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Hormonal Approaches to Male contraception

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Abstract

Purpose of review—Condoms and vasectomy are male controlled family planning methods but suffer from limitations in compliance (condoms) and limited reversibility (vasectomy); thus many couples desire other options. Hormonal male contraceptive methods have undergone extensive clinical trials in healthy men and shown to be efficacious, reversible and appear to be safe.

Recent Findings—The success rate of male hormonal contraception using injectable testosterone alone is high and comparable to methods for women. Addition of progestins to androgens improved the rate of suppression of spermatogenesis. Supported by government or non-government organizations, current studies aim to find the best combination of testosterone and progestins for effective spermatogenesis suppression and to explore other delivery methods for these hormones. Translation of these advances to widespread use in the developed world will need the manufacturing and marketing skills of the pharmaceutical industry. Availability of male contraceptives to the developing world may require commitments of governmental and non-governmental agencies. In a time when imbalance of basic resources and population needs are obvious, this may prove to be a very wise investment.

Summary—Male hormonal contraception is efficacious, reversible and safe for the target population of younger men in stable relationships. Suppression of spermatogenesis is achieved with a combination of an androgen and a progestin. Partnership with industry will accelerate the marketing of a male hormonal contraceptive. Research is ongoing on selective androgen and progesterone receptor modulators that suppress spermatogenesis, minimize potential adverse events while retaining the androgenic actions.

Keywords

androgens; progestins; selective androgen receptor modulators; suppression of spermatogenesis

Introduction

Male hormonal contraception relies on the exogenous administration of testosterone either alone or in combination with a progestin or GnRH analog to suppress gonadotropins (LH and FSH) to levels below that required to maintain spermatogenesis. Spermatogenesis is dependent on high intratesticular testosterone concentration and the action of FSH on the Sertoli cells. The decrease in LH leads to marked suppression of testosterone production by the Leydig cells; the decrease in intratesticular testosterone coupled with suppression of FSH leads to a decrease in Sertoli cell function required for germ cell maturation and survival. Low intratesticular testosterone levels result in decrease proliferation of spermatogonia, accelerated apoptosis and defects in spermiation and sequestration of mature

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spermatozoa by Sertoli cells. Testosterone administered exogenously will support the androgen effects on sexual function and other target organs of testosterone without supporting spermatogenesis (1,2).

The use of androgens to suppress spermatogenesis was initiated in the 1970s by the Contraceptive Development Branch of NICHD, NIH and other research agencies (3–8). In two landmark studies conducted in the 1990s by the World Health Organization (WHO) in partnership with the Contraceptive Research and Development Program (CONRAD), healthy male volunteers were administered weekly injections of testosterone enanthate. These two studies showed that suppression of spermatogenesis by exogenous testosterone achieved contraceptive efficacy (1.4 per 100 person-years, 95 percent confidence interval [CI] 0.4 to 3.7) which was equivalent to female hormonal methods of contraception. Of the over 700 men participating in the two studies about 2% of the men did not reach azoospermia or severe oligozoospermia (< 3 million/ml ejaculate). Despite the weekly injections, the participants tolerated testosterone well with minor side effects (9,10). Addition of a progestin in many subsequent studies showed enhanced, more rapid and complete suppression of spermatogenesis (11,12). There was a short period when GnRH analogs were coupled with testosterone as experimental suppressors of spermatogenesis but GnRH agonists were found to be inadequate suppressors of gonadotropins and the antagonists while effective were thought to be too expensive for wide application and required daily injections (13–18). Since then, most studies supported by WHO, CONRAD and other government and non-governmental organizations are focused on combinations of testosterone (injectables, pellets, patches) plus a progestin (e.g. medroxyprogesterone acetate, levonorgestrel, desogestrel and norethisterone). These studies showed more rapid suppression of sperm production to very low levels (19–24) and contraceptive efficacy (25,26).

Efficacy of Male Hormonal Contraception

The first large placebo controlled trial for male hormonal contraception solely supported by industry used various combination of injectable testosterone undecanoate and etonogestrel implants or placebo injections and implants. This study also used a centralized laboratory for sperm concentration determination. Suppression of spermatogenesis to 1 million/ml or less with the higher doses of the progestin etonogestrel averaged 94% in all groups which was maintained until the end of treatment. Treatment was tolerated by the participants but compared to the control group, more men on active treatment reported weight gain, mood changes, acne, sweating, or libido change. These adverse effects are anticipated from the androgen and progestin administration and may be minimized by optimizing the dose regimen or the delivery method (27).

Efforts are on going to use provider independent methods of delivery of testosterone and progestins. Testosterone gel and Nestorone (a progestin) gel when applied to the skin daily resulted in adequate serum levels to severely suppress gonadotropin levels (28). Supported by the NIH, NICHD, a longer term study with this combination to assess the effectiveness of transdermal application of testosterone and Nestorone gel is ongoing.

The largest study for male contraception was conducted in China supported by the Chinese Government and the WHO. This phase 3 study recruited 1045 men from 10 centers in China and used the longer acting Chinese preparation of testosterone undecanoate injections every month for about 30 months. 4.8 % of men did not reach severe oligozoospermia (sperm concentrations < 1 million/ml) at 6 months and did not enter the efficacy phase. During the study 1.3 % of men experience rebound of sperm concentration to > 1 million/ml. These two items resulted in a method failure rate of 6.1%. During the efficacy phase when the couples

were not using another method of contraception, the contraceptive efficacy was 1.1 per 100 person-years. The authors concluded that monthly injection of testosterone undecanoate provides safe, effective, reversible contraceptive protection (29).

Factors affecting Suppression of Spermatogenesis

A recent integrated analysis examined co-variables that might influence the rate and extent of suppression of spermatogenesis to severe oligozoospermia in male hormonal contraceptive trials. This report included 1756 healthy men aged 18–51 years, predominantly Whites (two thirds) or Asians (one third). This represents about 85% of all the published data on male hormonal contraceptive trials from 1990 to 2005. The most important variable that increased both the rate and extent of suppression of spermatogenesis was the addition of a progestin to the androgen regimen. Caucasian men showed an initial faster rate of suppression but a less complete extent then Asian men. Lower baseline sperm concentration and serum testosterone levels, and younger age were also associated with more complete suppression but the overall effect size was small. The conclusion from this analysis was that combination of a progestin with an androgen results in faster and more complete suppression of sperm output (30).

In the two studies sponsored by the WHO, the proportion of Asian men reaching azoospermia was higher than non-Asian Men (Liu et al, 2008;World Health Organization Task Force on methods for the regulation of male fertility, 1990;World Health Organization Task Force on methods for the regulation of male fertility, 1996). The reasons for the apparent ethnic differences in suppression of spermatogenesis by exogenous hormones are not clear. The production rate of testosterone was lower in Asian men residing in China but not in those residing in Western countries, but their metabolic clearance rates was not different (31,32). Serum 5 alpha dihydrotestosterone (DHT) has been reported to be lower in Asian men compared to white and black men (33–35) but serum levels may not reflect intratesticular androgen levels which are critical for spermatogenesis (36). Studies from our group showed that the LH pulses are suppressed more when exogenous T was administered to healthy Asian men versus non-Asian men (37). We also showed the spontaneous male germ cell rates may be higher in Asian versus non-Asian men (38).

Recovery from Hormonal Suppression of Spermatogenesis

Utilizing the same data base as described above on 1549 healthy men, the same group of investigators completed an integrated analysis for 30 studies on male hormonal contraceptive trials using androgens alone or androgens plus progestins from 1990 to 2005. In men who showed suppression of spermatogenesis to very severe oligozoospermia or azoospermia, the median time for sperm concentration to recover to over 20 million/ml was 3.4 months. Higher rates of recovery were associated with older age, Asian origin, shorter treatment duration, shorter-acting testosterone delivery systems, higher baseline sperm concentration, faster rate of suppression and lower serum LH levels at baseline. The probability of recovery to over 20 million/ml was 67 % in 6 months, 90 % in 12 months and 100 % within 24 months. This study conclusively showed that hormonal male contraceptive methods are fully reversible with a predictable time course (39).

Issues of Acceptability (female trust of male partner; male willingness to participate; and cultural issues)

Earlier studies on acceptability of hormonal contraception in 199 men participating in clinical trials from six different cultural setting showed that about 76 % of men claimed definite or possible intent of using a male method in the future when available (40).

Following the WHO studies showing efficacy of male hormonal methods of contraception, studies were conducted both in men and women on the acceptability of a male contraceptive method. About 450 men and 450 women were interviewed at each of the centers in Edinburgh, Shanghai and Hong Kong and a slightly larger group in Cape Town. 44 to 83% of men stated that they would used a male method and the preferred method would be a daily contraceptive pill (41). The parallel study in women asked whether they would trust their partners to use a male pill. 71 (Hong Kong) to >90 % (Scotland and South Africa) of women thought a male method was a good idea. Only 2% women indicated that they would not trust their partner to use a male method. This study concluded that women would trust their partners to use a male method reliably and showed the potential market for male contraceptive methods (42). A cross-cultural survey was conducted in over 9000 men aged 18 to 50 years in 9 countries in 4 continents to examine the knowledge, attitudes and acceptability of male methods of contraception. In this survey, 55 to 81.5 % reported that both partners were involved in selecting the method for family planning. 79.4 % of men had used condoms while 31.3 to 82.6 % would not consider vasectomy as a family planning method. Over 55% would accept a male contraceptive method and 28.5 to 71.4 % of men were willing to use such a method with large variations in responses between countries. Overall a daily oral pill would be the preferred new method followed by a monthly injection and then a yearly implant (43).

Challenges for Pharmaceutical Support for Development and Marketing of Hormonal Male Contraceptives

Pharmaceutical companies have been very generous in providing many of the testosterone esters, implants, and gels as well as oral, injectables and implants of various progestins for clinical trials. In recent years, industry supported a male contraceptive clinical trial using a combination of testosterone undecanoate injections and etonogestrel implants (27). Supported by two pharmaceutical companies, this was the first placebo controlled male contraceptive study allowing careful analyses of adverse events that may be associated with the hormones. The study also developed a centralized method for semen analyses and defining azoospermia (44). Despite the very high rate of suppression of spermatogenesis to severe oligozoospermia, the pharmaceutical companies decided not to proceed with male hormonal contraception development. Possible reasons may include the liability of administering hormones to healthy men, method failure leading to unwanted pregnancies, acceptability and adherence issues by men, and reversibility of the methods. However, recent evidence as reviewed above provided more conclusive evidence that hormonal methods of male contraception are reversible, appear to be safe and acceptable and will be used if available in over half of couples from many countries around the world. Government (e.g., US and China) and non-government agencies (e.g., World Health Organization, Contraceptive Research and Development Program, Population Council) have collaborated with industry for phase 2 and 3 clinical trials. These agencies as well as academic institutions have completed phase 3 studies for lead methods and submitted New Drug Applications to the Food and Drug administration for regulatory approval. Application of these advances into widespread availability requires these agencies to seek industry partners either to complete the phase 3 pivotal studies or perform large scale, long term safety trials.

Future approaches for Hormonal Male Contraception

Current studies are attempting to optimize testosterone and progestin combinations into an efficacious, safe, and a practical method. Partnership with pharmaceutical industry is highly desirable and likely critical for a hormonal male contraceptive method to be approved by regulatory agencies, marketed and widely available to men in the developed world. Co-operation and support from donor nations and non-governmental agencies may prove to be a

wise investment in furthering health and political stability in the less well developed world that suffers from imbalance between basic resources (e.g. food, water, energy) and population. The future approach is to develop new chemical entities that are steroid or non-steroidal selective androgen receptor and progesterone receptor modulators (SARMs and SPRMs) that will effectively suppress gonadotropins, maintain the beneficial effects of androgens on sexual function, bone, and fat mass, and minimize the stimulation of the prostate and negative effects on lipoproteins. A steroidal SARM, 7 alpha-methyl-19-nortestosterone has undergone clinical trials (45,46) as implants and others such as dimethandrolone (47,48) are in development as potential components for male contraceptives. It should be noted that dimethandrolone is not aromatized or 5 alpha reduced but acts on both the androgen and progesterone receptor *in vitro*. Non-steroid SARMs are being developed by multiple pharmaceutical companies not only for the treatment of hypogonadism but also for the treatment of frailty (49). These SARMs do not have the steroid ring and cannot be aromatized or 5 alpha reduced to dihydrotestosterone and thus while maintaining the benefits of androgens but may reduce the stimulating effect on the prostate (50,51). Clinical studies for the potential action of these new medications for suppression of spermatogenesis have not been reported.

Conclusion

Clinical trials have demonstrated that if sperm output is suppressed to very low levels by exogenous testosterone alone or with a progestin, contraceptive efficacy is comparable to female methods such as the contraceptive pill. Current studies are optimizing the method of delivery of the hormones and the progestin to use in combination with testosterone. New modified androgens are in development that may be more potent than testosterone and non steroidal compounds will allow the flexibility of delivering and androgens as oral pill, transdermal gels or implants. Input and support by industry will accelerate the availability of a male contraceptive method which could be administered as an injectable, implant, oral pill or transdermal gel.

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Table 1

Mechanisms of Action of Hormonal Methods of Contraception produced by exogenous administration of testosterone (androgen) ± progestin

- Suppression of secretion of gonadotropin releasing hormone from the hypothalamus and the gonadotropins, LH and FSH, from the pituitary gland.
- Decreased LH results in decreased testosterone production from Leydig cells, low intratesticular testosterone level, decreased Sertoli cell function and suppression of spermatogenesis
- Decreased FSH results in Sertoli cell dysfunction and impaired spermatogenesis
- Decreased in spermatozoa production occurs via:
  - Decreased proliferation of spermatogonia
  - accelerated germ cell apoptosis
  - defective spermiation