development stage:	Discovery
Ingredients and mechanism of action:	Inhibition of LDH-C4 leads to impaired protein-protein interactions. In particular, the interaction between LDH-C and Ant 4 (ATP/ADP translocase) is affected, which appears to be essential for sufficient flagellar function.
Side effects:	The high level of specificity would avoid potential adverse effects.

3.6.2 Sperm transport inhibiting substances and targets

1. ADAM™[89,106–108]	
Development stage:	Clinical trial
Ingredients and mechanism of action:	ADAM™ is a semi-permeable hydrogel that is injected directly into a man's vas deferens, creating a permanent physical barrier to incoming sperm. The blocked sperm are broken down and absorbed while fluids are allowed to pass through. The location and composition of the gel can be regularly monitored by ultrasound to ensure contraceptive efficacy.
Reversibility:	After one or two years, the hydrogel liquefies again and drains naturally. It can also be dissolved and flushed out with a reversal solution to restore fertility sooner.
Application:	The hydrogel is injected directly into the vas deferens on an outpatient basis under local anaesthetic. The procedure is similar to a no-scalpel vasectomy
Side effects:	No systemic side effects are expected as Adam doesn't interfere with the body's internal processes.

2. (Smart) reversible inhibition of sperm under guidance (RISUG)[106,109–111]	
Development stage:	Clinical trial
Ingredients and mechanism of action:	60 mg of styrene-maleic anhydride (SMA), a copolymer dissolved in 120 µL of dimethyl sulfoxide (DMSO), is injected into the vas deferens, which forms a barrier to incoming sperm. DMSO helps SMA to penetrate the folds of the inner walls of the vas deferens and form an adherent complex. DMSO is then released and absorbed. Within 72 hours of injection, RISUG forms electrically charged precipitates in the lumen. The precipitates create an acidic environment, causing ionic and pH stress to the sperm, resulting in acrosomal damage. The mechanical barrier and denaturation of the sperm leads to inhibition of fertility. SMA also forms a complex with the proteins of the seminal fluid, protecting them from dissolution. Smart RISUG contains copper and iron oxide particles so that the gel can be moved by a magnetic field and seen on X-ray and magnetic resonance imaging. In addition, the metal ions act as a spermicide.
Reversibility:	RISUG can be removed by injecting DMSO or NaHCO3, which acts as a partial solvent. Smart RISUG contains copper particles that allow the polymer to conduct heat, so it can be liquefied with microwave heat and there is no need for an invasive procedure to remove the gel.
Application:	RISUG is administered through a small incision in the scrotum under local anaesthetic, like a no-scalpel vasectomy
Side effects:	As DMSO reacts with the tissue, morphological changes of the mucosa were observed, which disappeared after DMSO absorption. After long-term vas occlusion, focal degeneration of the seminiferous epithelium was observed in the central part of the testis.

Advantages:	RISUG showed antibacterial activity against Escherichia coli and it was hypothesised that it would also be effective against Candida albicans, Pseudomonas aeruginosa and Staphylococcus aureus. In addition, RISUG has been presented as a potential candidate for the development of an antiretroviral drug or a male vas deferens implant for HIV-free semen, suggesting that viruses may be more sensitive to the antimicrobial action of RISUG. However, further research is needed.

3. Vasalgel[112,113]	
Development stage:	Preclinical phase
Ingredients and mechanism of action:	Vasalgel is a polymer gel that is injected into the vas deferens. It blocks sperm so that they can't fertilise an egg during sexual intercourse. The sperm are absorbed by the body, similar to when men don't have sex for a while or after a vasectomy.
Reversibility:	Pre-clinical studies showed rapid restoration of sperm flow after dissolution of the hydrogel.
Application:	The gel is injected into the vas deferens during an in-office procedure.
Side effects:	Vasectomy often leads to increased pressure on the epididymis. As Vasalgel only blocks sperm and allows semen to pass through, the pressure is reduced. More information may be available after clinical trials.

4. Clean Sheets Pill[114,115]	
Development stage:	Development has stalled due to lack of funding.
Ingredients and mechanism of action:	Coordinated contractions of the longitudinal and circular muscles in the vas deferens are required to propel sperm into the female reproductive system. This compound inhibits this propulsive function by inactivating the contractility of the longitudinal muscle in the vas deferens, but not the circular muscle contraction. This results in temporary closure of the lumen of the vas deferens and inhibition of ejaculation.
Reversibility:	The effect of the pill should last 24 to 30 hours.
Application:	Clean Sheets Pill can be taken by mouth 3 hours before intercourse.
Side effects:	Ejaculatory activity and the simultaneous sensation of orgasm are not affected.

5. Tamsulosin[89,116–118]	
Development stage:	FDA (Food and Drug Administration) -approved drug for the treatment of benign prostatic hyperplasia.
Ingredients and mechanism of action:	Tamsulosin acts as an alpha1-A and alpha1-B adrenoreceptor antagonist. It is an FDA-approved drug for the treatment of benign prostatic hyperplasia. Research has shown that inhibition of the alpha1A-adrenoceptor together with the P2X1-purinoceptor results in infertility without affecting sexual behaviour or function. Combined inhibition prevents ejaculation and the presence of sperm in any ejaculatory fluid. There is potential for this or a similar compound to be used as an 'on-demand' male contraceptive, as the effect of these drugs is transient.
Application:	Tamsulosin is taken by mouth.
Side effects:	Higher doses were associated with side effects, including transient discomfort lasting up to 10 hours. At lower doses, side effects were reduced, but higher numbers of functional sperm were found in the seminal fluid.

3.6.3 Sperm mobility inhibiting substances and targets

1. Human Contraceptive Antibody (HCA)[89,119]	
Development stage:	Preclinical phase, Clinical trial Phase I
Ingredients and mechanism of action:	The Human Contraceptive Antibody (HCA) is an IgG1 monoclonal antibody that has the potential to agglutinate and immobilise sperm by binding to CD52g, a glycoprotein found in the male reproductive tract and on sperm. As a result, sperm stick together and lose their motility, leading to male infertility. HCA is currently being developed as a contraceptive delivered to women through vaginal films and as a contraceptive for couples incorporated into lubricants. Other work with HCA aims to incorporate it into a multipurpose prevention technology (MPT) that could provide protection against both pregnancy and sexually transmitted infections (HIV-1 and HSV-2 infection).
Side effects:	Pre-clinical safety evaluation using the EpiVaginal™ tissue model showed that the monoclonal antibody and its immune complexes did not affect vaginal tissue integrity or induce the release of pro-inflammatory cytokines; this was an expected result since IgG, together with IgA isotype antibodies, are naturally present in vaginal secretions.

2. Epididymal Peptidase Inhibitor/Eppin[89,120–123]	
Development stage:	Preclinical phase
Ingredients and mechanism of action:	Eppin is a surface protein found on sperm cells. In a normal fertilisation scenario, Eppin binds to the seminal plasma protein semenogelin1 (SEMG1), causing a temporary loss of forward motility. To restore mobility, SEMG1 is removed by prostatic specific antigen (PSA). Blocking Eppin with anti-Eppin antibodies or other compounds (e.g. EP055) results in permanent inhibition of sperm motility, reduced sperm pH and calcium levels, preventing fertilisation to a contraceptive level.
Side effects:	The target EPPIN is only present in the male testis and epididymal tissues thereby reducing non-specific binding concerns.

3. Sodium, Potassium, ATPase α4 (ATP1A4)[89,124]	
Development stage:	Discovery
Ingredients and mechanism of action:	Every cell in the body needs to maintain a certain ion concentration. Sodium, potassium, ATPase α4 (ATP1A4) regulates sodium and potassium concentrations, which are essential for functional sperm motility and fertilisation. Inhibition of this enzyme would result in contraception.
Side effects:	Strong side effects are not expected because ATP1A4 is a sperm-specific isoform.

3.6.4 Fertilisation inhibiting substances and targets

1. Soluble Adenylyl Cyclase 10 (sAC10)[89,125,126]	
Development stage:	Preclinical phase
Ingredients and mechanism of action:	Soluble adenylyl cyclase 10 (sAC10) is a regulatory cytosolic enzyme found in almost every cell. In sperm cells, sAC10 is activated by bicarbonate to enable motility and other aspects of capacitation. sAC10 is responsible for intracellular cAMP production. cAMP is essential for capacitation. Inhibition of this enzyme may be another contraceptive option.

2. Cation Channel of Sperm1 (Cat Sper1)[89,127,128]	
Development stage:	Discovery
Ingredients and mechanism of action:	CatSper 1 is a calcium-selective ion channel located at the tail of mature spermatozoa. Calcium influx is required for hyperactivated sperm motility during fertilisation. Four different genes make up the pore of the channel. Inhibition of CatSper or manipulation of the genes results in male infertility.

3. Abhydrolase Domain-containing Protein 2 (ABHD2)[89,129,130]	
Development stage:	Discovery
Ingredients and mechanism of action:	ABHD2 is an enzyme expressed in human sperm cells and is a key regulator of sperm hyperactivation. In the presence of progesterone, it cleaves 2-arachidonoylglycerol (2AG) into glycerol and arachidonic acid (AA). 2AG inhibits CatSper, so when ABHD2 removes 2AG, calcium enters the cell through the CatSper channel, leading to hyperactivation. By inhibiting ABHD2, 2AG doesn't inhibit CatSper anymore, so there is no hyperactivation of the sperm cell. Testosterone, hydrocortisone, lupeol, pristimerin act as ABHD2 inhibitors.

4. Izumo 1 [89,131,132]	
Development stage:	Discovery
Ingredients and mechanism of action:	The IZUMO1 protein is located on the surface of the sperm where it is required for fertilisation. During fertilisation, IZUMO1 binds to its egg receptor counterpart, Juno, to facilitate the recognition and fusion of the gametes. This is the last step before the sperm and egg combine to form a zygote. Blocking the interaction between IZUMO1 and Juno would prevent pregnancy.

5. KCNU1[89,133]	
Development stage:	Discovery
Ingredients and mechanism of action:	KCNU1 is a pH-sensitive and weakly voltage-sensitive potassium channel. KCNU1 is required for hyperactivation, acrosome reaction and fusion with the oocyte. KCNU1-dependent hyperpolarisation by potassium is required for Ca2+ influx through CATSPER. The aim is to use KCNU1 activators to induce premature sperm capacitation.

6. ATPase Plasma Membrane Calcium Transporting 4 (ATP2B4)[89,134]	
Development stage:	Discovery
Ingredients and mechanism of action:	ATP2B4 is a calcium pump located mainly in the sperm tail. It catalyses the hydrolysis of ATP coupled with the transport of calcium from the cytoplasm to the extracellular space. It is crucial for maintaining intracellular calcium homeostasis by removing calcium ions from cells against very large concentration gradients. If ATP2B4 doesn't function, sperm cannot hyperactivate because of the close interaction of ATP2B4 with CatSper. 5-(and-6)-carboxyeosin diacetate succinimidyl ester is a known inhibitor of ATP2B4.

7. Binding/Penetration Enzymes[89,135]	
Development stage:	Discovery
Ingredients and mechanism of action:	When sperm and egg meet, enzymes in the sperm begin to dilute the egg membrane. By prematurely mimicking the interaction in epididymitis with certain substances, the sperm cells are no longer able to penetrate the egg membrane.

8. Bromodomain Testis-Specific Protein (BRDT)[89,136,137]	
Development stage:	Discovery
Ingredients and mechanism of action:	BRDT is a transcriptional regulator expressed in the testis. BRDT is involved in chromatin organisation and transcriptional regulation during spermatogenesis. BRDT is also present in the pituitary gland and appears to be involved in the timing of male puberty. Inhibition of BRDT results in infertility. JQ1 is a small molecule that inhibits BRDT.

9. Calcium Binding Tyrosine Phosphorylation Regulated Protein (CABYR)[89,138,139]	
Development stage:	Discovery
Ingredients and mechanism of action:	CABYR is a protein that is essential for the development of a major part of the flagellum during spermiogenesis. It is also important for signalling, regulation of flagellar motility, capacitation, and the acrosome reaction. Inhibition of the expression of this protein results in severe subfertility.

10. Adenine Nucleotide Translocase 4 (ANT4)[89,140]	
Development stage:	Discovery
Ingredients and mechanism of action:	This is the most abundant protein in male germ cell mitochondria. This protein is responsible for the exchange of ADP (adenosine diphosphate) / ATP (adenosine triphosphate) across the inner mitochondrial membrane. ANT4 is particularly active during male meiosis. Inhibition or premature activation of ANT4 could deprive sperm of the energy they need to reach and fertilise an egg.

11. Protein Phosphatase 3 Catalytic Subunit Gamma / Protein Phosphatase 3 Regulatory Subunit B (PPP3CC / PPP3R2)[89,141]	
Development stage:	Discovery
Ingredients and mechanism of action:	The somatic phosphatase calcineurin consists of a catalytic subunit (i.e., PPP3CC) and a regulatory subunit (i.e., PPP3R2). PPP3CC and PPP3R2 appear to be involved in sperm motility via an inflexible middle section of the flagellum. Molecules have been identified that act on sperm calcineurin and cause infertility. In mice, fertility returned one week after treatment was stopped.

12. CRISP1[89,142]	
Development stage:	Discovery
Ingredients and mechanism of action:	CRISP1 is secreted into the lumen of the epididymal tubule and is found on the surface in the post-acrosomal compartment. Two populations of CRISP1 proteins are bound to the gametes. One fraction with a labile association and another fraction with a firm association. Release of the labile fraction appears to be necessary to prevent premature capacitation. CRISP1 stimulates sperm orientation by modulating sperm hyperactivation and regulates CatSper. The inhibition of CRISP1 could lead to infertility.

3.6.5 Alternative methods

1. Cryopreservation[143]	
Development stage:	Available
Ingredients and mechanism of action:	Cryoprotectants (glycerol, dimethyl sulfoxide, ethanediol and propanediol) are used to protect sperm from the damaging effects of cold and to preserve sperm. This procedure is recommended before a non-scalpel vasectomy.

2. Artificial Cryptorchidism[144]	
Ingredients and mechanism of action:	For adequate spermatogenesis, the testes need to be kept 2°C below body temperature. Pushing the testes up into the inguinal canal and keeping them there during the day has a significant effect on sperm count and motility.

4 Conclusion and Discussion

Effective family planning is the cornerstone of a stable, prosperous, and equal society. Meeting the needs of reproductive couples would prevent 68% of unintended pregnancies, 72% of unsafe abortions and 62% of maternal deaths.[145] By making reproductive autonomy a priority, everyone has the opportunity to complete their individual development before starting a family. All parents want to be able to provide for their offspring. A prerequisite for this is the availability of sufficient resources. The United Nations predicts the world's population will reach 10.4 billion by 2080.[146] As the availability of resources declines, meeting everyone's basic needs will become a challenge. For this reason, the development of safe, reliable, cost-effective, and reversible contraceptive methods is coming to the fore.

In the past, many attempts to develop alternative methods have failed because pharmaceutical companies have questioned the profitability of these methods. Recent surveys have shown that 50-85% of men would be willing to use the product and pay out of pocket if it were commercially available.[46]

In general, the aim of new contraceptive methods is not to free women from contraceptive choices but to give everyone access to a method that is right for them. New contraceptive methods should include the demands of the whole sexuality spectrum of lesbian, gay, bisexual, transgender, queer, intersex, and asexual people. An increase in public interest and research would therefore encourage the development of multipurpose prevention to protect people from sexually transmitted diseases. These technologies would be an excellent success for sexual and reproductive health.

Male contraceptives can be divided into two different groups hormonal and non-hormonal methods:

Researchers and the pharmaceutical industry already have much experience with hormonal contraceptives for women. The experience has positively affected the speed of development of hormonal contraceptive methods for men. Because hormones mediate the body's response to external changes, there is high variability in hormone levels, making it difficult to determine the optimal dose. So, there are potential side effects, such as acne, mood changes, and decreased libido.[147] Additionally, these methods require regular administration to find the optimal dose

and may not be suitable and accessible for all men. Safety and a low side-effect profile are top priorities in developing new contraceptives, as they should not affect the user's health. Some hormonal options benefit body composition, myelin repair or libido.[59,71,148] This would increase the acceptability of the hormonal contraceptive method. Nevertheless, a recent survey of 1,500 potential male contraceptive users has shown that men prefer to use a non-hormonal method of contraception.[44]

The development of non-hormonal contraceptives is benefiting from the latest technologies, which have identified a large number of compounds that offer the prospect of safe, reversible options with few side effects because they do not act on systemic receptors but on targets that interrupt the process from sperm development to egg fertilisation. Vas occlusion procedures, which physically block vas deferens, are already in clinical trials. A mechanism called RISUG could be a potential candidate for developing a multipurpose device with beneficial antimicrobial and antiretroviral effects.[110]

Clinical trials are still in their infancy for many of the molecular targets. As research progresses, more information about their side-effect profile and reversibility will be available.

The level of compliance with male contraceptives will depend on various factors, including the acceptability and accessibility of the method, the side effects and risks, and the level of education and information provided. Factors such as social and cultural norms, as well as the availability and cost of the methods, also play an important role in shaping men's decisions to use male contraceptives. Non-profit organisations such as the Bill and Melinda Gates Foundation, the Male Contraceptive Initiative and the Guttmacher Institute are promoting education, developing alternative contraceptive methods, and investing in sexual and reproductive health care. This paper aims to provide an overview of current research on male contraception and demonstrate the importance of contraception for every human life. To participate and spread the message of reproductive autonomy for all, the Male Contraceptive Initiative (https://www.malecontraceptive.org/) and the Centre for Male Contraceptive Research and Development (https://www.malecontraception.center) provide structural information on their website.

To sum up, it is clear that it is only a matter of time before a new contraceptive is available, so it is not just an illusion but will hopefully soon become a reality.

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