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Review Article

Comparison of Testosterone Undecanoate (TU) and Testosterone Enanthate (TE) with Combination of Depot Medroxyprogesterone Acetate (DMPA) on Spermatogenic Cells in Men

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Abstract

Introduction: Male hormonal contraception known as safe, effective, and reversible contraception. World Health Organization (WHO) multicentre study has been conducted a clinical study administrating of testosterone regimens and progestin to male with a remarkable result. Azoospermia or severe oligozoospermia occurred in men with injection of Testosterone Enanthate (TE) and Depot Medroxyprogesterone Acetate (DMPA) as well as Testosterone Undecanoate (TU) and DMPA for a longer period. Decreasing gonadotropin as well as testosterone could lead to the amount of spermatogenic cells population declining by suppressing the development of many kinds of cells. This narrative review was to compare how spermatogenic suppression in TE and TU with Combination of DMPA. Method: We are randomly select article or journal from several databases and individual journal in certain keywords. The keyword used were : (male hormonal contraception) OR (regimen testosterone)) AND (progestin) OR (DMPA) OR (Testosterone enanthate) OR (Testosterone undecanoate) OR (male hormonal contraception combination)) AND (DMPA to spermatogenic cells) OR (Testosterone and DMPA to germ cell development)). After initial searching from databases and individual journal website, 16 scientific articles or journals selected for the review. Result: The result indicated that injection of TE and DMPA had suppressed spermatogenesis, might not suppressed sperm production for a longer period but the decreasing in type B spermatogonia until pachytene spermatocyte did occur. On the other hand, injection of TU and DMPA could maintain the suppression of sperm production for a longer period due to sustainable higher serum MPA with combination to even longer-acting TU would have more profound effect for that. Conclusion: It was known that combination of TU and DMPA might have better suppression on sperm production than TE and DMPA, otherwise further research needs to be obtained from the combination of TU and DMPA on spermatogenic development and the association with intratesticular testosterone.

Keywords: *Male hormonal contraception; Gonadotropin; Testosterone; Testosterone Enanthate and DMPA; Testosterone Undecanoate and DMPA; Spermatogenic suppression.*
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INTRODUCTION

We know that density of population still become one of global problem which affect family's health and economic situation.[1] Population census of Indonesia in 2020 have report that there was an increasing of population almost 35.56 million inhabitant led into 141 inhabitant per km^2 of population density.[2] Stakeholder then urge to do a program to control population, Keluarga Berencana (KB), which implementing contraception, provided for woman and men.[3]

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As men have an equal contribution in this program, male contraception had been developed, but only limited on condom and vasectomy. Condom was indicated effective for protection against sexual transmission disease but leads to high rate of pregnancy until 17% per year. Vasectomy had failure rate less than 1% with operation procedure that effective to suppressed spermatogenesis but permanent and irreversible.[4]

Hormonal contraception become an alternative man contraception that potentially safe, viable, effective, and reversible.[5] DMPA is one of them, the long-acting progestin from progesterone derivate. DMPA acts as suppressor of pituitary gonadotropin secretion, previously used by female contraception, thus suppressing spermatogenesis, and decreasing the total of sperm.[6] Using DMPA as contraception, especially for woman, indicated 97% effective to prevent pregnancies. However, as single-agent contraceptive for men has lower effect on non-gonadal tissue androgen dependent.[4] So, we need a combination of DMPA with ester testosterone, which had been researched as men hormonal contraception, to replace the depleted of peripheral testosterone by DMPA.[7]

The combination of two kinds of steroid, progestin, and ester testosterone would pull together, giving more suppression effect on hypothalamus-pituitary axis and secretion of gonadotropin. In other study, injection ester androgen indicated could supress the secretion of gonadotropin and become the replacement of androgen loss due to suppression of gonadotropin by DMPA.[5] As we know, androgen/testosterone contribute to the development of spermatogenic cells[8] which also decreasing its total population due to androgen negative feedback mechanism. During late 1980 until 1990, WHO have been done the research for TE as male hormonal contraception. On clinical study indicated that, 65% men became azoospermia and 30% became severe oligozoospermia due to TE injection alone with 0-0.8 pregnancies per 100 person-years in first trial.[9] Study in combination of DMPA and TE injection resulting higher azoospermia, until 95.7%.[1] Unlike TE, the other ester androgen, a long-acting TU, have been undergo phase II and III efficacy of clinical trial. In this study, injection of 500 mg TU every month achieving 299 men azoospermia and oligozoospermia in 308 Chinese men within 6 months. From phase III trial, 95% Chinese men became azoospermia and severe oligozoospermia after same dose and period of injection.[4] However, reappearance of sperm was observed in six men and resulting in one pregnancy, also in severe oligozoospermia men, nine pregnancies occurred. This might be due to incomplete gonadotropin suppression resulting in variation of androgen action for spermatogenesis then failure to suppress spermatogenesis.[4]

As well as TE combination with DMPA, this kind of therapy achieving superior result than TU alone. Thirty Chinese men conducted in injection TU and the addition of DMPA, increasing the rate of azoospermia and/or severe oligozoospermia until 100%.[5] In Indonesia, dose-ranging study indicated that injection of combination 250 mg DMPA and 500 mg TU every 6 weeks resulting in rapid decreased of spermatogenesis and stopped after 12 weeks, yet the recovery of spermatogenesis turns out slower than TE and DMPA combination. TU and DMPA combination increasing the inhibition of gonadotropin and endogen testosterone, moreover higher suppression of FSH and LH and disruption of spermatogenesis.[10] It is assumed a better constant condition to decreasing spermatogenic cells population. Short-acting TE could rise testosterone after administration, otherwise to maintain the concentration, injection occurs every 2-3 times a week. Inconvenient injection and fluctuation of testosterone concentration might become one of reason long-acting TU was needed.[4]

Decreasing of gonadotropin as well as androgen (testosterone) could lead to the amount of spermatogenic cells population declining by suppress the development of many kinds of cells in spermatogenesis disruption. On every subtype spermatogenic cells (Spermatogonia A until round spermatid) indicating significant decrease after 12 weeks injection of DMPA and testosterone regimen.[11] Among those regimen, comparison TE and TU with combination of DMPA are unlikely discovered, how both combinations affecting the amount of spermatogenic cells. This review summarizes the comparison between two main combinations of hormonal contraception in men, TE, and TU with combination of DMPA.

METHODS

For this narrative review, literature search was conducted in three databases: PubMed, SpringerLink, and ScienceDirect, also individual article journal website. We searched for studies that were performed in male hormonal contraception, that some of the regimen which Testosterone Enanthate (TE) and Testosterone Undecanoate (TU), also those combination with progestin. Furthermore, we described outcome and compared both regimens that could influence the development of germ cell or spermatogenic cells.

The keyword used were : (male hormonal contraception) OR (regimen testosterone)) AND (progestin) OR (DMPA) OR (Testosterone enanthate) OR (Testosterone undecanoate) OR (male hormonal contraception combination)) AND (DMPA to spermatogenic cells) OR (Testosterone and DMPA to germ cell development)), which resulted 54 articles in PubMed, 7 articles in ScienceDirect, and 5 articles in SpringerLink. We also found 3 articles in Journal of Endocrinology Metabolism. After initial searching, the articles were filtered to exclude duplicated studies, conference abstracts, letter/editorials cases and other irrelevant studies. Sixteen scientific articles or journals were selected for the review. We also conducted hand searching, especially for finding eBook. Full-text articles were obtained using our institutional access to databases.

THE MECHANISM OF HORMONAL CONTRACEPTION IN MEN

Hormonal contraception works on axis hypothalamus-pituitary-gonad, a mechanism that released the hormone by glands through circulation and stimulate specific organ. From hypothalamus, Gonadotropin-releasing hormone (GnRH) stimulates anterior pituitary to release gonadotropins, Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH), then activate gonad. In men, testes as gonad had

several kinds of cells which receiving the stimulation of gonadotropins such as Sertoli cell and Leydig cell. These stimulate the production of androgen/testosterone (T) which essential for sperm development and maturation.[8]

Suppression of hormonal release is the main purpose of hormonal contraception. Regulating the release of pulsatile GnRH and gonadotropin would affect the process of spermatogenesis. Sertoli cell function depends on FSH stimulation to support germ cell development, furthermore Leydig cell produces androgen-dependent physiological to maintain androgenic action on spermatogenesis and in various tissues such as muscles development and skin, also affecting libido.[8] Decreasing of these hormones are prevent to normal spermatogenesis, leading to the decline of spermatogenic cells population and sperm production. Inhibition of GnRH and gonadotropin also interrupting the feedback loop mechanism. Negative feedback mechanism occurs when testosterone, and a lesser extent, inhibin B regulating hypothalamus and pituitary.[12] In the moment of intratesticular testosterone is being suppressed by exogenous progestin, it no longer giving negative feedback and lowering the concentration even more. In the future, peripheral androgenic action declining. Exogenous testosterone alone also used to suppress the release of FSH and LH, also testosterone by utilizing the negative feedback mechanism on hypothalamus-pituitary-testis axis (Figure 1).[9]

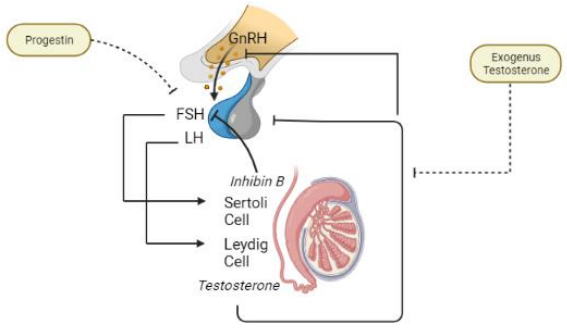

Figure 1. Regulation of testosterone under the pulsatility of GnRH and gonadotropin.
Testoterone produced by the stimulation of LH, begin to active by FSH (androgen binding protein). Circulating testosterone and lesser extent of inhibin B, give negative feedback mechanism to hypothalamus and pituitary to interrupt further gonadotropin and testosterone secretion. As contraceptive combination, progestin inhibits gonadotropin secretion and intratesticular testosterone. While exogenous testosterone inhibits negative feedback mechanism, its role also to maintain testosterone level that have been suppressed by progestin. (Created from BioRender.com)

We know then FSH action on Sertoli cells, whereas LH stimulates the testosterone synthesis.[9] Diffusion of testosterone from interstitial space through the basement membrane and converted into Dihydrotestosterone (DHT) by Sertoli cells. FSH, which stimulates Sertoli cells, accumulating testosterone and DHT around germ cells and synergistically play a crucial role in normal spermatogenesis. The secretion of testosterone affects GnRH release from hypothalamus through positive feedback mechanism that regulates FSH and LH. Otherwise, when testosterone level rises, mechanism of negative feedback occurs to block LH secretion by influencing GnRH pulsatility. Exogenous testosterone action based on this mechanism, that parallel blocks sperm and intratesticular testosterone production.[13]

TESTOSTERONE REGULATION ON SPERMATOGENIC CELLS

Action of testosterone occurs when binding to its androgen receptor (AR).[8] Location of AR is known in the somatic Leydig, peritubular and Sertoli cells. In germ cells, some studies finding AR positive and some other not. Otherwise, testosterone support germ cells development through Leydig, peritubular dan Sertoli cells that express AR. Testosterone transduction signal occurs in Sertoli cells to adjacent germ cells. Studies on Sertoli cell specific AR knock out (SCARKO) mice have shown that there was abnormality of spermatogenesis due to inactivating testosterone on Sertoli cells.[13] In this study, testosterone is required to maintain the blood testes barrier through AR in Sertoli cells for meiosis completion, to maintain the attachment of germ cells to Sertoli cells and to release spermatozoa.[18]

As testosterone required for germ cell progress on meiosis, testosterone also required for the release of mature spermatids during stage VII-VIII in rats and II-III in human. Instead, studies indicated lack of evidence of direct testosterone to support germ cell meiosis or may act indirectly to permit germ cells to complete meiosis. Spermatogonia can enter meiosis even the absence of androgen, but androgen action is required during long meiotic prophase and their subsequent meiotic division. In Cre-Lox conditional SCARKO mice indicated that the absence of Sertoli cell androgen receptor causing lower progress beyond the pachytene and diplotene stages of meiosis (spermatocytes survival) and blood-testis barrier associated with tight junction became not maintained.[13]

Reduction of three tight junction components of blood testes barrier is occulin, claudin-11 and claudin-3 that occurred in the absence of AR expression in Sertoli cells. Moreover, another study showed that a shift in the phosphorylation of proteins (focal adhesion kinase and β-catenin) could decrease the integrity of the cadherin/cadherin and α-6-β-1-integrin/laminin-γ-3 intracellular connection leading to early detachment of elongated spermatids. Study on rats indicated the premature detachment of round spermatids at the beginning of elongation phase that preventing the production of elongated spermatids due to suppression of intratesticular testosterone about 3% from normal. This condition can be completely restored within four days of testosterone replacement. When there is no stimulation of testosterone due to the absence of AR expression in Sertoli cells, recycling process of blood testis barrier protein will decrease and unable to assist in cyclical formation of the blood-testis barrier after leptotene spermatocytes get through the barrier.[14]

To support on spermatogenesis, intratesticular testosterone is required as its levels exceedingly high (50-100-fold serum levels). Study on rat models have shown the minimal and optimal of this intratesticular testosterone levels required for the initiation, restoration, or maintenance of spermatogenesis. Induction to increase intratesticular testosterone can be obtained from

exogenous testosterone in high dose (passive diffusion) or hCG/LH administration (Leydig cell stimulation). However, there was lack of evidence that zero or extremely low (unmeasurable) intratesticular testosterone levels were not providing support for limited spermatogenesis. One thing that we could know that spermatogenesis happens while testosterone levels are lower than in normal puberty.[13]

As low level of intratesticular testosterone associated with limited degree or complete failure of spermatogenesis, while excess intratesticular testosterone showing immeasurably low serum LH (<0.5% baseline) proves the existence of LH-independent androgen secretion. These occur when androgen-based male hormonal contraception, especially the gonadotropin withdrawal, indicate ineffective universally with ±5% of normal men to maintain sperm densities ≤1 million/ml. In contraception matters from androgen-progestin combination, indicating of significant (13-55 nM) intratesticular testosterone level in man with spermatogenic suppression, meanwhile high dose exogenous testosterone may allow the diffusion and reducing contraceptive efficacy.[13]

MALE HORMONAL CONTRACEPTIVE REGIMENS

Male hormonal contraception had been discovered since early 1970, with the thought of how hormonal methods function in women.[5] Contraception for male, biologically have an aim to blocks sperm transport into female reproductive tract, to suppress spermatogenesis or to disrupts the maturation or sperm ability to fertilization. Hormonal contraceptive protection by means of suppress spermatogenesis and reducing sperm production.[15] A few studies have been done by administration different hormonal contraceptive regimen. Testosterone/androgen become the important regimen to suppressing sperm concentration. Otherwise, the feasibility of male hormonal contraception that achieving sperm concentration < 1 million/ ml ejaculate (severe oligozoospermia until azoospermia), for acceptable contraceptive efficacy.[9] Combination with exogenous progestin indicated prolonged and effective suppression of spermatogenesis. In WHO Task Force multi-centre studies, variety of androgen and or progestin formulation and form has been evaluated in trial to know those efficacy studies and the ability to prevent pregnancy.[8] In this review, we will evaluate two of main testosterone regimens; TE and TU, with each remarkable result for male hormonal contraceptive regimens.

Testosterone Enanthate (TE)

TE is testosterone ester from testosterone derivate with adding the seven-carbon chain moiety into 17 carbon position (17C). The first evaluation contraceptive efficacy as prototype regimen by WHO Task Force on Methods for the Regulation of Male Fertility was intramuscular (IM) injection TE 200 mg weekly in 6 months. From the trial proved that 60% respondents became azoospermia from the first trial and 95-98% men achieving severe oligozoospermia (about < 3 million/ml ejaculate) for the second. After 120 average day respondents that become azoospermia, recovery time for spermatogenesis after stopping injection was 3.7 months. Yet there was a side effect such as mood changes, libido alteration, acne, polycythaemia, weight gain, hypertension, and abnormal liver function from testes. Weekly injection also inconvenient and painful for a few men before the end of second study.[4]

Testosterone Undecanoate (TU)

TU is testosterone ester with 11-carbon chain at the 17-carbon position (17C), which another depot testosterone that administrated once every 8-12 weeks, making these regimens more convenient and practical with long-acting process in IM injection.[4] Its formulation in tea seed oil at initial dose 1000 mg followed by 500 mg every month, have been evaluated in two trials to Chinese man. After 6-month suppression, achieving severe oligozoospermia and azoospermia with total efficacy was 94.8%.[1] Later on the phase III trial to Chinese men after monthly injection of 500 mg of TU indicating similar manifestation about 95% within 6 months. Meanwhile, the men whose sperm concentrations were suppressed to < 1 million/ml ejaculate, some pregnancy occurred. Incomplete gonadotropin suppression of androgenic action due to high concentration of serum testosterone might be the problem of this regimen. It can be a hypothesis that higher doses of testosterone indicating the sperm suppression in lower degrees occurred.[4]

Another side effect including erythrocytosis, acne, weight gain, libido alteration, mood swings remained the same, yet found a small decrease in testicular volume.[4] From monthly injection of 500 mg TU, indicated a promising result otherwise spermatogenic recovery in all men occur within 12 months. The returning of spermatogenesis into normal fertile reference have not been with any serious adverse events.[9] There is a limitation of using male hormonal contraception, one of that are adversity to develop a suitable preparation because most of which have unfavourable pharmacokinetics profile and require frequent administration to maintain it serum level. This challenging condition have become another study for researcher to develop a new androgen formulation. Unlike TE, injection TU on tea seed oil or castor oil has more stable (until 33.9 ± 6 days half-life), long-term release of T into circulation of men.[16] It becomes of one reason to know that TU is an ideal male hormonal contraception with favourable pharmacokinetics and pharmacodynamics.

TESTOSTERONE AND PROGESTIN COMBINATIONS TO SPERMATOGENIC SUPPRESSION

Progestin have been used in clinical as female contraception also experimenting to man since early 1970s.[17] Its mechanism might interfere hypothalamic-pituitary-gonadal axis by suppressing gonadotropin release and impairing spermatogenesis.[8] Study indicated that progestin could became a potent inhibitor of LH and FSH which leading to improved sperm supperession.[18] DMPA is one of progestins that had been tested for male contraception by WHO and Population Council. As male hormonal contraception, DMPA acts in synergistic way

with testosterone on hypothalamus-pituitary axis resulting in more rapid and solid gonadotropin also sperm suppression.[19] These dual-agents regimens give an effort to increase effectiveness and minimizing side effects.[20] A trial conducted that progestin/progestogen could suppress sperm production but lowering intratesticular testosterone concentration leading to androgen deficiency.[17] Androgen peripheral activity to other functions such as libido, erection, ejaculation and maintaining muscle mass would have agitated. Adding testosterone regimen into combinations is a compulsion to maintain these functions.[19] In different efficacy, combination of progestin and testosterone achieving more persistent suppression of spermatogenesis (Table 1).

DMPA has androgenic activity that more effective to suppress LH, as other progestin does, such as levonorgestrel.[4] WHO's Medical eligibility criteria for contraceptive use has been stated for administration of DMPA for intramuscular is 150 mg/ml and 104 mg/0.65 ml for subcutaneous injection, which implemented for female hormonal contraception at first.[6] Due to side effect on other functions, recent preparation of DMPA now using combination to testosterone, with variety formulations.

TE was one that been used as prototype for male hormonal contraception by WHO Task Force trials, showed highly effective to induce severe oligozoospermia after 6 months[4], sustained and reversible contraception in the shortest time with minimal side-effects. Thirty normal fertile man randomly have received TE (200 mg intramuscular injection weekly) plus DMPA (300 mg intramuscular injection once) showed that adding DMPA led to a more rapid fall in serum FSH/LH concentration after 6 weeks. In the study also showed that FSH concentration significantly lower compared to TE only, with maximum suppression until 12 weeks. More rapid decline of gonadotropin by DMPA affecting germ cell suppression. Intratesticular testosterone levels at 2 weeks after administration TE and DMPA combination significantly lower than TE only, however there was no further changes after 6 and 12 weeks. Furthermore, the decreasing of intratesticular testosterone was not associated with sperm count, which indicated there were no differences between the groups at any time during the treatment period.[11] This might become an answer that testosterone-dependent germ cell is not support germ cell development directly, regarding TE injection.

Evaluation of spermatogenic cells or germ cell numbers on TE and DMPA combination associated with the declining of FSH and LH. Study shown that gonadotropin level decreasing due to DMPA have had correlation to impairment of type B spermatogonia after 2 weeks. Later spermatogenic suppression occurred at early spermatocytes maturation but not significantly different until spermatid transformation after 12 weeks. After 6 weeks, elongated spermatid remains indifferent as control which indicated inhibition of spermatogenic cells at time point. The addition of progestin indicated more rapid gonadotropin suppression and unorganized germ cell development but does not change the pattern of germ cell association.[11]

It is known that type Ap spermatogonia mitosis into inactive type Ad spermatogonia and these Ad number changes were seen, while gonadotropin suppression occur in a short-term period. In the study indicate that type Ap spermatogonia begin to stop proliferated into type B spermatogonia and differentiated into type Ad spermatogonia after 2 weeks. The direct effect of gonadotropin suppression leading to decrease in number of type B spermatogonia due to these cells are well known affected by hormone and FSH. Pachytene spermatocytes showed also decreased in population after 6 weeks gonadotropin suppression. At this time, spermatid wouldn't be affected by suppression because the duration of spermatogenic cycle in human is 16 days.[11]

Another testosterone regimen that has been used as WHO multicentre efficacy study was TU indicated more stable and long-acting ester testosterone. The result showed better than TE which achieving severe oligozoospermia and azoospermia until 95% after 6 weeks treatment period. This regimen also preferable as longer-gap intervals injection such 2-3 months.[4] Doses of 1000 mg of TU in tea seed oil preparation (every 8-week injection) has been developed as effective male contraceptive regimen due to better sperm suppression[1], however TU formulation would need to be in combination with progestin such as DMPA to profound suppress gonadotropin. This was based on recent dose-finding study in Indonesia that injection of 500 mg TU in tea seed oil every 6 week and 250 mg DMPA every 12 week was completely sustained the suppression of spermatogenesis.[10]

Table 1. Testosterone alone and Testosterone plus DMPA efficacy studies

Progestin	Regimen Testosterone	Persons study of participant	Year of Study	Sperm threshold	% Subject reaching threshold
None	TE (200 mg/ week)[4]	271	1990 (6 months)	0	60
None	TE (200 mg/ week)[4]	399	1990 (6 months)	< 3 million/ml	95-98
None	TU (1000 mg + 500 mg/month)[1]	308	2006 (30 months)	< 1-3 million/ml	94.8
None	TU (1000 mg + 500 mg/month)[4]	1045	2006 (30 months)	≤ 1 million/ml	95%
DMPA (300 mg)	TE (200 mg/ week)[11]	30	2000 (3 months)	< 1 million/ml	80-90%
DMPA (250 mg/12 week)	TU (500 mg/6 week)[10,21]	30	2002	< 1 million/ml	100%

In fact, induction of more profound in gonadotropin (FSH and LH) also disrupt spermatogenesis due to hypothalamic-pituitary-gonad axis feedback regulation on spermatogenesis.[8] Thirty man has been conducted to intramuscular injection every 8-week of 1000 mg TU, 1000 mg TU plus 150 mg DMPA and 1000 mg TU plus 300 mg DMPA showed that both serum FSH and LH significantly suppressed after 4 weeks and maintain at very low level until the end of treatment. Otherwise, regimen TU only could not maintain the suppression of gonadotropin after 4 weeks. Concentration serum testosterone after 8-week interval injection were significantly lower in combination group than TU-only group, which indicated a better suppression to testosterone by TU and DMPA. Even though suppression of sperm remained lower, azoospermia occurred and maintained below the baseline until week 24th.[21]

Unlike TE, in this study longer-acting TU seem have an ability to maintain the decreasing of serum testosterone and sperm suppression in a longer period. However, an acknowledgement of definitive intratesticular testosterone level after TU and DMPA injection have not been done, but consistently high serum of MPA and combination with an even longer acting ester testosterone may have a profound effect for that, rather than TE combination. These also happened in sperm suppression that TE and DMPA combination was not significantly lowering the concentration and in this case the germ cell numbers had only lower until week sixth. Higher serum MPA that could stand until 3-4 month[15] may portrays more on germ cell numbers due to direct suppression of gonadotropin (FSH and LH), than TE does. In this study, TE seem unable to hold role of suppression that poorly indicate maintenance so later DMPA does these works. But DMPA without testosterone ability may not maintain germ cell and sperm suppression due to derivation of testosterone activity to germ cell development.

As for TU and DMPA combination, one thing can predict that germ cell count for spermatogenic suppression also have a decent result. Importantly this combination might maintain the suppression at longer period, significantly different from TE-only. However, the observation of spermatogenic effect of TU and DMPA combination should be obtained to show the longer impact to each germ cells.

CONCLUSION

A male hormonal contraception has become the answer to safe, convenient, and reversible for man using it. The ester testosterone became a prototype of this development was TE and TU for longer-action formulation. Those shown remarkable results by suppressing sperm production and achieving severe oligozoospermia and azoospermia for a couple of months.

Spermatogenic suppression of TE and DMPA combination has been indicated in FSH, and LH was decreasing after until 12 weeks. The significant decreased of FSH associated with spermatogenic suppression on spermatogenic cells after 12 weeks but there was no different at sperm count. Furthermore, this combination seems cannot maintain sperm suppression for a long time, but the decreasing of testosterone could continue in the future. Short-acting TE rather than long-acting TU might be unable to replace the decreasing of intratesticular testosterone and the combination of TU and DMPA would have more profound suppression of testosterone and sperm count until week 24th. Furthermore, combination of TU and DMPA on spermatogenic development and the association with intratesticular testosterone.

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