Would male hormonal contraceptives affect cardiovascular risk?

Michael Zitzmann

The aim of hormonal male contraception is to prevent unintended pregnancies by suppressing spermatogenesis. Hormonal male contraception is based on the principle that exogenous administration of androgens and other hormones such as progestins suppress circulating gonadotropin concentrations, decreasing testicular Leydig cell and Sertoli cell activity and spermatogenesis. In order to achieve more complete suppression of circulating gonadotropins and spermatogenesis, a progestin has been added testosterone to the most recent efficacy trials of hormonal male contraceptives. This review focuses on the potential effects of male hormonal contraceptives on cardiovascular risk factors, lipids and body composition, mainly in the target group of younger to middle-aged men. Present data suggest that hormonal male contraception can be reasonably regarded as safe in terms of cardiovascular risk. However, as all trials have been relatively short (<3 years), a final statement regarding the cardiovascular safety of hormonal male contraception, especially in long-term use, cannot be made. Older men with high risk of cardiovascular event might not be good candidates for hormonal male contraception. The potential adverse effects of hormonal contraceptives on cardiovascular risk appear to depend greatly on the choice of the progestin in regimens for hormonal male contraceptives. In the development of prospective hormonal male contraception, data on longer-term cardiovascular safety will be essential.

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INTRODUCTION

Methods of hormonal contraception for women have been available for many years. Why there is a need to develop a hormonal form of contraception for men as there are non-hormonal applications such as condoms and vasectomy? There is a demand from men and women that a reversible and reliable method for sexual activity, sex steroid hormone production, and spermatogenesis. Since recent studies estimate that 8%–18% of maternal deaths worldwide are due to unsafe abortion, and the number of abortion-related deaths in 2014 ranged from 22,500 to 44,000.

However, hormonal male contraception represents an unusual class of drugs. It would be a medication that is given to one person to prevent a health event (pregnancy) in another person. Stricter ethical barriers than in the development of a drug to treat a disease might be applied in this case. Such a pharmaceutical regimen must withstand special scrutiny and pass high safety prerequisites. In light of discussions about the cardiovascular safety of hormonal treatments for hypogonadism in men and also reports of adverse effects of anabolic steroid abuse, the question of how a young man desiring to use hormonal male contraception should be counseled arises.

ENDOCRINE MECHANISM AND EFFICACY OF HORMONAL MALE CONTRACEPTION

The aim of hormonal male contraception is the reversible suppression of spermatogenesis to a level that is consistent with infertility. The principle is based on the suppression of circulating gonadotropin concentrations, thus suppressing testicular Leydig cell and Sertoli cell activity, sex steroid hormone production, and spermatogenesis. Since endogenous testosterone production is suppressed by male hormonal contraceptive regimens, these regimens must include androgens at a dosage that is sufficient for replacement therapy (Figure 1). Adequate suppression of spermatogenesis (to $<1 \times 10^6$ ml$^{-1}$) had been achieved in more than 95% of men within a few months of treatment in the six efficacy studies published to date.$^6,7$ The goal of hormonal male contraception can be best achieved by testosterone (or a chemical derivative of testosterone) alone or by testosterone in combination with...
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Some trials demonstrated the contraceptive efficacy of hormonal male contraception when couples used no other method of contraception; it is highly efficacious and results in failure rates of approximately 5%, provided sperm concentrations are maintained ≤1 x 10^6 ml⁻¹. The failure rates compare favorably to the effectiveness of female oral contraceptives. Upon cessation of hormonal male contraception, sperm quality fully recovers in a predictable manner resulting in pregnancies and live birth.

The most recent multicenter efficacy trial in hormonal male contraception was sponsored by the World Health Organization and Contraception Research and Development, and it tested the combination of intramuscular injections of testosterone undecanoate plus cyproterone acetate, levonorgestrel, or nestorone. The success of this contraceptive regimen is predictable resulting in pregnancies and live birth.

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Figure 1: Schematic principle of the endocrine mechanism of hormonal male contraception. Testosterone or the androgen used suppresses GnRH release as well as the production of gonadotropins. This effect is augmented by additional use of a progestin or a long-acting GnRH antagonist. Testicular functions mediated by Leydig cells and Sertoli cells are attenuated and spermatogenesis is inhibited. Systemic androgen activity is maintained due to the administered androgen. DHT: double hydrogen testosterone; FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; LH: luteinizing hormone.

**ANDROGEN EFFECTS IN HORMONAL MALE CONTRACEPTION RELATED TO TESTOSTERONE REPLACEMENT THERAPY OF HYPOGONADAL MEN**

A potential user of any novel hormonal male contraception would have to be advised of the safety profile of the androgenic and the progestin components.

The most prominent question is whether the androgenic effects of hormonal male contraception more closely resemble those of testosterone replacement therapy of hypogonadal men or those seen in abusers of anabolic-androgenic steroids. The dose of testosterone used in hormonal male contraception is often slightly higher than that used in testosterone replacement therapy. Nevertheless, serum levels of testosterone remain generally within the normal range with the most recently developed hormonal male contraceptives. Trough serum testosterone concentrations are lower than pretreatment concentrations with some male hormonal contraceptive regimens that have been tested. This effect is most likely due to the suppression of endogenous androgen production and nonphysiological androgen regimens in the regimens.

The important androgen-related aspects during the application of hormonal male contraception regarding cardiovascular health are possible changes of hematocrit, lipids, and blood pressure as peak serum and trough testosterone concentrations may vary considerably from the baseline, eugonadal concentrations of men. A general picture reported by most trials is a slight but statistically significant increase in hematocrit (mean change by 1%–2%) and a slight, statistically significant decrease in serum high-density lipoprotein (HDL) cholesterol (mean change by 0.1–0.2 mmol l⁻¹). Changes in other lipid, blood pressure, or glucose metabolism have been reported, but the results are variable and might be due to chance.

**ARE THE EFFECTS OF HORMONAL MALE CONTRACEPTIVES COMPAREABLE TO ANABOLIC ANDROGEN (AAS) SUBSTANCE ABUSE?**

Abuse of AAS is widespread. A study focusing on the effects of such abuse used a cross-sectional cohort design and recruited 140 experienced male weight lifters in the age group of 34–54 years. The cohort comprised 86 men reporting ≥2 years each of cumulative lifetime AAS use and 54 controls. Transthoracic echocardiography and coronary computed tomography angiography revealed pathologic findings in the abuser group compared to controls including left ventricular systolic and diastolic function as well as increased prevalence of advanced coronary artery plaque volume. This is consistent with previous reviews of case reports on AAS abuse.

Studies of AAS use are problematic because of wide interindividual choice of AAS, cyclic use (“cycling”), and use of multiple AAS (“stacking”). In addition, men who abuse androgens often use diuretics, growth hormone, thyroid hormone, and insulin to enhance performance. Steroid abuse cannot be compared to hormonal male contraception in terms of cardiovascular risk.

**PROGESTINS IN HORMONAL MALE CONTRACEPTION**

Another aspect of hormonal male contraception that has to be discussed is the progestin component of the regimen. These substances have inherent properties and are necessary to suppress gonadotropin secretion to a level that allows spermatogenesis to stop in a reversible manner. Progestins bind to the progesterone receptor as well as to the androgen receptor. The putative cardiovascular risk depends on the choice of the progestin: its binding capacity to the progesterone androgen receptor. A recent comparative trial of progestins for hormonal male contraception demonstrated that these substances can induce hypergonadism with a decrease in hemoglobin concentrations, reduced insulin sensitivity, and increased inflammation markers. Such effects were counteracted by the application of transdermal testosterone gel normalized to serum testosterone concentrations.

It has been shown in male contraceptive clinical trials comparing testosterone alone versus testosterone plus norethisterone that...
individuals in the progestin-containing study arms exhibited increased plasma levels of pro-coagulant substances and also higher plasma concentrations of inflammatory markers than those in the testosterone only group.\textsuperscript{25,26} Inflammation is most likely promoting cardiovascular disease, and recent approaches involve anti-inflammatory treatment to reduce the incidence of cardiovascular events.\textsuperscript{27–29} The progesterone norethisterone enanthate administered intramuscularly in combination with testosterone undecanoate was associated with an increase in pro-inflammatory interleukin-6, whereas testosterone alone resulted in decreased interleukin-6.\textsuperscript{26}

A large multicenter, double-blind, placebo-controlled trial involving injectable testosterone undecanoate and implants of etonogestrel reported a slight decrease of serum HDL cholesterol (by 0.1 mmol l\textsuperscript{-1}) versus placebo but no other significant changes in serum lipids.\textsuperscript{26}

These results are comparable to those of the most recent large trial in hormonal male contraception also using both injectable testosterone undecanoate and norethisterone enanthate.\textsuperscript{7}

In general, trials of hormonal male contraception have shown consistent findings in regard to suppression of HDL cholesterol and gain weight. However, the pro-atherogenic LDL-cholesterol may be suppressed by androgens, too.\textsuperscript{12} There appears to be a dose-dependent effect of testosterone on serum HDL and weight; the second WHO efficacy trial that used high-dosage intramuscular testosterone alone was associated with an average decline of serum HDL of 13% and an average weight gain of 4 kg.\textsuperscript{31} Lower doses of testosterone alone cause markedly less HDL suppression (and weight gain) but are not as effective at suppressing sperm production, thus requiring an additional progestin for suppression of gonadotropins.\textsuperscript{12}

When combining lower, physiological doses of testosterone with a progestin, this regimen improves sperm suppression, but HDL and weight are also adversely affected.\textsuperscript{2,3} HDL cholesterol suppression and weight gain are associated with the dosage of the progestin.\textsuperscript{12}

Overall, the data suggest that the progestin component in hormonal contraceptive regimens contributes a significant proportion of the adverse effect of hormonal male contraceptives on metabolic risk factors for atherosclerotic heart disease.

The trials on hormonal male contraception have been too short to detect cardiovascular events or deep vein thrombosis, adverse events that occur with androgenic-anabolic steroid abuse,\textsuperscript{21} and it remains to be determined whether the changes in HDL cholesterol, lipids, and hematocrit are clinically significant. In the trials completed to date, no safety signal has been seen. One has to remark, however, that the trials have been for only 1–2 years and the young healthy controls represent a low-risk population.

Hormonal male contraception is similar to testosterone replacement in many aspects, but hormonal male contraception includes a progestin that has important metabolic effects. In future regimens of hormonal male contraception, the choice of progestin will be paramount.\textsuperscript{21} Hormonal male contraception also is used in healthy, eugonadal men, and the effects of testosterone and sex steroids might differ from those seen in hypogonadal men.

**ALTERNATIVES TO PROGESTINS IN HORMONAL MALE CONTRACEPTIVES**

An alternative to the use of progestins in hormonal male contraception is long-acting gonadotropin-releasing hormone (GnRH) antagonists such as acyline that suppress the release of gonadotropins without exerting progestin-like effects. In a recent trial, dose-response impacts of various doses of transdermal testosterone gel in men having been pretreated by a GnRH antagonist resulted in corresponding serum sex steroid concentrations and were related to shifts in body composition and adipokines.\textsuperscript{24} This trial demonstrated that body composition changed dose-dependently: lean mass increased and fat mass decreased with increasing serum concentrations of testosterone. As with other studies, weight gain was related to the testosterone dosage. There was no significant change in blood pressure in this study or previous hormonal contraceptive studies.\textsuperscript{12,34}

**CONCLUSIONS**

Since there have not been adequately powered, long-term randomized clinical trials of hormonal contraceptive regimens, it cannot be concluded that these regimens are safe. However, the present data support the view that hormonal male contraception can be reasonably regarded as safe in terms of cardiovascular risk. However, as the trials were short of duration (not longer than a maximum of 2 years) and the participants were healthy younger men, a final statement regarding the cardiovascular safety of hormonal male contraception, especially in long-term use, cannot be made. Older men with a high risk of cardiovascular event might not be good candidates for hormonal male contraception as serum HDL cholesterol might decrease and erythrocytosis might be more likely.\textsuperscript{15,30} The choice of progestin in regimens for hormonal male contraception has to be made carefully, as these substances might increase blood coagulation and inflammation.

In the development of prospective hormonal male contraception, data on long-term cardiovascular safety will be essential.

**COMPETING INTERESTS**

The author declares no competing interests.

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