Male hormonal contraception : a major cardiovascular disease risk factor?

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Introduction

Historically, females have carried the burden of contraception in the form of hormone pills and tubal sterilization, while men have attempted traditional methods of contraception such as periodic abstinence, coitus interruptus, and condoms, all of which have relatively high conception rates (Nieschlag, 2011). Male hormonal contraception works on the premise of decreasing the amounts of luteinizing hormone (LH) and follicle stimulating hormonal (FSH) which are released by the anterior pituitary gland. LH and FSH are stimulated by gonadotropin releasing hormone (GnRH) which is released as a signaling hormone from the hypothalamus.

LH is responsible for stimulating the Leydig cells in the testicles to produce testosterone (T), which in turn stimulates spermatogenesis. FSH is responsible for stimulating the Sertoli cells to produce androgen binding globulin and also functions to stimulate spermatogenesis. LH and FSH both relay negative feedback, via the production of T and inhibin respectively, to the anterior pituitary gland and hypothalamus. Therefore, by using a male hormonal contraceptive method consisting of T it is possible to inhibit the secretion of GnRH at the hypothalamus, thus inhibiting LH and FSH secretion and reducing, if not eliminating, spermatogenesis.

Male contraceptives such as condoms have a relatively high conception rate and vasectomy procedures are not easily reversible for those wishing to conceive in the future. Due to these limitations, it is thought that male hormonal contraceptive development will relieve the burden of birth control off women, control the increasing population rate, prevent incidental pregnancies, decrease the number of induced abortions, and reduce the number of death and illnesses related to pregnancy and birth complications (Guttmacher Institute, 2010). Further, these objectives allow people to be more empowered over how, when, and why they reproduce.

Male hormonal contraception is attainable; this is demonstrated by men achieving azoospermia or severe oligozoospermia in many studies that have already been completed. Azoospermia is defined as the absence of sperm within an ejaculate. Severe oligozoospermia is defined as less than 1.0×10^6 sperm/mL. Achieving azoospermia or severe oligozoospermia in men dramatically reduces the conception rate (World Health Organization, 1996). The states of azoospermia and severe oligozoospermia can be accomplished by suppressing the amount of T in the testes, which is necessary for stimulating the production of sperm. Moreover, the mechanism to limit sperm production within the testes can be caused by suppressing the hypothalamic-pituitary-gonadal (HPG) axis which is responsible for spermatogenesis.

The HPG axis can be suppressed by supplying the body with a supraphysiologic amount of T, which provides negative feedback to the hypothalamus, suppressing the amount of pulsatile GnRH secreted from the hypothalamus. The axis could also be suppressed by providing the body with a GnRH receptor antagonist. This antagonist would prevent GnRH from stimulating the release of LH and FSH, thus indirectly inhibiting spermatogenesis.

Presently, suppressing sperm production by adding supplemental T does have side effects, including, but not limited to, acne, increased libido, injection site pain, weight gain, mood changes, and others. Most of these side effects have caused some study participants to withdraw from studies. Studies are trying to decrease the number and percentage of side effects by reducing the amount of testosterone necessary to suppress the HPG axis; this has partially been accomplished by adding a progestin to the regimen.

Currently, a major side effect of male hormonal contraceptive treatment is its detrimental affect lipid profile. In particular treatment causes a decrease in HDL cholesterol levels. A low HDL cholesterol level, defined as <40 mg/dL or 1.03 mmol/L, is regarded as a major coronary

heart disease risk factor. In contrast, a HDL cholesterol level ≥60 mg/dL or 1.55 mmol/L is clinically regarded as a "negative risk factor" (Rosenson, UpToDate, 2010). Further, "Given the protective value of serum HDL-C, it has been suggested that the serum total-to-HDL-C is of greater predictive value than the serum total or LDL-C," illustrating that, "among men, a ratio of 6.4 or more identified a group at 2 to 14 percent greater risk than predicted from serum total or LDL-C" (Rosenson, UpToDate, 2010). Many completed male hormonal contraceptive studies have seen significant changes in serum lipid levels, particularly in that of the HDL cholesterol levels.

With regard to the different types of testosterone formulations, testosterone itself is rapid absorbed from the intestines, but it is quickly metabolized by the liver, therefore modification of the molecule has been necessary for the delivery of testosterone (Snyder, UpToDate, 2012). This has led to the development of several different testosterone preparations, including testosterone enathate, testosterone undecanoate, depot testosterone pellets, tesotosterone gels, 7α-Methyl-19 Nortestosterone, and percutaneous testosterone. There are also several progestin formulations, synthetic progesterones, including levonorgestrel, norethisterone enanthate, etonogestrel implants, and depot medroxyprogesterone acetate.

Methods

The goal of this paper is to educate the public, physician assistants, and physicians about the advances, drawbacks, risks, and benefits of male hormonal contraception. There appears to be both a market and need for another form of contraception that can no longer be overlooked. By educating the public and increasing awareness of male contraceptive possibilities, it is possible that a potential method may be at hand. The current methods of contraception are not enough, being that the rates of unwanted pregnancies and induced abortions are still high. Providing these contraceptive methods not only to developed countries, but also to lesser developed countries will allow for more controlled population increases and disease prevention amongst the underprivileged.

Search Terms

Male hormonal contraceptive, Hormonal contraceptive men, Male hormonal contraception efficacy, Pregnancy rates

Databases

Pubmed, UptoDate.com, World Health Organization, National Institutes of Health, Guttmacher Institute, Google

Inclusion and Exclusion Criteria for Articles

Articles selected for my scholarly project will abide by specific inclusion and exclusion criteria to ensure accurate, professional, unbiased information is presented. All articles will be from peer-reviewed journals. Epidemiological information will be within 25 years unless what is being measured is unavailable; in that case older data will be acceptable. The research population will be the world population. All articles will be in English. First tier studies will be double-blind randomized control trials with a placebo and large sample size. Second tier studies will resemble

first tier but will be lacking one of the characteristics, making it not as strong of evidence, but still valid enough to be included in the literature review. Third tier studies will include surveys, Guttmacher data, World Health Organization data, CDC data, and National Institute of Health data.

Exclusion criteria included articles that are not peer-reviewed, have serious methodological errors, and incorrect statistical analysis. All articles funded by corporations or associations were individually assessed to ensure the evidence is accurate and not influenced by their financial partners.

Male Hormonal Contraception

Testosterone enanthate

Testosterone enanthate, 200 mg

World Health Organization 1990

In 1990, a multicenter study done by the World Health Organization (WHO) set out to determine whether testosterone-induced azoospermia, also known as complete sperm suppression, was effective in preventing conception. These first clinical trials studied the contraceptive efficacy of long-acting T enanthate, 200 mg weekly, by intramuscular (IM) injection. WHO tested T enanthate with the purpose of determining whether it would be a suitable suppressor of spermatogenesis for up to 12 months. WHO also wanted to determine the level of treatment safety during all three phases of the study. These three phases included induction of sperm suppression, contraceptive efficacy, and sperm recovery. After 6 months, 70 percent of men reached azoospermia and within this group only one pregnancy was reported (WHO, 1990). Concerning the one partner who became pregnant, the male counterpart successfully reached azoospermia and had been placed into the efficacy phase of the study. In this study, all men not reaching azoospermia were removed from the study and not permitted progress through all three phases (WHO, 1990).

World Health Organization 1996

In 1996, WHO performed an adjunct study to further evaluate men developing oligozoospermia. Oligozoospermia is defined as less than 3.0×10^6 sperm/mL. This allowed for a contraceptive comparison of those participants with sperm counts greater than and less than 3 million/ml ejaculate. The men in this study received the same dose of T enanthate, 200 mg IM

weekly. The study revealed that men with sperm counts greater than 3 million/mL and only using male hormonal treatment as their method of contraception had higher rates of pregnancy in comparison to couples who used condoms exclusively. In contrast, men with less than 3 million/ml ejaculate had lower rates of pregnancy, compared with couples who used only condoms (WHO, 1996). This apparent contrast between the contraceptive rates of men with sperm counts greater than 3 million/mL and those with less than 3 million/mL established a clinical threshold to guide future studies. However, this single hormone method was not optimal, producing azoospermia in only 70 percent of men and requiring weekly IM injections. This lack of treatment efficacy and rigorous treatment regimen called for a method of male hormonal contraception that increased treatment response and decreased treatment dosing frequency.

Moreover, in the 1990 WHO study many side effects related to the testosterone treatment protocol were identified. After initiating testosterone injections, there was an increase in body weight, hemoglobin, and testosterone. The 1996 study reported the same expected results as the 1990 study, in addition to "significant decreases in total, LDL, and HDL cholesterol levels and their ratio during treatment, which returned to baseline levels after cessation of injections" (WHO, 1996). These effects on plasma cholesterol levels were not reported in the 1990 WHO study.

It was hypothesized that by combining a long-acting testosterone preparation with progestin, synthetic progesterone, would necessitate less testosterone to suppress the HPG axis, thus minimizing testosterones side effects, such as increased body weight and decreased HDL cholesterol levels. It was surmised that combining T and progestogen would enable further suppression of the HPG axis, thus helping the remaining 30 percent of non-suppressors achieve azoospermia or severe oligozoospermia.

Testosterone enanthate and Levonorgestrel

Testosterone enanthate, 100 mg, and Levonorgestrel, 500 µg

In 1996, Richard Bebb, MD led a study at the University of Washington School of Medicine testing the hypothesis that a progestogen in combination with a lower dose of T would suppress sperm production more effectively than T alone. Bebb also wanted to examine the effects of lower T doses on HDL cholesterol levels. The subjects were divided into three groups, T and levonorgestrel (LNG) (the T plus LNG) group, the placebo plus T group (LNG 0), and the T alone group. The progestogen and T preparations used were 500 µg levonorgestrel (LNG), orally, daily and 100 mg T enanthate, IM, weekly, respectively (Bebb et al., 1996). This was a 100 mg decrease in the amount of T enanthate administered each week from the WHO studies. A T dose of 100 mg was given because it has been found to be non-suppressive of HDL cholesterol levels (Bagatell, Knopp, Vale, Rivier & Bremner , 1992). One of the only concerns that the study did not address was subjecting men to weekly injections, which was a major cause for numerous of dropouts in the World Health Organization's earlier studies.

Azoospermia was defined as two or more consecutive sperm counts of zero, and severe oligospermia as two or more counts between zero and 3 million spermatozoa/mL (Bebb, 1996). The study showed a greater suppression of spermatogenesis in the T plus LNG group than in T alone. As the treatment period came to a conclusion, 67% of men in the T plus LNG group achieved azoospermia, while only 33% of men in the T alone group achieved sperm counts of zero. Severe oligozoospermia percentage numbers were 94% and 61% for the T plus LNG group and T alone group, respectively (Bebb *et* al., 1996). It was also noted that the T plus LNG protocol more rapidly suppressed spermatogenesis at a rate of almost 5 weeks faster than the T alone and placebo plus T groups (Bebb *et al*., 1996).

More men reached azoospermia or severe oligozoospermia in a shorter time period than the previous WHO studies, but the changes from baseline HDL, LDL, total C, or triglycerides levels in the T alone group were not found to be significant (Bebb et al., 1996). In the T plus LNG group HDL cholesterol decreased from 1.31 mmol/L (± 0.08) before treatment to 1.01 mmol/L (± 0.05) after treatment. The decrease in HDL cholesterol was significant in comparison to the T alone group. Bebb clarifies that although a low HDL cholesterol level puts people at a higher risk for atherosclerotic heart disease this has not been identified in a T plus LNG hormonal regimen, but the potential does exist (Bebb et al., 1996). Overall, men receiving the combination T plus LNG therapy had an increased likelihood of reaching azoospermia and severe oligozoospermia, but the risks associated with decreasing HDL cholesterol could be problematic.

Testosterone enanthate, 100 mg weekly, and Levonorgestrel, 125 µg daily OR Levonorgestrel, 250 µg daily

Bradley Anawalt, MD, led a follow-up study to determine the effects of LNG dosage levels and their subsequent effects on lipid levels such as total cholesterol, HDL cholesterol, and LDL cholesterol. They hypothesized that a lower dosage of LNG would result in a similar reduction in spermatogenesis when compared with Bebb's (1996) previous study (Anawalt *et al*., 1999).

The study was a randomized, single-blind design. Subjects were divided into two groups each receiving 100 mg of T intramuscularly weekly, then each group administered either LNG 125 µg (LNG 125) or LNG 250 µg (LNG 250) by mouth daily. Both groups were

compared to the Bebb's previous study's groups LNG 0, the placebo plus T group, and LNG 500, the group receiving LNG 500 µg plus T (Bebb, 1996).

Within the LNG 125 group 11 (61 percent) of the subjects achieved azoospermia, 5 additional subjects achieved oligoazoospermia, and another one subject (94 percent) achieved oligoazoospermia. The LNG 250 group had 14 (78 percent) men achieve azoospermia and 2 men (89 percent) achieve oligozoopermia. The authors state "there were no significant differences between the three groups receiving combination T plus LNG therapy in percentage nor rapidity of oligoazoospermia, severe oligoazoospermia, or azoospermia achieved during the treatment period" based on a p value of < 0.05 (Anawalt *et al*., 1999).

As for the lipid levels, subjects experienced a reduction in their HDL cholesterol levels from baseline. Reported as percents, HDL cholesterol levels decreased 3.7% (± 4.0) in LNG 0, 13.4% (± 3.7) in LNG 125, 20.2% (± 2.7) in LNG 250, and 21.7% (± 3.6) in LNG 500 (Anawalt *et al*., 1999). In each LNG treatment group, the reductions in HDL cholesterol levels were significant. The greatest and most significant reductions in HDL cholesterol levels were in the LNG 250 and LNG 500 groups (Anawalt *et al*., 1999). Total cholesterol, LDL cholesterol, and triglycerides had no significant changes.

Testosterone undecanoate and Noresthisterone enanthate

Testosterone undecanoate, 1000 mg every 6 weeks, and Norethisterone enathate, 200 mg

Although achieving azoospermia or severe oligozoospermia in treatment groups was the goal of therapy, neither Bebb nor Anawalt made any changes to the rigorous treatment schedule involving weekly IM injections of T. To address this issue, Axel Kamischke, MD of the Institute of Reproductive Medicine at the University of Münster in Germany led a trial designed to

establish the efficacy associated with a combination long-acting T and progestogen therapy in male hormonal contraception. Kamischke's study evaluated the compounds T undecanoate ester (TU) and Noresthisterone enanthate (NETE). TU was used because it was one of two long-acting injectable T esters. NETE was used because it demonstrated efficacy in female contraception (Kamischke, 2000).

The study compared the efficacy of suppressing spermatogenesis between two groups, TU alone and TU in combination with NETE. Those in the TU/NETE group received T and progesterone preparations consisting of 1000 mg TU dissolved in 4 mL castor oil, IM, and 200 mg NETE dissolved in 1 mL castor oil, injections, every 6 weeks. Those in the TU alone group took the same TU regimen, but they also received daily oral placebo treatments with undisclosed specifications (Kamischke, 2000). These preparations required fewer injections which was a significant difference from the previous studies that required weekly T injections.

TU/NETE induced a "profound suppression of gonadotropins and spermatogenesis that was greater than those achieved in nearly all other previous studies for male contraception," according to Kamischke (2000). They also discussed that 6 weeks between injections is acceptable amongst men (Kamischke, 2000). Kamischke found that 12 out of 14 participants in the TU alone group achieved either azoospermia or severe oligozoospermia. Within the TU/NETE group 13 out of 14 men reached azoospermia, while the other one man achieved oligozoospermia. The sperm suppression results were equivalent to previous studies, showing promise for long-acting T and progesterone preparations, but they also had similar effects on lipid cholesterol levels in the TU/NETE group seen in previous studies.

Significant results illustrated that the total cholesterol increased from 173 mg/dL (± 6) to a high of 194 mg /dL (± 7), HDL cholesterol decreased from 54 mg/dL (± 3) to a low of 45

mg/dL (± 2), and LDL cholesterol increased from 102 mg/dL (± 7) to a high of 122 mg/dL (± 8) (Kamischke, 2000). No significant changes were seen in the TU alone group. In the pursuit of limiting side effects and long-term adverse effects of male hormonal contraception many different T and progesterone preparations have been studied. Different preparations were studied in order to not only find substances with limited effects, but also to learn which combination treatments provided both spermatogenesis suppression efficacy while decreasing the frequency of necessary routine injections.

Testosterone undecanoate, 1000 mg, and Noresthisterone enanthate, 200 mg combined at varying intervals

Pelusi led a study in Italy in which they measured plasma lipid parameters in men treated with TU and noresthisterone enanthate (NETE) (Pelusi, Costantino, Cerpolini, Pelusi, Meriggiola & Pasquali, 2010). This study was introduced as an adjunct to an ongoing study also being led by Meriggiola (2005). Meriggiola's study researched the time intervals necessary to maintain spermatic suppression while exposing subjects to the "lowest and thus safest possible hormonal dose" (Meriggiola, Costantino, Saad, D'Emidio, Morselli Labate, Bertaccini, Bremner et al., 2005). The study did not measure the treatment effect on spermatogenesis suppression and sperm count, therefore treatment effects on sperm count reduction were not reported.

Study subjects were divided into five groups, four treatment groups and one placebo group. Treatment groups one through four were each given 200 mg of NETE plus 1000 mg of TU administered either: every 8 weeks (NETE-8 group); every 12 weeks (NETE-12 group); every 6 weeks for 12 weeks and then continued at 12 week intervals (NETE-6/12 group); or every 6 weeks for 12 weeks then a placebo plus 1000 mg of TU continued at 12 week intervals

(NETE-6/12/0 group). The placebo group received no NETE or TU treatment. As for the anthropometric, metabolic and biochemical parameters, Pelusi took samples to measure glucose, HDL cholesterol, Total C, triglycerides, and more (Pelusi et al., 2010).

The study results showed no significant changes in total cholesterol, HDL cholesterol, and triglycerides, but there were increases in the total cholesterol and triglyceride levels compared to baseline (Pelusi et al., 2010). LDL cholesterol levels were not presented. Total cholesterol increased from 179 mg/dL (± 28) to 188 mg/dL (± 34) in NETE-8, 183 mg/dL (± 33) to 185 mg/dL (± 30) in NETE-12, 190 mg/dL (± 43) to 201 mg/dL (± 47) in NETE-6/12, and 166 mg/dL (± 36) to 175 mg/dL(± 27) in NETE-6/12/0. Triglycerides increased from 85.2 mg/dL (± 29) to 96.5 mg/dL (± 32) in NETE-8, 104 mg/dL (± 58) to 109 mg/dL(± 62) in NETE-6/12, and 69.0 mg/dL (± 29) to 76.3 mg/dL (± 31). There was also a steady decrease in HDL cholesterol levels, though these changes were only seen in the NETE-8 group. HDL cholesterol levels within the NETE-8 group decreased from 52.2 mg/dL (± 8.8) to 48.7 mg/dL (± 12.2), but this decrease did not achieve significance by the end of the treatment phase (Pelusi et al., 2010). Pelusi discusses that the difference in the HDL cholesterol levels could be explained by the change in the treatment administration intervals (Pelusi et al., 2010), which could explain the difference found in the previous study where NETE was administered every 6 weeks (Kamischke et al., 2000).

Depot testosterone and Etonogestrel

Testosterone pellets, 400 mg, and three Etonogestrel implants, 68 mg

A study led by Brian M. Brady at the University of Edinburgh, Centre for Reproductive Biology, hypothesized that by increasing the daily dose of etonogestrel in combination with

depot T may improve sperm suppression. This spermatogenic suppression was seen when compared to a previous study where participants either had one or two etonogestrel implants, achieving azoospermia in 64% or 75% of participants, respectively (Anderson, Kinniburgh, & Baird, 2002). In this study 15 healthy men were recruited and three 68 mg etonogestrel implants were placed subcutaneously in the "medial aspect of the non-dominant upper arm to all subjects" (Brady, Walton, Hollow, Kicman, Baird, & Anderson, 2004). Further, each subject received 400 mg of T pellets placed subcutaneously into the anterior abdominal wall and replaced at weeks 12, 24, and 36 of the treatment phase (Brady *et al*., 2004). Within four weeks of the study one participant discontinued because of personal reasons, not attributed to any adverse events, his results are not included in the results analysis. Another four participants discontinued at 24 weeks due to personal reasons.

Results from the study revealed that all 14 participants who stayed in the treatment phase for 24 weeks achieved azoospermia. At 16 weeks 10 of the 14 participants were azoospermic, while three others achieved sperm suppression levels of less than 1.0×10^6/mL. Twenty-four weeks into the treatment phase, one participant that had not already achieved azoospermia became azoospermic. By week 28, three of the nine men who remained in the study and had only maintained severe oligozoospermia, maintaining levels of less than 0.1×10^6/mL, also achieved azoospermia (Brady *et al*., 2004).

In regard to the cholesterol levels shown in a previous study by Anderson (2002) there were insignificant decreases in HDL cholesterol in both groups throughout the treatment phase and there were no significant changes in total cholesterol. However, there was a significant increase in LDL cholesterol in both implant groups (Anderson *et al*., 2002). Brady's study revealed insignificant decreases in HDL cholesterol levels from 1.2 mmol/L (± 0.1)

to1.1 mmol/L (± 0.1) and LDL cholesterol levels from 3.7 mmol/L (± 0.4) 3.3 mmol/L (± 0.2) at 48 weeks (Brady et al., 2004). In contrast to the previous study there was a significant decrease in total cholesterol from 5.3 mmol/L (± 0.4) to 4.6 mmol/L (± 0.3) at 24 weeks. Triglyceride levels also decreased significantly from 2.1 nmol/L (± 0.3) to a low of 1.2 nmol/L (± 0.2) at 48 weeks (Brady *et al*., 2004).

Overall, the study showed an increase in spermatogenic suppression to azoospermia in all participants remaining in the treatment phase for 48 weeks. Although this study was able to demonstrate an intense effect on spermatogenesis there was still concern for the effects on cholesterol levels and on the size of the prostate (Brady *et al*., 2004).

7α-Methyl-19-Nortestosterone OR Testosterone pellets and Etonogestrel

7α-Methyl-19-Nortestosterone, two 135 mg implants, OR Testosterone pellets, 600 mg, and Etonogestrel, two 68mg implants

Melanie Walton led a study at The Queen's Medical Research Institute at the University of Edinburgh which aimed to determine whether implants of 7α-Methyl-19-Nortestosterone (MENT), a particular testosterone preparation, and etonogestrel, a progestogen, inhibited sperm production. MENT was selected as the testosterone preparation because of the belief that its androgenic properties would not affect the prostate's size, yet still remain an effective suppressor of spermatogenesis (Sundaram, Kumar, Bardin, 1993). Etonogestrel was used because it had been used in previous studies and found to have negligible systemic effects according to Anderson (2002) and Brady (2004).

Subjects were divided into the MENT/etonogestrel group or the T/etonogestrel group. Both groups received two 68 mg etonogestrel implants in one arm and either two 135 mg MENT

implants in the other arm or 600 mg T pellets, subcutaneously (SQ), repeated at weeks 12, 24, and 36. The MENT implants released 400 µg per day and the amount of etonogestrel released per day was not disclosed. The results of the study revealed that the MENT/etonogestrel group suppressed spermatogenesis initially, but after 12 weeks into the study only 4 out of 10 men remained at less than 1 x 10^6/mL, decreasing from the initial 8 out of 10 men within the first 12 weeks of the MENT/etonogestrel group (Walton, Kumar, Baird, Ludlow, & Anderson, 2007). In this same group, at 24 weeks only 4 men continued to be suppressed to levels less than 1.0 x 10^6/mL. The MENT/etonogestrel group was discontinued after 24 weeks of treatment, but the reasons were not disclosed. Those in the T/etonogestrel group maintained spermatogenic suppression and by the end of the treatment phase all of the subjects were azoospermic. Therefore, the time to achieve azoospermia ranged from 4-44 weeks in the T/etonogestrel group (Walton *et al*., 2007). Even though each intervention suppressed spermatogenesis to either severe oligozoopermia or azoospermia at some point, they also had significant effects on serum cholesterol levels.

The MENT/etonogestrel group showed a significant fall in HDL cholesterol levels from 1.4 nmol/L (± 0.1) to 1.2 nmol/L (± 0.2) at 12 weeks into the treatment phase when compared to levels before the pretreatment (Walton *et al*., 2007). Similarly, the T/etonogestrel group also had a significant fall in HDL cholesterol decreasing from 1.3 nmol/L (± 0.2) pretreatment to 1.1 nmol/L (± 0.1) at 36 weeks. Also, another difference occurred between the MENT and T groups with respect to blood pressure.

There was a significant rise in systolic blood pressure within the MENT/etonogestrel group with a P of 0.02, but no significant change in the diastolic blood pressure. This change was discussed as a possible increase in arterial stiffness and is “recognized to be a strong

cardiovascular risk factor" (Walton *et al*., 2007). This change in blood pressure was either not seen or was not significant in the T/etonogestrel group as the authors did not disclose any changes within this group. As for the effects on the prostate, there was a significant fall in serum prostate-specific antigen concentration in the MENT group, but no changes were seen in the T/ etonogestrel group (Walton *et al*., 2007).

Testosterone undecanoate and Etonogestrel

Testosterone undecanoate, 750 mg OR 1000 mg,

and Etonogestrel, Low-Release OR High-Release

Ellen Mommers, PhD, led the first large double-blind and placebo controlled multicenter study throughout Europe in order to test the efficacy of T undecanaote (TU) and etonogestrel (ENG) on suppressing spermatogenesis while maintaining a more constant testosterone serum concentration. A similar study was done by Brady using ENG and T decanoate (Brady, Amory, Perheentupa, Zitsmann, Hay, Apter, Anderson *et al*., 2006). Mommers decided that their goal could be achieved by increasing the dose of ENG and using TU (Mommers, Kersemaekers, Ellieson, Kepers, Apter, Behre, Beynon & Bouloux, 2008). TU was used because it is a longer acting preparation in comparison to T decanoate. The men were randomly assigned to three groups, the low release (LR) ENG implant group, the high release (HR) ENG implant group, and the placebo group. The LR and HR groups were further divided into three more treatment groups consisting of TU1, treated with 750 mg in 3 mL every 12 weeks, TU2, treated with 750 mg in 3 mL every 10 weeks, or TU3, treated with 1000 mg in 4 mL every 12 weeks (Mommers *et al*., 2008). Each group was also given a loading TU injection at week 4 for TU1 and TU3 and at week 6 for TU2 (Mommers *et al*., 2008).

The study consisted of 295 men completing treatment and 329 men completing follow-up. The highest suppression of spermatogenesis was found in TU2 at a rate of 93% and TU3 at a rate of 95% within the HR implants group. Between all the active treatment groups 45% of participants achieved sperm counts of less than 1 million/mL by week 6 and 90% by week 12 (Mommers *et al*., 2008). In regard to cholesterol levels, HDL levels decreased from 1.44 mmol/L ± 0.31 to 1.34 mmol/L ± 0.32. Total cholesterol decreased from 4.94 mmol/L ± 0.90 to 4.64 mmol/L ± 0.90 and LDL levels decreased from from 2.96 mmol/L ± 0.78 to 2.79 mmol/L ± 0.81 at the end of treatment (Mommers *et al*., 2008). These values were merely reported and a significance value was not disclosed for the lipid parameters.

Percutaneous testosterone and Medroxyprogesterone acetate

Percutaneous testosterone, 125 mg, and Medroxyprogesterone acetate, two 10 mg tablets

A study led by Soufir (2011) investigated the effectiveness of an oral progesterone preparation, medroxyprogesterone acetate, and percutaneous testosterone (PT) on spermatogenetic suppression. Participants took two 10 mg tablets of medroxyprogesterone acetate twice daily, 12 hours apart from each other. The study began with participants taking 100-125 mg/day of PT administered as a solution of 100 mg in 10 mL of 95% alcohol, which was subsequently changed to a 125 mg of testosterone/5 g water-alcohol gel (Soufir, Meduri & Ziyyat, 2011). Three months into the study 80 percent, 28 out of 35, of the subjects achieved sperm counts ≤ 1 million/mL, while 60 percent of those participants reached sperm counts of 0-0.1 million/mL. Six participants discontinued the study 6 months into the program, but 93 percent, 27 out of 29, of the remaining subjects achieved sperm counts of ≤ 1 million/mL.

With regard to the changes in lipid measurements, the mean cholesterol increased from 4.98 nmol/L (± 1.05) to a high of 5.68 nmol/L (± 0.68) at six months into the treatment. The mean HDL cholesterol increased from 1.29 nmol/L (± 0.35) to 1.36 nmol/L (±0.36) at 6 months, then decreased to 1.33 nmol/L (± 0.23) at 12 months into the treatment. LDL cholesterol levels were not reported. Neither the changes in the mean cholesterol or HDL cholesterol were reported as significant. The study authors do report that "only results obtained in the laboratory of our hospital are present," which was not further clarified by the authors (Soufir, Meduri & Ziyyat, 2011).

Testosterone gel and Depomedroxyprogesterone vs

Testosterone gel and Depomedroxyprogesterone plus Acyline

Testosterone gel, 100 mg, and Depomedroxyprogesterone,300 mg,

PLUS Acyline, 300 µg/kg

Page led a study to research the efficacy of a testosterone gel preparation in conjunction with depomedroxyprogesterone (DMPA) on spermatogenic suppression and whether this combination would be enhanced with the addition of a GnRH antagonist. The GnRH antagonist given was acyline (Acy). Subjects were randomly assigned to two treatment groups Group 1 and Group 2. Group 1 (T + DMPA) participants received 100 mg T gel, topically, daily and 300 mg DMPA, IM, every three months. Group 2 (Acy + T + DMPA) participants received 300 µg/kg, Acyline, SC, every two weeks for 12 weeks plus the T + DMPA as in group 1 (Page, Amory, Anawalt, Irwig, Brockenbrough, Matsumoto & Bremner, 2006).

The sperm count reductions were similar between group 1 and group 2. The mean time to reach severe oligozoospermia was comparable between the two groups. Within group 1

90 percent, 19 out of 21, had sperm counts of ≤ 1 million/mL by week 24. Within group 2 82 percent, 14 out of 17, had sperm ≤ 1 million/mL by week 24 (Page *et al*., 2006).

Concerning the lipid levels, the LDL cholesterol and triglyceride levels did not change significantly throughout the treatment period. However, there was a significant decrease in both the total cholesterol and HDL cholesterol levels during treatment. The change in total cholesterol was greater in group 1 when compared to group 2. In group 1 total cholesterol decreased from 175 mg/dL (± 6) to 166 mg/dL (± 6) by the end of treatment. In group 2 total cholesterol decreased from 193 mg/dL (± 8) to 188 mg/dL (± 8) by the end of treatment. HDL cholesterol levels decreased from 45 mg/dL (± 3) to 42 mg/dL (±2) and from 41 mg/dL (± 2) to 38 mg/dL (± 2) in group 1 and group 2, respectively. The authors state that the effects on HDL cholesterol could "be minimized by reduced doses of T gel in future studies of this regimen because T is known to decrease HDL…" (Page *et al*., 2006).

Discussion

It comes to question whether men are even interested in utilizing male hormonal contraceptives. Historically, it has been women whom have had to bear the brunt of the contraceptive burden because it is women whom carry the fetus. This has led to the theory that women should be responsible for "fertility control" and the directing numerous means of contraception towards women (Darroch, 2008, p. S8). Even though most contraceptive methods are geared toward women, most men spend a majority of their lives avoiding reproduction. Men have the capability to reproduce for a longer period of time than women and must avoid having children for a longer time. With this in mind men should form open discussion with their significant other about family planning wants and needs, but this attitude for open communication does not seem to exist in certain parts of Sub-Saharan Africa, Pakistan, and Egypt (Darroch, 2008).

In order to gauge men's willingness to participate in a new and different form of male contraception two studies were conducted. One study found that "44-83% of men surveyed said they would use the method if it was in pill form and 32-62% would use the method in an injection" (Darroch, 2008, p. S12). Another study found that 55 percent of men would use a contraceptive that was either "a pill, a jelly/salve, an injection or an implant with a high efficacy in birth control and good reversibility" (Darroch, 2008). Even though there is an apparent need for male hormonal contraceptives and most men are willing to participate in family planning through the use of new male contraceptives (Darroch, 2008), there are still many side effects from male hormonal contraceptive treatments which should be taken into consideration before the implementation of this contraceptive method.

Currently, suppressing sperm production by adding supplemental testosterone does seem to have significant side effects on lipid levels in men, including a possibly detrimental effect on HDL cholesterol levels. These affects also include, but are not limited to, acne, increased libido, injection site pain, weight gain, mood changes, and others. Studies have tried to decrease the number and percentage of side effects by reducing the amount of testosterone necessary to suppress the HPG axis. This has partially been accomplished by adding a progestin to the regimen, but even with the addition of a progestin effects on lipid levels could lead to increased cardiovascular risk factors.

Testosterone enanthate

The WHO study (1990) demonstrated the efficacy of testosterone as a potential male hormonal contraceptive due to its effect of spermatogenesis suppression, achieving azoospermia in 70 percent of participants. The WHO follow-up study (1996) states that the decrease in HDL cholesterol levels were significant, but quantitative metabolic analysis was not provided making it impossible to discern whether these levels put men at increased cardiovascular risk. These studies led to additional research in the area of male hormonal contraception and its overall therapeutic viability.

Testosterone enanthate and Levonorgestrel

Testosterone enanthate, 100 mg, and Levonorgestrel, 500 µg

Treatment with T enanthate and LNG, 500 mg, had a profound effect on sperm suppression achieving severe oligozoospermia in 94 percent of participants in six months. This regimen also had a decrease in HDL cholesterol quantified as a mean reduction to 1.01 mmol/L

(Bebb et al., 1996). This low HDL cholesterol level is below the range for HDL cholesterol level and considered a major coronary heart disease risk factor.

Testosterone enanthate, 100 mg weekly, and Levonorgestrel, 125 µg OR Levonorgestrel, 250 µg

Anawalt's study states that 89 percent of men participating achieved severe oligozoospermia and there was no significant difference in sperm suppression between the treatment groups. Those treated with LNG, 125 µg, or LNG, 250 µg exhibited significant decreases in their HDL cholesterol levels (Anawalt et al., 1999), but quantitative metabolic analysis was not provided making it impossible to discern whether these levels put men at increased cardiovascular risk. Further, the treatment protocol called for daily administration of oral LNG which could be problematic for compliance.

Testosterone undecanoate and Noresthisterone enanthate

Testosterone undecanoate, 1000 mg every 6 weeks, and Norethisterone enanthate, 200 mg

Even though Kamischke sees the combination of NETE and TU resulting in a profound suppression of spermatogenesis, his study initially only contained 42 male participants. In the TU/NETE group 13 out of 14 men reached azoospermia and one man only achieved oligozoospermia. The effect of TU, 1000 mg every 6 weeks, and NETE, 200 mg on HDL and LDL cholesterol levels were found to be significant, but the average HDL and LDL cholesterol levels are not clinically significant in regard to a major coronary heart disease risk factor. Though these results are not viewed as a major coronary heart disease factor the study contained a small sample size and these results are difficult to generalize due to these small sizes.

Testosterone undecanoate, 1000 mg, and Noresthisterone enanthate, 200 mg combined at varying intervals

TU, 1000 mg, and NETE, 200 mg combined at varying intervals did not reproduce a significant decrease in HDL cholesterol levels (Pelusi et al., 2010). Also, without a LDL cholesterol level being presented in the data it is difficult to determine the treatment's overall effect on all plasma lipid levels. Perhaps, by lengthening the intervals male hormonal contraceptive treatments are administered could lessen the long-term effects on plasma lipid levels, thus decreasing the cardiovascular risk factors for men. Also, a larger sample size may reveal significant changes in lipid levels. A recent trial with a collaboration between CONRAD and WHO was in Phase IIb investigating the efficacy of a TU/NETE combination male hormonal contraceptive. The study was discontinued in April 2011 because of possible side effects which occurred more often than expected, so it was deemed that risks may outweigh the benefits of TU/NETE therapy ("Male hormonal contraceptive," 2011).

Depot testosterone and Etonogestrel

Testosterone pellets, 400 mg, and three Etonogestrel implants, 68 mg

Most participants treated with Depot T pellets and Etonogestrel implants seemed to achieve some level of either severe oligozoospermia or azoospermia during the treatment phase. This is difficult to state because the study only recruited 15 participants and contained a high discontinuation rate (Brady et al., 2004. Further, those treated had an average HDL cholesterol level decrease but this change was not found to be significant over the 48 weeks of treatment. In comparison to Anderson's study (2002) this study demonstrated a decrease in the LDL cholesterol levels instead of the increase seen before. Perhaps, a new study with a greater number

of participants could lead to more external validity. Overall, this study shows promise due to its effects on spermatogenesis inhibition, long intervals between treatments, and minimal effects on LDL and HDL cholesterol levels.

7α-Methyl-19-Nortestosterone OR Testosterone pellets and Etonogestrel

7α-Methyl-19-Nortestosterone, two 135 mg implants, OR Testosterone pellets, 600 mg, and Etonogestrel, two 68mg implants

Those treated with MENT/etonogestrel did not maintain spermatogenesis suppression as demonstrated in the decrease in men remaining within the severe oligozoospermia after 12 weeks of treatment. The average HDL cholesterol level decreased in both the MENT and T alone groups. This change was found to be significant over within the treatment period, but the study only recruited 29 participants with five participants leaving the study. MENT does not seem to be a viable option for male hormonal contraception because of its apparent effect on systolic blood pressure, leading to the complete discontinuation of the MENT group altogether (Walton et al., 2007).

Testosterone undecanoate and Etonogestrel

Testosterone undecanoate, 750 mg OR 1000 mg, and Etonogestrel, Low-Release OR High-Release

This regimen suppressed spermatogenesis in 93 to 95 percent of men in both the LR and HR implant groups. The HDL levels in the TU and etonogestrel treatment protocol demonstrated a decrease, but significance was either not disclosed or not determined by the authors (Mommers et al., 2008). Whether this reduction in HDL cholesterol levels was significant could be

important even though the average reduction did not go low enough to meet the requirements for a major coronary heart disease risk factor.

Percutaneous testosterone and Medroxyprogesterone acetate

Percutaneous testosterone, 125 mg, and Medroxyprogesterone acetate, two 10 mg tablets

In this study, only 80 percent of the participants achieved sperm levels defined as either severe oligozoospermia or azoospermia. By six months into the study, 93 percent of the remaining men being treated attained severe oligozoospermia. This was after six participants withdrew from the study and the study already having a small sample size. For participants treated with percutaneous testosterone and medroxyprogesterone acetate there was a reported overall increase in the HDL cholesterol levels. Changes in LDL cholesterol levels were either not obtained or not reported. This lack of information of the treatment protocol's effect on LDL cholesterol levels is misleading. The author's also report an increase in the mean cholesterol levels, but these lipid levels were not reported as significant findings (Soufir, Meduri & Ziyyat, 2011). Further, the study only reports that the only metabolic and hematological levels presented were from their hospital, therefore not accounting for an unknown number of plasma lipid results from participants utilizing other hospitals (Soufir, Meduri & Ziyyat, 2011). Also, the treatment protocol called for taking two 10 mg pills of medroxyprogesterone acetate twice daily (Soufir, Meduri & Ziyyat, 2011). This may not be a feasible or acceptable method of treatment for many men, according to Darroch's study (2008).

Testosterone gel and Depomedroxyprogesterone vs.

Testosterone gel and Depomedroxyprogesterone plus Acyline

Testosterone gel, 100 mg, and Depomedroxyprogesterone, 300 mg,

PLUS Acyline, 300 µg/kg

This study demonstrated strong spermatogenesis suppression in the T + DMPA group achieving severe oligozoospermia in 90 percent of men. Page's study also demonstrated reductions in HDL cholesterol levels in groups 1 and 2, reaching significance in both groups (Page et al., 2006). Group 2, which was treated with T + DMPA + Acyline, had a reduction in its HDL cholesterol level that would be considered a major coronary heart disease risk factor. Group 1, treated with only T + DMPA, had a decrease in HDL cholesterol but this level did not meet the definition of a major coronary heart disease risk factor. This study could show promise by reducing the dose of T gel administered.

Singh lead a study to research "the dose-dependent effects of T on several risk factors of atherosclerotic heart disease in healthy young men" (Singh, Hsia, Alaupovic, Sinha-Hikim, Woodhouse, Buchanan, Shen & Bross, 2002, p.136). The risk factors being looked at were plasma lipids, Apo lipoproteins, insulin sensitivity, and C-reactive protein (CRP). In order to control the levels of endogenous T levels in subjects they were each administered a long-acting GnRH agonist at the beginning of the study (Singh et al., 2002).

After the administration of the GnRH agonist, each participant was randomly assigned to a treatment group. There were five treatment groups receiving different doses of T enanthate; group 1 received 25 mg, group 2 received 50 mg, group 3 received 125 mg, group 4 received 300 mg, and group 5 received 600 mg.

The plasma lipid levels of total cholesterol, LDL cholesterol, and triglycerides did not significantly change from the baseline levels at week 20 of treatment. They also state, "there were no significant correlation between T dose or serum total and free T concentrations during treatment and change in total cholesterol, triglycerides, LDL-C…concentrations" (Singh et al., 2002). With regard to the HDL cholesterol, the levels in each group, except group 1, decreased but did not reach significance. HDL cholesterol levels in group 1 increased 4.1 mg/dL (± 2.3). The only group to reach a significant drop in HDL cholesterol levels was group 5, receiving 600 mg T enanthate. "The changes in plasma HDL-C levels from baseline were inversely correlated with circulating total…and free T…" (Singh et al., 2002).

When comparing the results of Singh's studies to the WHO studies (1990) (1996), there is an initial recognition that Singh's (2002) study does not use the same concentration of T enanthate in any of their groups as the studies done by WHO. This brings to question why WHO found significantly reduced amounts of total, LDL, and HDL cholesterol levels when Singh (2002) found no significant decreases in any of their plasma lipid levels, except for the group receiving the largest dose of T enanthate, 600 mg. Additionally, the use of a GnRH agonist was not incorporated in any of the studies reviewed here. Moreover, the generalizability of this study when participants were pretreated with a GnRH agonist confounds the overall effect on plasma lipid levels. Further, this demonstrates that the size of treatment groups could be responsible for the discrepancy in significance between the two studies. Singh's study recruited 61 men with 53 completing the study (2002), while WHO (1996) had close to 400 participants initially enrolled in the study.

It is also difficult to compare Singh's study (2002) to the findings in the other treatment protocols because of the number different T preparations used and the use of progestins. Perhaps,

studying the effects of combination male hormonal contraceptives and measuring plasma lipids, Apo lipoproteins, insulin sensitivity, and CRP levels with and without the effects of a GnRH agonist would be beneficial to more accurately determine cardiovascular risk.

Conclusion

Male hormonal contraception currently uses several different testosterone preparations, including testosterone enanthate, testosterone undecanoate, depot testosterone pellets, testosterone gels, 7α-Methyl-19 Nortestosterone, and percutaneous testosterone. There are also several progestins, synthetic progestagen, formulations, including levonorgestrel, norethisterone enanthate, etonogestrel implants, and depot medroxyprogesterone acetate that are being utilized to increase the efficacy and decrease the adverse effects of hormonal contraception in men.

Depot testosterone in combination with etonogestrel implants and testosterone gel in combination with depomedroxyprogesterone could both be viable options for male hormonal contraception, but both studies reviewed lacked a large sample size, therefore making study results difficult to generalize. Both studies also contained treatment regimens that would be considered feasible for men and were long-acting. Testosterone undecanoate appeared to be a viable option for male hormonal contraception due to its minimal effects on HDL and LDL cholesterol levels, in spite of its small sample size. A collaboration between CONRAD and WHO was in the trial phase to determine "the safety and efficacy of a long-acting formulation of testosterone (testosterone undecanoate [TU]) combined with a long-acting progestin (noresthisterone enanthate) for sperm suppression and contraceptive efficacy," this study was discontinued in April 2011 due to the "possible side effects might outweigh the potential benefits to male participants" ("Male hormonal contraceptive," 2011). These side effects or the main reason for the study's abrupt cancellation were not made known.

Apart from the advances made in male hormonal contraception, there are other non-hormonal prospects for male contraception which may not have the same effects on lipid levels that hormonal contraception methods tend to have. Some of these non-hormonal contraceptive

methods include reversible inhibition of sperm under guidance (RISUG), contraceptive vaccines such as epididymal protease inhibitor (EPPIN), Ca++ channel blockers, indenopyridines such as CDB-4022, chemotherapeutic agents such as adjudin, and gamendazole (Cheng & Mruk, 2010). Some of these methods have shown some efficacy in rats and monkeys and others are in clinical trials. Quintessentially, finding a male contraceptive will be imperative in helping to relieve the unmet need for contraception around the world.

References

1. Anawalt, B.D., Bebb, R.A., Bremner, W.J., & Matsumoto, A.M. (1999). A lower dosage of levonorgestrel and testosterone combination effectively suppresses spermatogenesis and circulating gonadotropin levels with fewer metabolic effects than higher dosage combinations. *Journal of Andrology*, *20*(3), 407-414.
2. Anderson, R.A., Kinniburgh, D., & Baird, D.T. (2002). Suppression of spermatogenesis by etonogestrel implants with depot testosterone: Potential for long-acting male contraception. *The Journal of Clinical Endocrinology & Metabolism*, *87*(8), 3640-3649.
3. Bagatell, C., Knopp, R., Vale, W., Rivier , J., & Bremner , W. (1992). Physiologic testosterone levels in normal men suppress high-density lipoprotein cholesterol levels. *Ann Intern Med*, *116*, 967-973.
4. Bebb, R.A., Anawalt, B.D., Christensen, R.B., Paulsen, C.A., Bremner, W.J., & Matsumoto, A.M. (1996). Combined administration of levonorgestrel and testosterone induces more rapid and effective suppression of spermatogenesis than testosterone alone: A promising male contraceptive approach. *Journal of Clinical Endocrinology and Metabolism*, *81*(2), 757-762.
5. Brady, B.M., Amory, J.K., Perheentupa, A., Zitzmann, M., Hay, C.J., Apter, D., Anderson, R.A., Bremner, W.J., Pollanen, P., Nieschlag, E., Wu, F.C.W., Kersemaekers, W.M. (2006). A multicenter study investigation subcutaneous etonogestrel implants with injectable testosterone decanoate as a potential long-acting male contraceptive. *Human Reproduction*, *21*:285-294.

6. Brady, B.M., Walton, M., Hollow, N., Kicman, A.T., Baird, D.T., & Anderson, R.A. (2004). Depot testosterone with etonogestrel implants result in induction of azoospermia in all men for long-term contraception. *Human Reproduction, 19*(11), 2658-2667.
7. Cheng, C. Y., & Mruk, D. D. (2010). New frontiers in nonhormonal male contraception. *Contraception*, *82*, 476-482. doi: 10.1016.j.contraception.2010.03.017
8. Darroch, J. (2008). Male ferility control - where are the men?. *Contraception*, *78*, S7-S17. doi: 10.1016/j.contraception.2008.04.117
9. Guttmacher Institute. (2010). Facts on satisfying the need for contraception in developing countries. Retrieved from http http://www.guttmacher.org/pubs/FB-Unmet-Need-Intl.pdf
10. Kamischke, A. (2000). Intramuscular testosterone undecanoate and noresthisterone enanthate in a clinical trial for male contraception. *The Journal of Clinical Endocrinology & Metabolism*, *86*(1), 303-309.
11. Male hormonal contraceptive trial ending early. (2011, April 22). Retrieved from http://www.conrad.org/news-pressreleases-63.html
12. Meriggiola, M.C., Costantino, A., Saad, F., D'Emidio, L., Morselli Labate, A.M., Bertaccini, A., Brember, W.J., & Rudolph, I. (2005). Noresthisterone enthate plus testosterone undecanoate for male contraception: Effects of various injection intervals on spermatogenesis, reproductive hormones, testis, and prostate. *The Journal of Clinical Endocrinology & Metabolism*, *90*(4), 2005-2014. doi: 10.1210/jc.2004-1852
13. Mommers, E., Kersemaekers, W.M., Ellieson, J., Kepers, M., Apter, D., Behre, H.M., Beynon, J., & Bouloux, P.M. (2008). Male hormonal contraception: A double-blind, placebo-controlled study. *J Clin Endocrinol Metab*, *93*(7), 2572-2580.

14. Page, S.T., Amory, J.K., Anawalt, B.D., Irwig, M.S., Brockenbrough, A.T., Matsumoto, A.M., & Bremner, W.J. (2006). Testosterone gel combined with depomedroxyprogesterone acetate is an effective male hormonal contraceptive regimen and is not enhanced by the addition of a gnrh antagonist. *The Journal of Clinical Endocrinology & Metabolism*, *91*(11), 4374-4380. doi: 10.1210/jc.2006-1411
15. Pelusi, C., Costantino, A., Cerpolini, S., Pelusi, G., Meriggiola, M.C., & Pasquali, R. (2010). A placebo-controlled, randomized clinical trial using testosterone undecanoate with injectable noresthisterone enanthate: Effect on anthropometric, metabolic and biochemical parameters. *International Journal of Andrology*, *36*(6), 548-555. doi: 10.1111/j.1365-2605.2010.01122.x
16. Rosenson, R.S. (2010). ATP III guidelines for treat of high blood cholesterol. In: A.M. Rind (Ed.) UpToDate. Retrieved from http://www.uptodate.com/home/index.html
17. Singh, A.B., Hsia, S., Alaupovic, P., Sinha-Hikim, I., Woodhouse, L., Buchanan, T.A., Shen, R., & Bross, R. (2002). The effects of varying doses of t on insulin sensitivity, plasma lipids, apolipoproteins, and c-reactive protein in healthy young men. *The Journal of Clinical Endocrinology & Metabolism*, *87*(1), 136-143.
18. Snyder, P.J. (2012). Testosterone treatment of male hypogonadism. In: K.A. Martin (Ed.), UpToDate. Retrieved from http://www.uptodate.com/home/index.html
19. Soufir, J. -.C, Meduri, G., & Ziyyat, A. (2011). Spermatogenetic inhibition in men taking a combination or oral medroxyprogesterone acetate and percutaneous testosterone as a male contraceptive method. *Human Reproduction*, *26*(7), 1708-1714. doi: 10.1093/humrep/der138

20. Sundaram, K., Kumar, N., Bardin, C.W. (1993). 7 alpha-methyl-nortestosterone (ment): the optimal androgen for male contraception. *Annals of Medicine, 25*(2), 199-205.
21. Walton, M.J., Kumar, N., Baird, D.T., Ludlow, H., Anderson, R.A. (2007). 7α-methyl-19-nortestosterone (ment) vs testosterone in combination with etonogestrel implants for spermatogenic suppression in healthy men. *Journal of Andrology*, *28*(5), 679-688. (Walton, 2007)
22. United Nations. (2005). World population to increase by 2.6 billion over next 45 years, will all growth occurring in less developed regions. Retrieved from http://www.un.org/News/Press/docs/2005pop918.doc.htm
23. Walton, M.J., Kumar, N., Baird, D.T., Ludlow, H., Anderson, R.A. (2007). 7α-methyl-19-nortestosterone (ment) vs testosterone in combination with etonogestrel implants for spermatogenic suppression in healthy men. *Journal of Andrology*, *28*(5), 679-688. (Walton, 2007)
24. World Health Organization Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. *Fertility and Sterility* 1996; 65: 821-829.
25. World Health Organization Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia in normal men. Lancet 1990; 336: 955-959.

Abstract

Objective

Male hormonal contraception could help meet unmet contraceptive needs and share the contraceptive burden. Male hormonal contraception maintains efficacy in inhibiting spermatogenesis, but has a negative effect on serum cholesterol levels, particularly HDL and LDL, which may mean detrimental cardiovascular risks.

Methods

The databases PubMed, UptoDate, and Google were utilized as search engines to find literature related to male hormonal contraception, serum cholesterol levels, and incidental pregnancies.

Results

Most of the studies reviewed demonstrated significant reductions in HDL cholesterol levels with some reaching the definition of a major coronary heart disease risk factor. Regimens such as TU/NETE, Depot T with etonogestrel, and T gel with DMPA demonstrate efficacy in spermatogenesis suppression, while limiting effects on serum cholesterol levels.

Conclusion

Depot testosterone with etonogestrel implants and testosterone gel with depomedroxygrogesterone could both be viable options for male hormonal contraception. Non-hormonal male contraceptive methods are available and may be safer.