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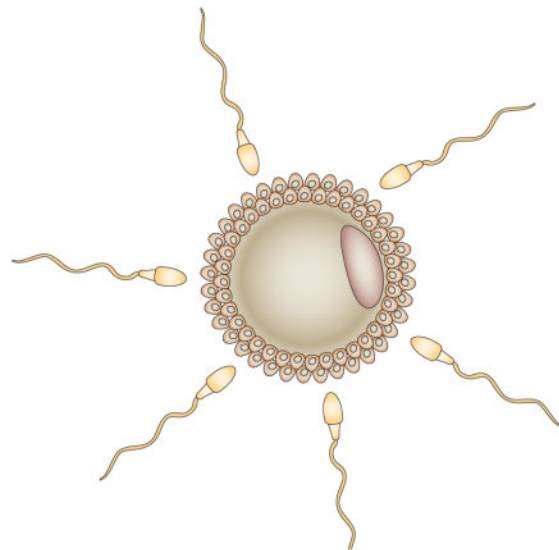
Male hormonal contraceptive passes efficacy test in China

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Abstract

Traditional methods of male contraception, such as condoms and vasectomy, are unacceptable to many couples as they can be unreliable or the effects not easily reversed. Depot administration of male hormonal contraception could provide a safe, effective, reliable and reversible alternative, report researchers in China.



The results of the largest study of male hormonal contraception performed to date were published online on 17 March 2009.¹ Monthly injections of the long-acting androgen testosterone undecanoate were associated with a very low rate of pregnancy in partners of treated men. The treatment regimen was well-tolerated, with no clinically significant adverse effects, and suppression of spermatogenesis was reversible after cessation of the drug.

Almost since the introduction of female hormonal contraceptives in the 1960s, efforts have been underway to develop analogous methods of male hormonal contraception. Testosterone injections can effectively inhibit spermatogenesis in most healthy men by suppressing pituitary secretion of follicle-stimulating hormone and luteinizing hormone. Low concentrations of these two hormones deprive the testes of the signals required for

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Competing interests

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spermatogenesis, leading to marked suppression of sperm production over a period of 10–12 weeks. A number of factors make a hormonal approach to male contraception appealing to both clinicians and patients. Such factors include universal reversibility after cessation of testosterone treatment and the fact that >90% of treated men exhibit suppression of sperm production to levels associated with a very low risk of pregnancy. In addition, hormonal approaches to contraception exploit established drugs that have a long track record of safety in the treatment of men with hypogonadism.

Gu and colleagues¹ enrolled 1,045 Chinese men with proven fertility in a multicenter, open-label, phase III trial of monthly injections of 500 mg testosterone undecanoate. Couples continued to use contraception for the first 6 months of treatment (the suppression phase). If the man's sperm concentration had dropped to <1 million per ml of ejaculate, the couple was instructed to discontinue other methods of contraception and rely only on the testosterone injections (the efficacy phase). Treatment was stopped after 24 months and a 12-month recovery phase followed. The study, therefore, provides a large database with which to judge the efficacy, safety, tolerability and reversibility of this hormonal approach to male contraception.

In terms of efficacy, 43 men (4.8%) failed to suppress spermatogenesis to <1 million sperm per ml of ejaculate, a level judged to be a reasonable goal for male hormonal contraceptives.² 19 pregnancies occurred during the initial 6-month suppression phase, which suggests that improved counseling might be required for men who opt to use hormonal contraception. 855 men who attained suppression of spermatogenesis entered the efficacy phase; nine pregnancies (~1%) occurred during this phase of the trial. Six of these nine pregnancies occurred when sperm concentrations in men who had previously achieved suppression 'rebounded' to >1 million per ml of ejaculate. By contrast, the remaining three pregnancies occurred despite the fact that sperm concentrations remained below this threshold, which demonstrates that pregnancy is possible even when male contraceptive methods suppress sperm production to extremely low levels.

When the 1% failure rate is combined with the 5% of men who did not suppress spermatogenesis to <1 million sperm per ml of ejaculate—and, therefore, did not enter the efficacy phase of the study—the overall failure rate of the treatment regimen used by Gu *et al.* was 6%. Serum concentrations of gonadotropins, but not genetic variation in the gonadotropin or androgen-receptor genes, might relate to an individual's ability to suppress spermatogenesis in response to male hormonal contraception.³

These data reported by Gu *et al.* corroborate the very high efficacy of male hormonal contraceptive observed in small studies previously conducted in China.⁴ Furthermore, the data reinforce those achieved internationally by the WHO using weekly injections of testosterone enanthate,^{5,6} and in trials of testosterone combined with a progestin.⁷ Even if the 19 pregnancies that occurred during the suppression phase are included in the overall rate of failure for testosterone undecanoate, this approach remains superior to the use of condoms (the only other truly reversible form of male contraception), the failure rate of which approaches 15% per annum.⁸

In terms of safety, no clinically significant adverse events were reported during the study. 18 men (~0.3%) discontinued the treatment during the efficacy phase, presumably as a result of adverse effects, which included change in libido (five men), skin rashes (five men), worsening of acne (three men), increased blood pressure (two men), fear of injections (two men), and injection-related fever (one man). In addition, around 4% of the participants complained of tenderness at the injection site, but none discontinued treatment for this reason. Other common adverse effects that were noted, but did not result in discontinuation,

included acne (77 men), severe cough after the injection (22 men), and change in mood or behavior (eight men). Participants' mean body weight increased by 1 kg during the course of the study, whereas testes volume decreased by 15%. Minor changes in clinical laboratory values were recorded, and included a 7% increase in mean hemoglobin levels and decreases in the mean levels of total cholesterol, HDL cholesterol and LDL cholesterol (21%, 23% and 29%, respectively). No changes were observed in the levels of prostate-specific antigen or biochemical assessments of liver or kidney function.

In terms of tolerability, 312 men withdrew from the study: nonsuppressors (43 men), adverse events (18 men), lost to follow-up (93 men), change in contraception (43 men), requested withdrawals (20 men), missed injections (40 men), rebound of spermatogenesis (10 men), pregnancy (nine men), and other reasons (36 men). The continuation rate was, therefore, >85%—a level higher than that associated with condom use,⁹ although this figure must be interpreted with caution. Men enrolled in this study were willing to have monthly intramuscular injections, and such men are not likely to be representative of the population as a whole. In terms of reversibility, sperm count had returned to normal in all but one man by the end of follow-up. This individual apparently developed epididymitis during the study, which was thought to be unrelated to the treatment regimen.

The study by Gu and colleagues demonstrates the very good efficacy, safety, tolerability and reversibility of monthly testosterone undecanoate for male hormonal contraception. Nevertheless, it seems unlikely that this particular regimen will receive regulatory approval in China. Additional studies of male hormonal contraception are underway, most notably a large, international trial cosponsored by the WHO and the US-based Contraceptive Research and Development (CONRAD) program.¹⁰ This study will enroll 400 couples who will use a combination of injections of testosterone undecanoate and norethisterone enanthate every 8 weeks—a regimen demonstrated to have a high degree of efficacy in previous small trials.¹⁰ Future goals of research into male hormonal contraceptives are to develop either an oral pill or an injectable agent that can be used every 2–3 months. Such work is hoped to eventually bring the dream of male hormonal contraception to fruition.

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Practice points

- Testosterone administration suppresses spermatogenesis and is an effective contraceptive in 95% of treated Chinese men
- Testosterone administration over a 2–3 year period is not associated with appreciable adverse effects
- improvements in methods of hormonal contraception for men could soon result in the clinical introduction of these methods