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EDITORIAL

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It is time for new male contraceptives!

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The development of new male contraception began in the 1970s supported by government agencies in many countries including China (gossypol, no-scalpel vasectomy) (Li *et al.*, 1991; Waites *et al.*, 1998), India (reversible intravasal occlusion) (Guha *et al.*, 1997), and the United States (hormonal male contraception) (Patanelli, 1978). Collaboration between the World Health Organization (WHO), United States National Institute of Child Health and Human Development, and other government and non-government organizations promoted male contraceptive development with many hormonal male contraception clinical trials (Waites, 2003). Led by the WHO in 1990s, two landmark studies provided evidence that if spermatogenesis is suppressed and sperm output is decreased to very low levels by exogenously administered testosterone, contraceptive efficacy of this male method is as effective as female hormonal methods (World Health Organization Task Force on Methods for the Regulation of Male Fertility, 1990; World Health Organization Task Force on the Regulation of Male Fertility, 1996). Since then, a number of studies confirmed that contraceptive efficacy comparable to female hormonal methods can be achieved with androgens alone or together with progestins (Gu *et al.*, 2003; Turner *et al.*, 2003). This included a multicenter male contraceptive study in China that recruited over 1000 couples who received injectable testosterone undecanoate (Gu *et al.*, 2009). Moreover, analyses of recovery of spermatogenesis after withdrawal of the hormones confirmed that hormonal male contraception is reversible in most if not all men (Liu *et al.*, 2006). Since then, the goal for researchers is to find combinations of androgens and progestins that are potent, user friendly, bioavailable as oral formulations or transdermal application and with least adverse events (Page *et al.*, 2008; Nieschlag, 2013; Piotrowska *et al.*, 2016; Wang *et al.*, 2016).

At the same time with the advance in the understanding of the molecular and cellular mechanisms of the regulation of spermatogenesis and sperm maturation, a number of promising non-hormonal targets are being investigated. These methods target a specific protein when inhibited by small molecules, or knocked out in mice will lead to infertility. Although these leads have enormous promise and preclinical studies are ongoing, clinical studies have not yet started (Tash *et al.*, 2008; Chung *et al.*, 2011; Matzuk *et al.*, 2012; Paik *et al.*, 2014; Zdrojewicz *et al.*, 2015; O'Rand *et al.*, 2016).

The Male Contraceptive Summit meetings organized by Dr. Eberhard Nieschlag brought together academics, non-government organizations, government funding agencies, industry partners, provided recommendations for Regulatory Approval for Male Contraception based largely on expert opinions (Aaltonen *et al.*, 2007). Although the pharmaceutical companies provided androgens and progestins for clinical trials, only two of them united to conduct a single placebo-controlled study. This study utilized a testosterone ester and a progestin implant that demonstrated the effectiveness of hormonal contraception and compared adverse events in the placebo versus treated groups (Piotrowska, *et al.*, 2016). Although the study was very efficacious, the pharmaceutical industry changes through mergers and acquisitions led to changes in strategies and no further interest in development of male contraceptives.

During these last 10 years, the development of male contraception is largely supported by the World Health Organization, Contraceptive Research and Development program, and the Population Council but the strongest and continuous support comes from the Contraceptive Research Branch of Eunice Kennedy Shriver National Institute of Child Health and Human Development. The NICHD is supporting male contraceptive clinical trials in new orally bioavailable androgens (Attardi *et al.*, 2006; Surampudi *et al.*, 2014) and a transdermal method (Ilani *et al.*, 2012) in collaboration with the Population Council. The institute also supports research in identifying and developing new targets of male contraception.

In 2013, Dr. David Serfaty, a founding member of the European Society of Contraception and Reproductive Health, together with Dr. Regine Sitruk Ware from the Population Council approached a number of academics and interested persons in government and non-government agencies and founded the International Consortium of Male Contraception (ICMC) (www.ic-mc.info). This consortium's mission is to advocate for the advancement of male contraception and promote collaboration among investigators, government and non-government agencies, industry and interested groups.

The ICMC sponsored sessions in 2014 and 2016 at the European Congress of Contraception and Reproductive Health generated interest among participants of these congresses, many of whom are gynecologists as well as family planning providers. In addition, the First International Congress on Male

Contraception, organized by the ICMC, was held on May 4, 2016, at the French National Academy of Medicine in Paris, France. International speakers presented the latest information on the research in this field and representatives from academia, government, non-governmental agencies, and industry participated in the meeting.

To support further research and development of male contraception; improve understanding of this major unmet need; and promote gender equality in family planning, the Faculty panel approved the 'Paris Manifesto' printed below, which stresses the need to foster advocacy and involvement of various stakeholders such as health authorities, pharmaceutical industry, philanthropists, consumer groups, and policy makers. We hope this manifesto will provide the impetus to engender enthusiasm, interest, and support for the development of new male contraception that is efficacious, safe, affordable, and available to meet the needs of many couples.

THE PARIS MANIFESTO: IT IS TIME FOR NEW MALE CONTRACEPTIVES DECLARATION OF THE INTERNATIONAL CONSORTIUM FOR MALE CONTRACEPTION (ICMC) ON MAY 4, 2016, AT THE FIRST ICMC CONGRESS IN PARIS, AT THE FRENCH NATIONAL ACADEMY OF MEDICINE

1 In 2016, unmet family planning needs remain a global issue. The 2012 London Summit on Family Planning called for innovative solutions for increasing contraceptive access for 120 million women by 2020. Equally important is the development of reliable, reversible and affordable male contraceptives which can be used by millions of sexually active men to allow men to participate in family planning and enhance reproductive health of the couple. Our goal is to help bring to market at least one reliable, reversible and affordable male contraceptive by 2026. While male contraception will not replace female contraception, it will improve options to meet couple needs.
2 At present, male contraception is limited to withdrawal, abstinence, condom use, and vas occlusion. However, research has shown that both men and their female partners are willing to use novel methods, including hormonal contraception, provided it is effective, reversible, and well tolerated.
3 The approaches to male contraception offered by hormonal methods, based on androgens alone or in combination with progestins, are closest to reaching the market. Clinical trials have demonstrated their effectiveness and acceptability by both partners. Researchers targeting differentiation of germ cells, maturation of spermatozoa, or factors inhibiting sperm motility and function have identified promising targets for non-hormonal male contraception, and clinical data may become available for some of them during the current decade. Developing methods with additional health benefits may increase acceptability and possibly lead to increased use and improved compliance. Also, several novel mechanical approaches to vas occlusion are being developed, one of which might eventually result in a reversible vasectomy.
4 The pharmaceutical industry has deserted the field of research in male contraception, partly because of unclear registration requirements and partly because of a perceived lack of acceptability and profitability. Only government, academic and philanthropic non-profit research organizations are continuing research in this area.
5 The authors of the Paris Manifesto urge the pharmaceutical industry and health agencies to become actively involved in the development of male contraceptives. We urge them to join advocacy groups and other stakeholders, as was the case in the development of the first contraceptive pill for women. We appeal to women's health groups and male health advocates to demand from industry and politicians an active involvement in male contraception. History of the female pill shows that public advocacy led to scientific discovery and success.
6 The Paris Manifesto follows the Weimar Manifesto signed by several of the current authors on June 29, 1997, at a Summit Meeting on Male Contraception in Germany. Since then, new technologies have made it possible to consider a range of new approaches to male contraception. Now is the time for the pharmaceutical industry, philanthropists, and other stakeholders to increase their support for the development of novel methods for men as a high priority on the research agenda for global health, ecologic improvements, and economic prosperity.

The Paris Manifesto was signed by David Serfaty, Founder and Coordinator of the ICMC, Paris, France; Regine Sitruk-Ware, Population Council; USA; Eberhard Nieschlag, University of Münster, Germany; and approved by the Faculty Panel: Richard A. Anderson, MRC Centre for Reproductive Health, University of Edinburgh, UK; Hermann M. Behre, Martin-Luther-University, Halle, Germany; Philippe Bouchard, University Pierre et Marie Curie, Paris, France; William J. Bremner, University of Washington, Seattle, WA, USA; Kristina Gemzell Danielsson, Karolinska Institutet, Stockholm, Sweden; Martin M. Matzuk, USA; Maria-Cristina Meriggiola, Department of Obstetrics and Gynecology, University of Bologna, Bologna, Italy; Stephanie T Page, University of Washington, Seattle, WA, USA; Nicholas L. Simmons, Baylor College of Medicine, TX, USA; David C. Sokal, Male Contraception Initiative, USA; Ronald Swerdloff, Harbor-UCLA Medical Center Los Angeles, USA; John Townsend, Population Council, USA; Christina Wang, Harbor-UCLA Medical Center Los Angeles, USA; Frederick Wu, University of Manchester, UK.

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