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OPINION

Progress in male contraception: A brief summary of the Third International Congress on Male Contraception, May 2022

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The Third Congress on Male Contraception organized by the International Consortium on Male Contraception was held in the historic Academie Nationale De Medicine, Paris, France on May 23, 2022 (https://www.ic-mc.info/3rd-icmc-international-congress-paris-2022/). The focus of the congress is on recent progress in male contraception development including pre-clinical and clinical trials on new methods and studies on men and women's willingness to accept male contraception.

The World Health Organization is positioning male contraception in the contraceptive methods mix to improve reproductive needs and health for all. Contraceptive gaps are identified that include a contraceptive choice for men. It is now widely accepted that universal access to sexual and reproductive health services and information, including access to the full range of safe and effective contraceptive methods, is fundamental to the rights and well-being of adolescents and adults of all genders, and men's role is essential in achieving family planning goals.[1]

The International Consortium on Male Contraception's mission is to disseminate knowledge on the research progress in male contraception by organizing symposia addressed to various audiences and to foster advocacy for this research field (www.ic-mc.info)

The Male Contraceptive Initiative is advancing male contraception by providing funding and training for research and development of novel non-hormonal male contraceptives; advocacy for male contraception through social media and a comprehensive website, and establishing a for-profit subsidiary to rapidly advance programs from pre-clinical through clinical research to reach the market (https://www.malecontraceptive.org).

The efforts of the Contraceptive Development Program (CDP), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Institutes of Health (NIH) in the United States are supporting the clinical development of male contraception through the Contraceptive Clinical Trials Network (CCTN). In collaboration with the Population Council and sixteen academic centers on four continents, NICHD has developed a male hormonal method that effectively inhibits sperm production. This transdermal gel product containing two hormones, Nestorone (a potent non-androgenic progestin) and Testosterone, is currently under evaluation in a Phase IIb efficacy clinical trial in couples using the method to prevent pregnancy. Perspectives from participating couples reveal how important a reversible method of male contraception is to their family planning needs. Interim results demonstrate high efficacy, acceptability, and reversibility. The results strongly support a safe and successful product profile that may allow the product to proceed to Phase III pivotal evaluation.

The NICHD CDP CCTN is conducting Phase I safety, tolerability, and dose-finding studies of novel modified androgens with progestin activity in healthy volunteers. Preliminary studies showed that though the endogenous production of testosterone is suppressed by the exogenous androgen, sexual function and androgenicity appeared to be maintained by these novel androgens (https://malecontraception.center). Hormonal agents may have non-reproductive effects that may be beneficial including inducing myelin regeneration and repair.[2] Prior efficacy trials of hormonal male contraceptive prototypes in couples have demonstrated that suppression of sperm concentration to ≤1 million/ml (independent of motility) is sufficient to prevent

pregnancy in the female partner at rates equal to or better than typical use failure rates of pills approved for female contraception.[3–5] It should be noted that most men have sperm concentration near or at azoospermia during the efficacy phase of these hormonal contraceptive trials. Data from prior contraceptive clinical trials showed that there may be ethnic/racial differences in the responsiveness of hormonal male contraceptives both in the suppression of spermatogenesis and serum concentrations of the hormones.[3,6] These data emphasize the importance of diversity and inclusion of different populations in pivotal hormonal contraception clinical trials.

Male contraception is acceptable in Europe, North and South America, Australia, and Asia.[7,8] In France, there is a movement for contraceptive equity for men including acceptance of vasectomy, condoms, and thermal methods in efforts to promote male responsibility for preventing pregnancy.[9] In the United States, a recent unpublished online survey of over 2000 men (18–50 years) showed over three-quarters of men reported willingness to use new male contraception which was strongly related to gender-equitable attitudes. These data suggest cultural changes may lead to increased demand for male contraception. Preliminary data from an ongoing cross-sectional survey of ~17,000 men across the 8 geographies (Seven Low- and Middle-Income Countries and the United States) found that, in Kenya, 52% of men would use a male contraceptive compared to 39% of men in the United States who would use the product within 1 year of availability. There were also geographical differences in the uptake of potential male contraceptive pills, gels or patches on the skin, nasal spray, or injections.

Novel non-hormonal male contraception includes approaches that target the testis and the male reproductive tract without involving exogenous administration of hormones. The goal is to utilize mechanisms of action restricted to the target organ without affecting other body systems. The main approaches are 1) drugs that interfere with testicular retinoic acid production or signaling or inhibit testis-specific bromodomain and therefore impair spermatogenesis, 2) drugs that interfere with sperm motility or maturation via numerous mechanisms, and 3) drugs that alter sperm morphology during spermiogenesis. These non-hormonal methods, though promising, have not yet reached clinical trials.[10] A hydrogel implanted into the vas deferens through a minimally invasive, outpatient procedure is being developed. The hydrogel works by blocking sperm from traveling through the vas deferens and is designed to last for 0.5–2 years and be reversible (https://www.malecontraceptive.org/contraline). Additional vas occlusion methods which inject polymers into the vas deferens that may be dissolved with a second injection when the reversal is desired are also in development. In male infertility, next-generation sequencing has greatly contributed to the discovery of novel infertility genes. Some of these newly discovered genes show exclusive testicular expression and may be explored as new contraceptive targets. Targets with putative reproductive tissue specificity may be explored using a new Contraceptive Infertility Target Database available to the public (https://www.citdbase.org/).[11]

In addition to the sponsors of the meeting (Population Council, NICHD, The Male Contraceptive Initiative, The European Academy of Andrology, and International Society of Andrology), representatives from the World Health Organization, FHI360, and the Bill and Melinda Gates Foundations discussed their roles in male contraceptive development. Currently, active support for basic and clinical research is provided by the NICHD, NIH, The Population Council, and the Male Contraceptive Initiative, without support or interest from the industry.

In the wake of the overturn of Roe Vs Wade by the United States Supreme Court in June 2022, there is increased urgency to provide reproductive rights for all and ensure that all pregnancies are planned and wanted. Men are ready and willing to take on the challenge and responsibility of contraception. Government agencies, professional societies, advocacy groups, academia, and the pharmaceutical industry must work together to hasten the development of contraceptives that are safe, accessible, and acceptable to both women and men. The burden of birth control has rested with women for too long. Now is the time to provide new options for men, allowing them to actively participate in sharing the responsibility of family planning. The approaches are ready and increased resources will make male contraceptive methods a reality sooner.

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