Male contraception

Where do we go from here?

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The use of either testosterone alone, or a combination of testosterone and progesterone, seems like a promising male “pill” for men,¹⁻⁵ based on a recently completed Phase III, multi-center contraceptive efficacy clinical trial in China that tested injectable testosterone undecanoate (TU, a long-acting androgen) in 1,045 healthy Chinese men over a 30-mo period.⁶ No serious adverse side-effects were reported in the study participants with a cumulative contraceptive failure rate of just 1.1 per 100 men,⁶ yet a similar trial conducted in the US sponsored by WHO and CONRAD that used a combination of TU and norethisterone enantate (NET-EN, a long-acting progestin) was terminated unexpectedly earlier this year due to side effects that outweighed the potential benefits in healthy male participants (see www.conrad.org/news-press-releases-63.html). This, perhaps, is due to the differential responses of Asian men vs. their Caucasian counterparts to exogenous androgens since there are reports in the literature reporting baseline differences in testicular morphology and testosterone metabolism between these two ethnic groups, illustrating that men from different ethnic groups respond differently to androgen-based male contraceptives.⁷ Nonetheless, this is a major disappointment to investigators in the field since hormonal-based contraception is the most advanced and explored approach for men (Fig. 1).

In order to sustain spermatogenesis in the testis and to maintain sperm output, the testosterone level in the testis must be maintained at ~100-fold higher than its level in the systemic circulation at $\sim 1 \times 10^{-7}$ M in the testis vs. 1×10^{-9} M in the blood, and this is applicable to both rodents⁸ and men.^{9,10} Thus, when rodents or men receive

Figure 1. A schematic drawing that illustrates the various targets for male contraception under development in the field, which include potential targets in the hypothalamic-pituitary-testicular axis, the testis, the epididymis, and the vas deferens. Various methods are under development in the field to induce reversible or irreversible contraception in men. Abbreviations: T, testosterone; E, estradiol-17 β , P, progesterone; CDB-4022, [4a5,5R,9bS]-2-ethyl-2,3,4,4a,5,9b-hexahydro-8-iodo-7-methyl-5-[4-carbomethoxyphenyl]-1H-indeno-[1,2-c]-pyridine-hydrochloride, also known as RTI-4587-073; BMS-189453, 4-[[[E]-[5,6-dihydro-5,5-dimethyl-8-phenyl]-2-naphthalenyl]ethenyl] benzoic acid; WIN 18,446, N,N'-bis-(dichloroacetyl)-1,8-octamethylenediamine; RISUG, Reversible Inhibition of Sperm Under Guidance; DMSO, dimethylsulfoxide.

TU or other androgens (e.g., testosterone) via injection, gels or implants, the elevated circulating androgen level thus suppresses the secretion of GnRH and LH from the hypothalamus and the pituitary gland, respectively, thereby “switching off” the production of testosterone by Leydig cells located in the interstitial space of the testis via steroidogenesis and reducing the intratesticular testosterone level needed to sustain spermatogenesis.^{11,12} In short, the hypothalamic-pituitary-gonadal axis

is disrupted (Fig. 1). Thus, the WHO-CONRAD sponsored trial that ended prematurely is a disappointment to investigators in the field because this is one of the most notable approaches for male contraception based on decades of research, yet due to ethnic differences in testicular responses to exogenous androgen or a combination of androgen and progestin, this approach has to be carefully re-evaluated. Regardless, this technical issue may be overcome in the near future with better

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regimens and/or more potent long-acting steroids.

Furthermore, there are other major developments in the field that lie outside of the hormonal-based approach for male contraception, as depicted in **Figure 1**. For instance, there are other potential products under intense investigation in the field that target either the events of spermatogenesis in the testis (e.g., the use of retinoic acid synthesis inhibitors¹³ and retinoic acid receptor antagonists^{14,23} to block retinoic acid function;¹⁵ the use of analogs of indazole-3-carboxylic acid to perturb spermatid adhesion in the testis¹⁶⁻²⁰) or by occluding sperm transport in the vas deferens with RISUG (Reversible Inhibition of Sperm Under Guidance which is a copolymer of styrene/maleic anhydride (SMA) and dimethylsulfoxide (DMSO) that induces sperm membrane disruption once sperm come into contact with RISUG which is surgically placed in the vas deferens to induce reversible infertility).^{21,22}

With current advances in the field, it is anticipated that effective contraceptive products may be available for men in the next decade or two. It is likely that hormonal-based “pills” will first be available, to be followed by other products that exert their effects locally in the testis and vas deferens (**Fig. 1**).

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