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REVIEW ARTICLE

An Update of Male Contraception: A Review of Cellular Perspective

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Abstract

Introduction: Similar to the world, Indonesia also undergoes a population explosion. One solution to overcome this population problem is to conduct contraception. Although woman contraception is widely used, still the role of man is needed. There are a few methods in male contraception, but all is still not proven optimally. Therefore, it is intend to understand more about the cellular mechanism of male contraception. Methods: A computerized finding process of database in Pub med which related to the key words was performed for obtaining data. After that, the most update and relevant articles were reviewed and selected. Results: The results are mainly revealing the regimens that are administered in male hormonal contraception and substances that are used in immunocontraception. Furthermore, this reviews also reveales the cellular mechanism of both types of male contraception. In male hormonal contraception, the mechanism was depends on negative feedback in hypothalamic-pituitary-gonadal axis by regimens to impair the spermatogenesis into severe-oligozoospermia or azoospermia. In addition, immunocontraception was based on 'vaccination' concept in which antibodies recognize proteins in the spermatozoa as "non-self" thus spermatozoa may be destroyed. Conclusion: It is necessary to understand the cellular mechanism, thus the development of male contraception increases. Further researches should be conducted to confirm the cellular mechanisms.

Keywords: *Male hormonal contraception, Testosterone, Progestin, Negative feedback, Immunocontraception, Sperm antigen.*

Introduction

As one of the developing countries, Indonesia was also poses population explosion. Indonesia population has exceeded more than 255 x 10^6, while the world population is 6.43 x 10^9 [1, 2]. The large population is also accompanied by an increasing growth rate, thus encouraging the government pass through a program that control population growth, namely family planning by contraception method. Contraception successfully suppressed the population growth rate of 0.33 in decade of 1980-1990, then decreased by 0.49 in decade of 2000-2010 and again decreased by 0.113 in 5 years of 2010-2015 [3].

Contraception is aimed to prevent pregnancy, maintain distance between pregnancies, and limit the number of family members; thereby population density in an area can be reduced. Contraception is available in both women and men, but the most widely used contraception method is in women by 93.66% and in men by only 6.43% [4]. Although contraception in women is very effective, there are contraindications of using contraception in certain groups of women. This issue encouraging men to play a role in preventing pregnancy by applying specific contraception for them [5].

The use of contraception methods in men is still less and has many disadvantages, such as the use of condoms and vasectomy. Meanwhile, the hormonal contraception which affects the spermatogenesis process was still not proven optimally.

In addition, the non-hormonal contraception, such as immunocontraception was also still under research. Up till now, there have been many publications about male contraception. With the intention to understand more about the different response of both methods, this review was focused on revealing the cellular mechanism, therefore the indefinable marvel of male contraception is breaking and useful for the development of the advanced researches.

Methods

A computerized finding process of database in Pub med was underwent to obtain data. The role of men in contraception whether hormonal or non-hormonal (immunocontraceptive), specially the cellular mechanism comprised of surfing database. The words such as male hormonal contraception, testosterone, progestin, negative feedback, immunocontraception, sperm antigens were applied in database surfing process. Then, the most update and relevant articles were reviewed and selected.

Results

Male contraception

Requirements for contraception are : 1) methods must be effective, 2) can be accepted by the acceptor and their partners, 3) have minimal or no side effects, 4) can be reversible, and the last 5) is available and affordable [6]. According to biological actions, the method of male contraception is categorized into three, namely 1) the method that blocks sperm transport into the female reproductive tract, 2) methods that suppress spermatogenesis, and 3) methods that impair the maturation or sperm ability in fertilization.

Spermatozoa that are blocked from transporting into the female reproductive tract are based on contraception with the vas deferent as the target organ, i.e vasectomy method. In addition, there are also other methods, namely the use of intravas copper and injection of non-sclerosing agents (styrene maleic anhydride=SMA) into the vas deferens. Another method of contraception is to suppress spermatogenesis using hormones in men, such as testosterone and progesterone. Methods that impair sperm maturation or the ability to fertilize are methods that change the structure of proteins that can bind spermatozoa. The structure of the protein has a function in spermatozoa maturation; thereby the target organ is the epididymis. The categories include condoms, vasectomy, hormonal contraception, medicinal plants, ultrasound, intravascular devices, reversible inhibition of sperm under guidance (RISUG) and immunocontraception [7].

Condom

Condoms are contraception made from latex and polyurethane. This type of contraception has advantages, such as low prices, easy use, few side effects and reduced transmission of sexual infections. However, this contraception has a failure rate of 17% per year [7].

Vasectomy

Vasectomy was first performed in the early 19th century in dogs in England. This method eventually developed into clinical practice as a contraception method. Vasectomy has a high level of effectiveness with a failure rate of less than 1%. Side effects of about 1 to 2% experience symptoms of hematoma, 3.4% experience infection and 15 to 52% experience chronic pain in the scrotum. [7]

The use of medicines derived from plants which can cause infertility.

The lack of available contraception makes the searching for ingredients that can be candidates for contraception use. Contraception methods that use plants include:

- Gossypol which can inhibit spermatogenesis and sperm motility.
- Triptolide which is a derivative of the *Trypterigium wilfordii* plant causes a decrease in sperm count.
- Indenopyridines which inhibits spermatogenensis.
- Lonidamine which impairs the adhesion between spermatids and Sertoli cells which results in early spermiation.

- Retinoic acid which inhibits testicular specific acetaldehyde dehydrogenase thus inhibiting spermatogonia from entering the meiosis phase. This will inhibit the process of spermatogenesis and others [7].

Ultrasound

This method uses treatment by placing the scrotum on the water bath with field beams in the form of ultrasound transduction. The advantage of this method is that ultrasound is relatively affordable and widely available, works locally without systemic effects, and is suitable for people who do not want to use drugs. This method will inhibit spermatogenesis, but unfortunately, this method is still unclear yet.

Intravas device

This tool inserts nylon on the urethra, which prevents sperm from allowing liquid to keep passing through it. The method is also inserted through a small incision in the scrotum which prevents the formation of motile sperm. This method may be inadequate during recovery [7].

Reversible Inhibition of Sperm under Guidance (Risug)

This method injects styrene maleic anhydride (SMA) dissolved in dimethyl sulfoxide (DMSO) into the vas deferens with a small incision. This will cause damage to the sperm membrane which results in sperm that are not alive. This method is still being developed to be an alternative to vasectomy [7]. The last two male contraception methods, namely hormonal contraception and immunocontraception will be explored in separate sections for cellular mechanism.

Male Hormonal Contraception

Male hormonal contraception refers to the hypothalamic-pituitary-gonadal axis that affects the process of spermatogenesis by regulating the release of pulsatile gonadotropin-releasing hormone (GnRH) in the hypothalamus and stimulating episodic hypogonadotropin secretions such as follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the pituitary.

FSH triggers Sertoli cell stimulation, while LH triggers the production of testosterone, which both promotes the process of spermatogenesis. The level of intratesticular testosterone is much higher compared in serum for normal spermatogenesis process [8-10].Conversely, dihydrotestosterone (DHT) as a testosterone conversion product, doesn't not appear to be related to the process of spermatogenesis [11]. In addition to testosterone, there are other substances that play role in the hypothalamic-pituitary-gonadal axis, such as 1) kisspeptin, a group of amino-acid peptides that have an important function in GnRH secretion, 2) estradiol as a product of testosterone conversion through aromatase and 3) inhibin B as a product secretion by Sertoli cell [12].

Cellular Mechanism of Male Hormonal Contraception

In the process of spermatogenesis, type a spermatogonia develops into type B spermatogonia, which differentiates through mitosis into primary spermatocytes. Then this process is continued by meiosis into secondary spermatocytes and spermatids. Spermatid will experience the process of spermiogenesis into spermatozoa. In addition, there are androgen receptors in the testis, such as immature germ cells, Sertoli and Leydig cells, smooth muscle and myoid cells. Certain effects on Sertoli and Leydig cells may disturb the spermatogenesis, which is different from the effect on germs and myoid cells that do not disturb spermatogenesis [13-17].

Moreover, inhibition of androgen receptor may impair spermatogenesis [18]. This process of spermatogenesis demands a high level of intratesticular testosterone, which is related to hypothalamic-pituitary-gonadal axis. The concept of hypothalamic-pituitary-gonadal axis underlying the male hormonal contraception mechanism.

The disruption of the negative feedback mechanism on the hypothalamic-pituitary-gonadal axis by impaired pulsatile release of GnRH and suppression of gonadotropin secretion results in loss of endocrine activity and spermatogenesis in the testes (Fig. 1). This can be performed by using only high doses of testosterone alone or combination regimens, as listed on the table. (Table 1).

This high dose will prevent hormonal release of GnRH from stimulating the formation of FSH and LH; thereby spermatogenesis is disrupted [19]. In developing hormonal contraception, spermatogenesis is expected to be impaired; hence sperm are not produced

[5]. The target of male hormonal contraception is to achieve severe-oligozoospermia (sperm concentration less than 5 million/ml) or even azoospermia (no sperm in the ejaculate/semen).

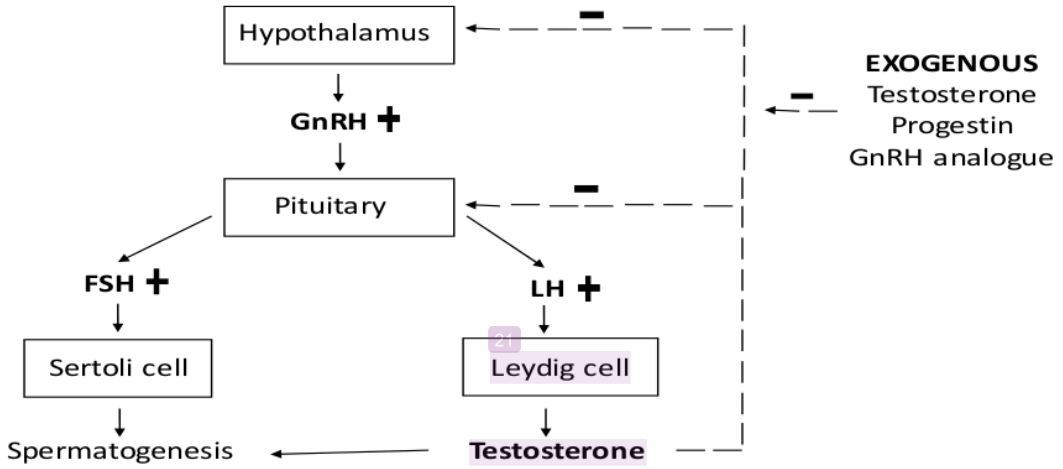

Figure 1: The mechanism of male hormonal contraception

Table 1: The regimen of male hormonal contraception

Testosterone alone	Testosterone + Progestin	Testosterone + GnRH analogues
Testosterone propionate Testosterone enanthate Testosterone undecanoate Testosterone buciclate 7 alpha – methyl-19-nortestosterone (MENT) Testosterone gel	Medroxyprogesterone acetate (MPA) Cyproterone acetate Levonorgestrel Desogestrel Norethisterone (NET)	GnRH agonist GnRH antagonist

Testosterone Alone

A study conducted by Reddy PR and Rao JM showed azoospermia from respondents who were injected by 25 mg of testosterone propionate (TP) daily in 60 days [20]. Furthermore, a multicenter study conducted by the WHO Task force on methods for regulation of male infertility proved that 70% of respondents who had a musculary injection with 200 mg of testosterone enanthate (TE) weekly in 6 months became azoospermia [21].

In addition, this study also revealed differences in endocrine responses between Asian (91%) and Caucasian (60%) respondent who became azoospermia. Other studies demonstrated the probable rationalization for exploring ethnic differences, such as alpha reductase levels, lower baseline testosterone level, testosterone susceptibility and metabolic clearance rate and body fat content [22, 23].

Besides studies on TP and TE, there were studies of testosterone undecanoate (TU) performed by Gu YQ which proved that a long-acting monthly injection of TU resulting in 76% of respondents to < 3 million/ml or azoospermia with one pregnancy, while Gu Y proved that injection of 500 mg TU monthly effecting respondents to < 1 million/ml or azoospermia with 9 pregnancies (1.1%) [24, 25].

Furthermore, other long-acting testosterone, was also being investigated by administering 1200 mg IM of monthly testosterone buciclate (TB) and demonstrating suppression of spermatogenesis [26]. Finally, 7 alpha-methyl-19-nortestosterone (MENT) as a synthetic androgen which is more effective than testosterone, was also impaired spermatogenesis by effecting gonadotropin level [27].

Testosterone and Progestin

Since testosterone alone regimens cause many side effect and is not high efficacy, the development of male hormonal contraception studies focuses on a combination of testosterone and progestin regimens. The mechanism of progestin is assumed to play

role in negative feedback on the hypothalamic-pituitary-gonadal axis, disturbance of LH receptor expression and straight impair with sperm [28, 29].

The combination of these hormones is proposed to achieve high efficacy of sterility by progestin action, but less side effect by maintaining physiological level of testosterone. A study of testosterone with medroxyprogesterone acetate (MPA) showed that 67% of respondent reached azoospermia, while another study of 19-nortestosterone with depot MPA proved 97.8% respondent achieved azoospermia [30, 31].

Other progestins, such as levonorgestrel, desogestrel and etonogestrel are oral contraception. A study with 300 µg of desogestrel per day and 400 mg of depot testosterone s.c guided to azoospermia in the all respondent [32]. The same result was demonstrated also by studies using etonogestrel and testosterone [33]. As female contraception, norethisterone (NET) combined with TU showed high efficacy [34, 35].

Testosterone and GnRH Analogues

If the GnRH antagonist works by inhibiting the GnRH receptor, the GnRH agonist acts by organizing the antigonadotropic influence that is contradictory through GnRH downregulation. There were studies about combination of testosterone and GnRH agonists which resulted resulted in 23% respondent becoming azoospermia.[36, 37] Conversely, there were also studies that investigated the combination of testosterone and GnRH antagonists that showed better results [38-41].

Immunocontraception

Furthermore, the development of male contraception is focused on post-testicular, with the aim that spermatozoa is still produced but cannot fertilize the oocyte [6]. One method that applies this post-testicular concept is called immunocontraception. Immunocontraception will influence the immune system to produce antibodies that can recognize proteins that are in the body and are "self".

Antigen-like proteins are made into "non-cells" by combining or placing them in experimental animals. Animal injected by proteins will make antibodies to it. As a result of the presence of these antibodies, the biological function of the proteins used as antigens will disappear, resulting in conditions that cannot cause fertilization [6].

In other words, this method will provide vaccines that can recognize proteins in spermatozoa, oocytes, or reproductive hormones that can prevent pregnancy or the formation of gametes. According to Naz et al, immunocontraception could be categorized into categories namely 1) gamete production, 2) gamete function and 3) game outcome [42]. Gamet production involves the role of reproductive hormones in producing gametes, namely GnRH, FSH and LH, while gamete outcome includes the role of human chorionic gonadotropin (hCG) in maintaining pregnancy.

Moreover, gamete function includes gamete formation. In addition, gamete function is associated with gametes, both spermatozoa and oocyte by manipulating spermatozoa/oocyte-zona pellucida (ZP)-based mechanisms. Since in this review is about male contraception, discussion of cellular mechanism is limited to GnRH and spermatozoa antigens.

Cellular Mechanism for the Administration of Antibodies to GnRH

GnRH plays a role in controlling and producing sex steroid hormones through FSH and LH.[43] Success in performing GnRH as an immunocontraception target is also aided by the presence of adjuvants that act to damage immune tolerance to GnRH and make it more effective.

The results of the vaccine given to GnRH are that the synthesis of LH and FSH is terminated, thus completing testosterone production and spermatogenesis. The mechanism of administering the anti-GnRH vaccine is GnRH which is the blood circulation recognized by GnRH antibodies.

These antibodies will bind GnRH so that when it reaches the pituitary, GnRH cannot bind to its receptor. GnRH receptors that cannot bind to these proteins will make the signal transduction process in synthesizing FSH and LH not occur.

FSH and LH that are not produced will make the test is unable to process spermatogenesis or gonadal atrophy that occurs, thus spermatozoa are not produced. The process of

spermatogenesis cannot be performed, due to FSH and LH whose receptors contained in the testes are not produced thus signal transduction does not occur too [44].

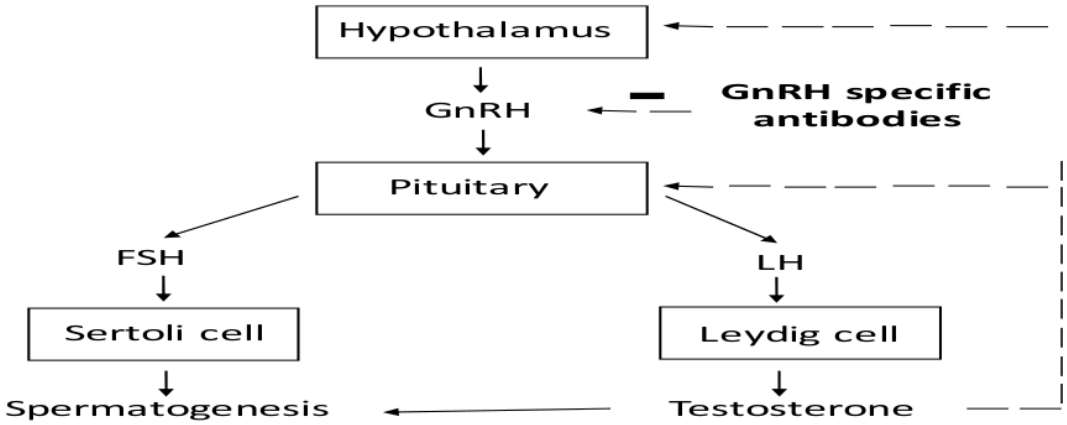

Figure 2: Immunocontraception with GnRH as a target

In experiments conducted with deer by Killian L, GnRH was tied to a keyhole limpet hemocyanin (KLH) so that the protein became immunogenic.[44] The KLH-GnRH was given as much as 500 mg, which added as much as 1: 1 adjuvant then one month later, boosting added containing 300 mg KLH-GnRH with 1: 1 adjuvant.

The results of the test, namely in the control when not mating season, showed testosterone concentration of less than 100 ng/ml and became normal again by 350 to 400 ng /ml in October and November. The deer given by KLH-GnRH in September and added boosting in October showed a low testosterone level of around 11-74 ng/mL with antibody titer of 12,000 to 18,000 during the mating season. Apart from a decrease in testosterone, there is also a decrease in the testicular period of half of the normal testes [44].Cellular mechanism for the administration of antibodies to LDHC4 Spermatozoa antigens could be isolated from spermatozoa such as lactate dehydrogenase (LDH-C4), or could be glycoproteins on the spermatozoa surface acquired from epididymic secretions during transit through the epididymis, such as epididymal protease inhibitor (Eppin) and PH-20. (Fig. 2) LDHC4 is an enzyme that is used to metabolize energy in spermatozoa.

This enzyme is widely distributed in the cytoplasm and spermatozoa mitochondrial matrix. This enzyme is also found in small amounts in the acrosome external membrane and acrosome capsule [45].

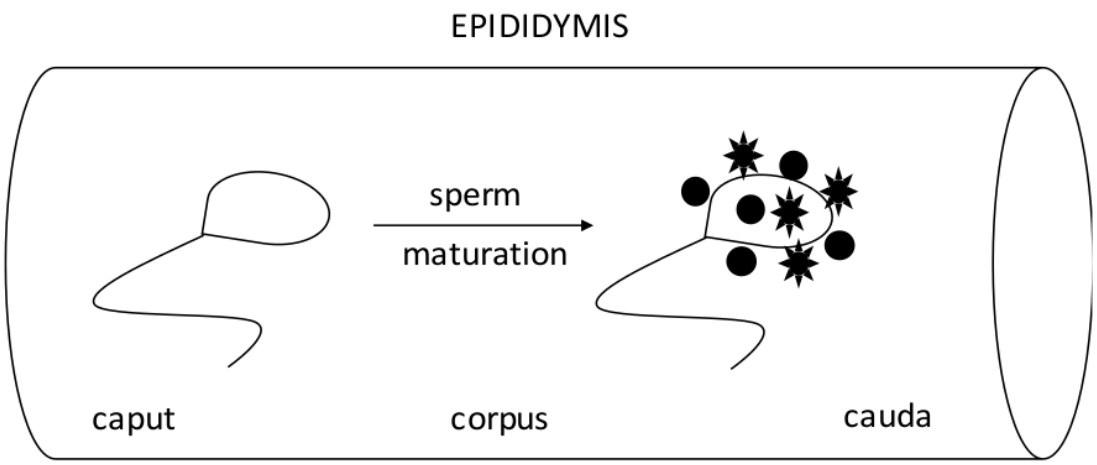

Figure 2: Spermatozoa surface protein profile at spermatozoa maturation

LDHC4 given antibodies will inhibit enzyme activity of the spermatozoa cells. These obstacles interfere with energy metabolism and spermatozoa motility. LDCH4 antibodies bind these enzymes to the cytoplasm and acrosome capsule in spermatozoa.[45] The antibody-bound enzymes cannot make the conversion of pyruvate to lactate in the presence of NADH oxidation to NAD+ which is essential for producing adenosine triphosphate (ATP) by glycolysis so that metabolism for motility is disturbed [46].

Administration of antibodies to LDCH4 results in a decrease in volume when spermatozoa are ejaculated at 30-45 days after immunization around 1.25%.The motility of immunized spermatozoa also decreased by around 47%. Viability that occurs after immunization decreases by about 48% and HOS that occurrs also decreases by about 37% and abnormalities in spermatozoa increase by 63%. These results proved that LDCH4 plays a role in spermatozoa maturation [47].

Cellular Mechanism of Giving Antibodies to Eppin

Eppin is a protein that is specific for male reproductive tissue. When this protein is secreted, it will be on the surface of the spermatozoa in a complex containing lactotransferin, clusterin, and semenogelin. This protein complex will modulates protease prostate-specific antigen (PSA) activity and protects spermatozoa from microbes. Active PSA will break down cementogelin thus it will liquidate spermatozoa [48].

Contraception using anti-Eppin antibodies will damage the cAMP regulation pathway in spermatozoa. Production of cAMP by adenylcyclase requires $HCO3^-$ and Ca^{2+} and loss of progressive motility which correlates directly with the loss of cAMP from the inactivation of the Adcy10 gene. In addition to the Adcy10 gene, damage to specific genes for ion exchange of Na^{2+} / H^+ ions (Slc9a10) affects the motility of spermatozoa.

Provision of anti-Eppin correlates with the motility component of cAMP, Ca^{2+}, and pH. Anti-Eppin antibodies also damage the intracellular pH of spermatozoa. Damage to internal pH is due to the absence of exchange between Na^+/H^+ in spermatozoa flagella so that motility or movement of flagella becomes disrupted. In addition, antibodies to Eppin will make semenogelin unable to be decomposed by PSA and no liquidation of spermatozoa will occur thus the motility of spermatozoa will be inhibited [49]. Motility of inhibited spermatozoa due to the administration of anti-Eppin antibodies (B4) made spermatozoa mileage shorter of 81 ± 9.6 with controls without antibodies giving a distance of 131.4 ± 36.

In addition to travel distance, the spermatozoa motility distance that moves straight due to antibody (B4) was only 8.7 ± 2.7 while the control was 21.8 ± 5.4. Decreasing the spermatozoa mileage given by anti-Eppin antibodies also correlates with a decrease in the speed of movement of the spermatozoa.

The speed of movement of the spermatozoa in the control was 129 ± 13 and in spermatozoa the administration of anti-Eppin antibody was (B4) 86.8 ± 10.3.[48] These results indicate that administration of anti-Eppin antibodies has an inhibitory effect of motility and accelerate the movement of spermatozoa resulting from intracellular changes such as decreased cAMP and intracellular pH which makes spermatozoa flagella unable to move as normal.

Cellular Mechanism of Giving Antibodies to PH-20

The presence of antibodies to Eppin also shows other proteins in spermatozoa that play a role in the maturation of these spermatozoa and become candidates for immunocontraception. The protein is PH-20 and LDH-C4 testis specific lactate dehydrogenase. PH-20 protein is an antigen present in the plasma membrane spermatozoa.

This protein has hyaluronidase activity so that the acrosome reaction can occur by attaching spermatozoa and can penetrate the cumulus layer and bind spermatozoa to the pellucida zone. PH-20 immunization with its antibodies provides changes in the form of orchitis, loss of germ cells (aspermatogenesis), phagocytic macrophages of spermatozoa in the lumen of the testis and proximal cauda of epididymis, as well as abnormal forms of spermatozoa or absence of spermatozoa in the lumen of distal epididymal. PH-20 stimulates IgG formation

against it and makes cytolysis and form the immune system. Antibodies that bind to spermatozoa can activate complementary pathways and facilitate cell destruction. Antibodies bind to germ cells that can facilitate these cells to be removed through opsonization and phagocytosis of macrophages from spermatozoa in the testis and proximal cauda epididymis. Macrophages penetrate the testicular blood barrier to reach the lumen of the seminiferous tubules [50].

Experiments carried out by injecting PH-20 antibodies made spermatozoa lose the acrosome structure. The injected antibodies make the presence of neutrophils in the epididymis. PH-20 antibodies will react with the posterior head and inside the acrosome membrane. The lumen testis and the proximal caudal epididymis in this immunization show the presence of macrophages that phagocytize germ cells and spermatozoa [50].

Conclusion

The cellular mechanism of male hormonal contraception depends on negative feedback in hypothalamic-pituitary-gonadal axis by testosterone or combination plus progestin regimens to suppress the gonadotropin secretion and affect intratesticular testosterone then finally impair the spermatogenesis process become severe-oligozoospermia or azoospermia.

In addition, immunocontraception in men uses antibodies that can recognize proteins in the spermatozoa as "non-self" so that the testicular barrier in the male reproduction becomes disrupted and the immune system can attack the antibody's target protein, thus the spermatozoa lost its motility or vitality. By understanding cellular mechanism, hopefully the development of male contraception is in increasing, although it still requires further researches.

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