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Review article

7α-Methyl-19-nortestosterone (MENT^R): the Population Council's contribution to research on male contraception and treatment of hypogonadism

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Abstract

Testosterone is an essential part of all regimens for hormonal male contraception tested to date. Initial efficacy trials revealed that the half-life of the testosterone preparations available at that time was too short to be used for male contraception. The ensuing search for long-acting preparations yielded testosterone buciclate and undecanoate as well as 7α-methyl-19-nortestosterone (MENT). Following description of the principle of male hormonal contraception and the efficacy trials performed to date, the systematic development of MENT for substitution of male hypogonadism and use in male contraception by the Population Council is reviewed here.

Keywords: Male contraception; Clinical trials; MENT; Hypogonadism

1. Introduction

Men are increasingly expected and willing to share the responsibility for family planning by using contraceptive methods [1]. However, traditional male methods of contraception such as periodic abstinence or *coitus interruptus* are associated with a relatively high rate of unwanted pregnancies as well as disturbances in sexual activity. Condoms are the oldest barrier method available, but when using condoms, conception rates remain relatively high, with 12/100 couples conceiving during the first year of use. Nevertheless, condom use has increased since the beginning of the AIDS epidemic, but more for protection from AIDS infection and other sexually transmitted diseases than for contraceptive purposes. Vasectomy is a safe and surgically relatively simple method for male contraception. The rate of unwanted pregnancies after vasectomy is less than 1%. The drawback of vasectomy is that it is not easily reversible. Achieving fatherhood after vasectomy requires either surgical refertilization or sperm aspiration from the epididymis or testicular sperm extraction and intracytoplasmic sperm injection into the ovum. Only about 50% of these men will ultimately become fathers.

Considering these disadvantages of the traditional male contraceptive methods mentioned above, the prerequisites for an ideal pharmacologic male contraceptive become clear, they should [2]:

- be applied independently of the sexual act,
- be acceptable for both partners,
- not interfere with libido, potency or sexual activity,
- have neither short- nor long-term toxic side effects,
- have no impact on eventual offspring,
- be rapidly effective and fully reversible and
- be as safe and effective as comparable female methods.

Of all the different experimental approaches to pharmacological methods for male contraception tested so far, hormonal methods come closest to fulfilling the criteria set out above. The endocrine feedback mechanism operating between hypothalamus, pituitary and testes is the basis on which hormonal approaches to male contraception rest. Their goal is to suppress spermatogenesis and to reduce

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sperm concentration, if possible, to azoospermia or at least to a sperm concentration low enough to provide contraceptive protection to a degree at least as good as generally accepted female contraceptive methods.

Sperm production and secretion of testicular testosterone are so closely interwoven [3] that it has remained impossible to interrupt spermatogenesis by hormonal means without inhibiting androgen production. Inhibition of follicle-stimulating hormone (FSH) alone, e.g., by active immunization against FSH, leads to a reduction of sperm concentration but not to azoospermia, as monkey studies have shown [4]. Suppression of both FSH and luteinizing hormone (LH) will indeed lead to azoospermia, but will also induce symptoms of androgen deficiency affecting libido, erectile function, male behaviour and general metabolic processes (including erythropoiesis, protein, mineral and bone metabolism). For this reason, inhibition of gonadotropins will always necessitate androgen administration [5]. Therefore, the principle of hormonal male contraception consists of [2]:

1. suppression of LH and FSH,
2. depletion of intratesticular testosterone and atrophy of spermatogenesis and
3. substitution of peripheral testosterone to maintain androgenicity.

Testosterone itself is a first choice for hormonal male contraception as it simultaneously suppresses gonadotropins and maintains androgenicity, and indeed, testosterone alone was the first hormone tested for male contraception and has remained part of any steroid combination to date [5].

2. Clinical trials for hormonal male contraception to date

In the early 1970s, the World Health Organisation (WHO), the Population Council and the National Institutes of Health (NIH), USA, initiated programmes for the development of new contraceptive methods for females as well as for males. Within these frameworks and by additional individual investigators, about 60 published clinical trials on hormonal male contraception have been performed (for review, see Ref. [6]). Most of these trials used sperm counts as surrogate end points to test substances and regimen, and only eight were true contraceptive efficacy trials in which couples used no other method of contraception. Surprisingly, more reviews than original trials on hormonal male contraception have been published, and the reader can thus easily obtain an overview from the literature. Therefore, in order to highlight the current status of the field, here we will only summarize the eight efficacy trials based on hormones and published to date.

2.1. First efficacy trial by the Population Council

The first efficacy trial which was sponsored by the Population Council was performed in four centres in Austria, Brazil and the Dominican Republic, and 100 couples participated. The men received a combination of intramuscular depot medroxyprogesterone acetate (DMPA) 100–150 mg/4 weeks with either intramuscular testosterone enanthate or subdermal testosterone implants. Once sufficient suppression of spermatogenesis appeared to have been achieved, half of the couples were advised to use no further contraceptive. Nine pregnancies were encountered, and sperm counts in the last sample before and the first samples after conception ranged from 0 to 8 million sperm/mL [7].

2.2. The pioneering role of WHO

This surprisingly high pregnancy rate demonstrated that, obviously, male contraceptive protection could not be achieved easily, that the steroid combination in the regimen was not effective and that further dose-finding surrogate studies would be required before ensuing efficacy trials. Meanwhile, it also became clear that the methodology used for semen analysis was not standardized and that the results of semen analysis varied tremendously between laboratories. For this reason, WHO made great efforts to standardize and harmonize the techniques for semen analysis, first in the centres participating in WHO trials and then worldwide. As a basis for this effort, the WHO Laboratory Manual for the Examination and Processing of Human Sperm became an important tool which was published in a first edition in 1980 and which developed into a fifth edition published in 2010 [8]. Although the techniques prescribed in the WHO manual have still not been universally accepted to date [9], at least in centres participating in clinical trials for male contraception, they have increased the quality of semen analysis, decreased interlaboratory variability of results and led to better comparability in a multicentre setting.

Following these preparations, WHO performed an efficacy study based on weekly injections of 200 mg of testosterone enanthate to volunteers in 10 centres worldwide. One hundred fifty-seven men (70%) reached azoospermia within 6 months of treatment and entered the efficacy phase for a further year during which no other contraceptive was used by the couple. Only one pregnancy was reported [10].

As only 70% of the volunteers reached azoospermia, the question was whether contraceptive protection was given in the remaining men developing oligozoospermia of varying degrees. Therefore, WHO initiated a second efficacy study involving 357 couples, again using weekly injections of 200 mg testosterone enanthate. This study revealed that when sperm concentrations failed to drop below 3 million/mL ejaculate, resulting pregnancy rates were higher than when using condoms. When sperm concentrations decreased below 3 million/mL, which was the case in 98% of the participants, then protection was not as effective as for azoospermic men, but was better than that offered by condoms. These results provided a consensus that the goal in contraceptive trials should be azoospermia, but sperm

concentrations below 1 million/mL would be acceptable for contraceptive purposes [11].

The WHO studies also showed that Chinese and other East Asian men reached azoospermia at a higher rate than Caucasians and, while a method based on testosterone alone might be acceptable for East Asian men, Caucasians would require an additional substance to suppress spermatogenesis below 1 million sperm/mL ejaculate.

2.3. Searching for long-acting testosterone preparations

Both WHO efficacy trials proved the proof of principle of hormonal male contraception, but also showed that the available testosterone preparations were not suitable for male contraception as they required weekly injections which would not be acceptable for long-term use. Therefore, a search for long-acting testosterone preparations started (Fig. 1). In this search, the Population Council looked for an androgen that would not be a substrate for 5α-reductase and began to develop 7α-methyl-19-nortestosterone (MENT^R) (see below). Under WHO auspices, testosterone buciclate was synthesized, which, despite promising initial investigations [12], was not developed further because an industrial partner could not be identified. Thus, WHO turned to testosterone undecanoate (TU) for a further efficacy study.

2.4. Trials with Chinese TU

While TU had been developed as an oral preparation in Europe in the 1970s, in China, it was formulated into an intramuscular injection using tea seed oil as a vehicle and is used as such in China for the treatment of hypogonadism and in trials for male contraception. This preparation allows injection intervals of 4 weeks for replacement therapy. Back in Europe, with further improvement to the initial formulation, the half-life of this Chinese preparation could be extended even further when TU is dissolved in castor oil, and it is now available for clinical use as a 1000-mg depot injection in most countries worldwide [13].

In China, clinical investigations using the tea seed oil preparations were initiated, and after dose-finding studies, a phase III efficacy trial followed. TU was administered at monthly intervals. Those men who suppressed their sperm counts to azoospermia or severe oligozoospermia did not induce pregnancies in their partners. However, reappearance of sperm occurred in six men during this efficacy phase, and one pregnancy was attributed to this "sperm rebound" [14].

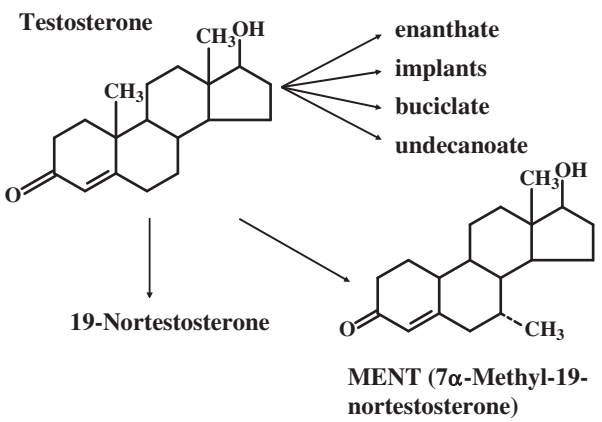

Fig. 1. The search for long-acting testosterone preparations.

Encouraged by these promising results, the largest efficacy study to date was also performed in China based on a TU loading dose of 1000 mg followed by monthly injections of 500 mg. A total of 898 men entered the efficacy phase during which only nine pregnancies were recorded. This represents a pregnancy rate of 1.1/100 person years, a failure rate in line with many methods approved for female contraception [15]. Thus, in China, TU provides better protection against pregnancy than condom use. Although injection intervals of 4 weeks appeared to be an achievement over the weekly injections of testosterone enanthate, participants in the Chinese study considered the frequency of injections the most inconvenient part of this regimen [16]. Were TU in castor oil also to be used in China, this complaint could certainly be overcome by injection intervals extended for longer periods.

2.5. Trials with European TU

Although 19-norethisterone is the oldest synthetic gestagen, it entered the field of male contraception relatively late. In a dose-finding study, 19-norethisterone enanthate (NETE) was combined with TU in castor oil and was found to be superior to the combination with levonorgestrel or to TU alone [17,18]. After subsequent studies had shown that the injection interval could be extended even further [19], WHO together with the US CONRAD programme initiated a multicentre worldwide efficacy study for male contraception based on a combination of 1000 mg TU and 200 mg NETE every 8 weeks [20]. This phase IIb study was intended to include 440 couples, but by the time 260 couples had entered the efficacy phase and 114 had completed the efficacy phase, the study was interrupted in April 2011 [21]. This was due to side effects, especially mood changes in some centres, although the contraceptive protection appeared to be very good. While evaluation of the study is ongoing and results are expected with greatest interest, the early termination represents a tremendous setback for the entire field.

Of the many surrogate trials, two recent ones using TU should be mentioned briefly because they deal with fundamental questions concerning study design and inclusion criteria of volunteers. The first (and so far the last) clinical trial performed by the pharmaceutical industry (i.e., Schering and Organon at that time) used etonogestrel as an implant (Implanon^R) in combination with injectable TU. This study involved 354 volunteers in seven treatment groups and included — for the first time in hormonal male contraception — a placebo group. Although this trial showed a high rate of sperm suppression and acceptability, the companies did not continue their efforts for various reasons

including the belief that men would not use it, but mainly because they were bought up by larger companies with different priorities. Especially the placebo group proved to be of enormous value, as it helped to interpret side effects appropriately [22].

So far, in all trials, only men with so-called normal values for sperm concentration, morphology and motility — as suggested by the WHO manual —were included. This made recruiting of volunteers cumbersome, as about a quarter of men screened for participation did not fulfil these criteria, and it would be difficult to produce a male contraceptive for general use which could only be used by "normal" men who would need to be identified by laboratory testing. The reason for this exclusion policy was the fear that sperm parameters in men with subnormal values might not return to baseline after cessation of hormonal contraception. The question whether men with subnormal semen parameters would react differently to those with normal parameters has been investigated only recently. This pilot study showed that men with subnormal parameters displayed the same pattern of suppression and, most importantly, that recovery of spermatogenesis was the same as in those with normal semen parameters [23]. If this can be confirmed in a larger group of subnormal volunteers, future recruiting of trial participants would be much easier. In general, it should be pointed out that, in all volunteers participating in clinical trials for hormonal male contraception performed to date, semen parameters returned into the normal range [24].

2.6. The Australian experience

Using the same steroid combination as the early Population Council trial, namely, DMPA and testosterone, another efficacy study was performed in Australian men [25]. Instead of testosterone enanthate, testosterone implants (800 mg/4–6 months) plus 300 mg DMPA/3 months were used. No pregnancy was encountered in the 55 couples enrolled.

2.7. A self-applicable regimen

Meanwhile, the latest efficacy trial using a self-applicable regimen based on 2×10 mg MPA taken orally daily and transdermal testosterone daily has been published [26]. Of the 25 couples who entered the efficacy phase when sperm concentrations had dropped <1 million/mL, 15 completed the protocol, and only one pregnancy was encountered. Although this was a small trial, it certainly serves as a proof of principle and additionally demonstrates that even a self-applicable male steroid combination may be effective.

3. Development of MENT^R for the treatment of hypogonadism

From the initial unsuccessful efficacy trial performed by the Population Council [7] and further preclinical and clinical investigations (e.g., [27]), it became clear that constant suppression of gonadotropins would be required to achieve or at least to approach azoospermia in the semen of the volunteers. As the existing depot testosterone preparations at that time (i.e., testosterone enanthate and cypionate) had to be injected too frequently to be applicable in male contraception, the search for suitable depot formulation began. At that time, the Population Council had developed Norplant^R as a long-acting female contraceptive based on levonorgestrel delivered from subcutaneous Silastic implants lasting for 7 years [28]. As this proved to be a very successful method for steroid delivery, the possible use of implants for testosterone delivery was obvious. However, a year's supply of testosterone for male contraception would be in the gram range and thus would have exceeded the capacity of a practical implant. Therefore, for implant delivery, a more potent androgen requiring less volume was needed. In addition, the search was made for an androgen that would not be a substrate for the 5α-reductase enzyme in order to spare the prostate from the androgenic effect. Several molecules were screened, and the final choice was MENT^R.

MENT^R had been synthesized by the Upjohn Company in the early 1960s as an androgenic–anabolic steroid for potential use in oncological therapy. In the immature castrated rat, MENT^R had shown an apparently five times higher potency than testosterone (propionate) with regard to levator ani and seminal vesicle weights [29] and thus appeared to be an appropriate candidate for male contraception [30] as well as for androgen substitution in hypogonadal men [31]. Under C.W. Bardin's and K. Sundaram's aegis, a systematic development of MENT^R for clinical purposes was started. The necessary toxicology was undertaken, and a radioimmunoassay for MENT^R to be used in pharmacokinetic studies in animals and humans was established [32,33]. In rats and later in humans, the high androgenic potency of MENT^R could be confirmed [34]. As preclinical studies ascertained that MENT^R was acceptable for human use, the manufacturing of Silastic^R implants was initiated. First, implants with a length of 4.5 cm and a diameter of 2.7 cm containing 112 mg MENT^R acetate were produced. When two or four of these rods were implanted subcutaneously in volunteers, MENT^R serum levels ranged between 1 and 3 nmol/L, and LH and FSH were suppressed in a dose-dependent fashion during the 4-week trial period [35,36].

In an ensuing study in 16 hypogonadal men using one or two implants of slightly higher potency for 24 weeks, the suitability of MENT^R for substitution purposes was demonstrated, especially in regard to sexual functions, but two special features emerged [37]. As shown earlier in monkeys [38], MENT^R appeared to have a prostate-sparing effect in men since the prostate did not grow to the extent expected under full testosterone substitution. This effect was attributed to the fact that MENT^R is not converted to 5α-dihydrotestosterone and therefore might have a less effect on prostate growth. However, in the same study, it was also observed that bone density in the hypogonadal men treated

with MENT^R did not reach the same level as in the control group treated with testosterone enanthate. This could indicate that the MENT^R dose delivered in the study was not high enough for full androgenicity and triggered a thorough investigation into the effect of MENT^R on bones. In the aged male castrated rat model, it was demonstrated that MENT^R was well suited to restore fully normal bone structure if administered at the appropriate dose [39]. The supposed "tissue selectivity" of MENT^R [37] in regard to prostate and bones could reflect the phenomenon of different threshold levels for the effects of testosterone (and androgens in general) for fully normal functions of tissues and organs as reflected by the occurrence of specific symptoms at specific testosterone levels when lowering testosterone levels in testosterone-treated hypogonadal men [40,41].

Overall, using the proper dose, MENT^R appears to be well suited for substitution of male hypogonadism. For this purpose, Schering Pharma further developed MENT^R into a transdermal gel preparation by adding a fluor atom in position 11 (11-fluoro-7α-methyl-19-nortestosterone= eF-MENT^R). In phase I studies, effectiveness in treating sexual symptoms of hypogonadal men and a reduced stimulation of the prostate could be demonstrated [42]. Despite these promising results, when Bayer acquired Schering to become Bayer HealthCare, the company decided to discontinue their research in this field. Therefore, the future of MENT^R and eF-MENT^R gels for treatment of hypogonadism is uncertain at this stage.

4. MENT^R in clinical trials for male contraception

Simultaneously with the development of MENT^R for the treatment of male hypogonadism, investigations into its possible use as a male contraceptive started in the Population Council laboratories. As a first step, a trial in bonnet monkeys using MENT^R Silastic implants delivering 100 mcg MENT^R/day was performed. In 10 treated animals, a rapid decline in sperm counts occurred, and while the animals continued to display their normal sexual behaviour, they were unable to induce pregnancies in females of proven fertility, as did the five placebo-treated controls [43].

These encouraging results stimulated the first dose-finding study in human volunteers investigating suppression of gonadotropins and sperm counts [44]. For this study, 35 men were recruited in three centres in Germany, Chile and the Dominican Republic. The volunteers received either one, two or four MENT^R acetate implants inserted at the inside of the upper arm and delivering initially 400 mcg/day of MENT, then declining to levels of about 240–340 mcg/day over 1 year. The number of implants and the resulting serum MENT^R levels corresponded positively with the degree of suppression of gonadotropins and sperm counts. In 8 of the 11 men receiving four implants, sperm counts dropped rapidly to zero and, following removal of implants after 12 months, returned to normal within 3 months (Fig. 2).

This study demonstrated that the subdermal implants could provide sustained release, maintaining sustained serum

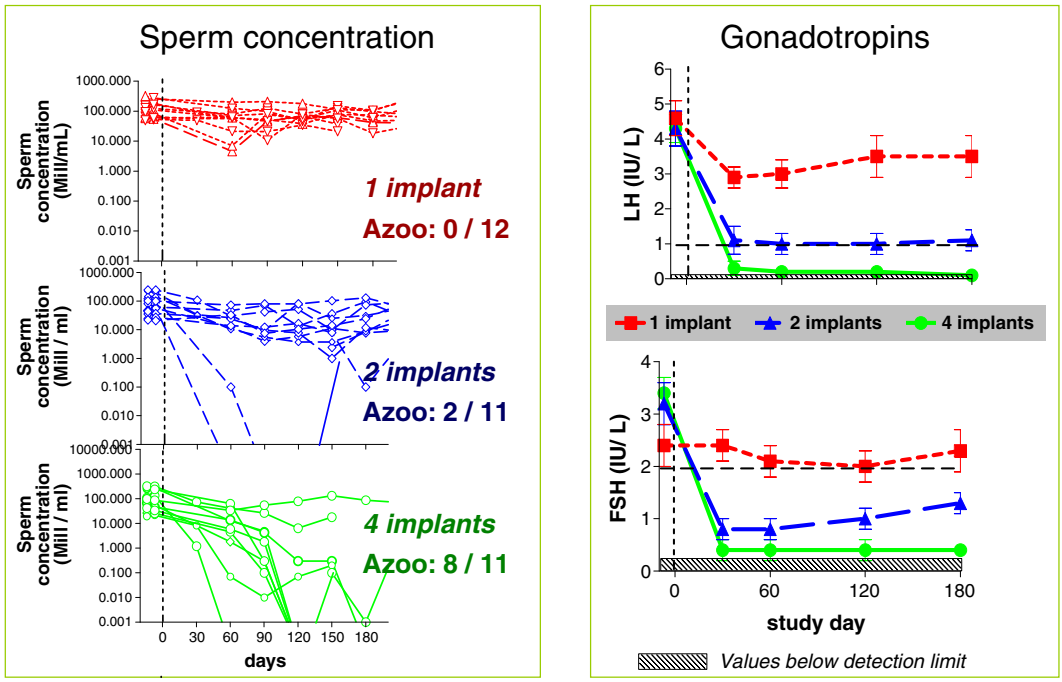

Fig. 2. Suppression of sperm concentrations, LH and FSH in 34 normal men treated with one, two or four MENT implants [44].

MENT^R levels for at least 1 year and sufficient to suppress gonadotropins and spermatogenesis. The rate of suppression was similar to the effects of testosterone alone in other studies involving Caucasians, as only about two thirds of them achieved suppression of sperm counts compatible with contraceptive protection, i.e., azoospermia or sperm counts <1 million/mL. Therefore, to be fully effective in all volunteers, MENT^R needs to be combined with another antigonadotropic agent.

As etonogestrel implants licensed for female contraception (Implanon^R) had been used successfully with testosterone pellets in a trial aiming at suppression of spermatogenesis [45], this study design was repeated in a further trial, and a group of 10 men received Implanon^R together with MENT^R implants [46] (Fig. 3). While all volunteers receiving the Implanon^R implants plus testosterone achieved azoospermia by week 28, in the 10 volunteers receiving Implanon^R plus 2 MENT^R implants, sperm counts dropped by week 12 to about 1 million/mL, but thereafter increased again, approaching normal levels (Fig. 4). In addition, six men in the MENT^R group experienced loss of libido and therefore withdrew from the study. Obviously, although manufactured under the same conditions as the previous implants containing 135 mg of MENT^R and anticipated to release 400 mcg MENT^R per day per implant, the batch manufactured for that study did not release MENT^R in concentrations sufficient for maintaining androgenicity on the one hand and suppressing spermatogenesis in a sustained fashion on the other.

For the next study, new implants were produced, 4.9 cm in length, containing 171 mg MENT^R acetate, designed to release 24% more MENT^R than the implants used in the previous studies. In four study groups, each composed of 18 male volunteers, two or three of these implants were combined with zero, two or four levonorgestrel implants (Jardelle^R). In terms of suppressing sperm below 1 million/mL and reaching azoospermia, three MENT^R implants alone resulted in the same suppression rate as two MENT^R implants combined with two or four Jardelle^R implants (about 60%), and even less suppression was observed in the group with three MENT^R implants plus two Jardelle^R implants (only 50%) [47].

These unexpected and disappointing results were obviously due to the design of the MENT^R implants and

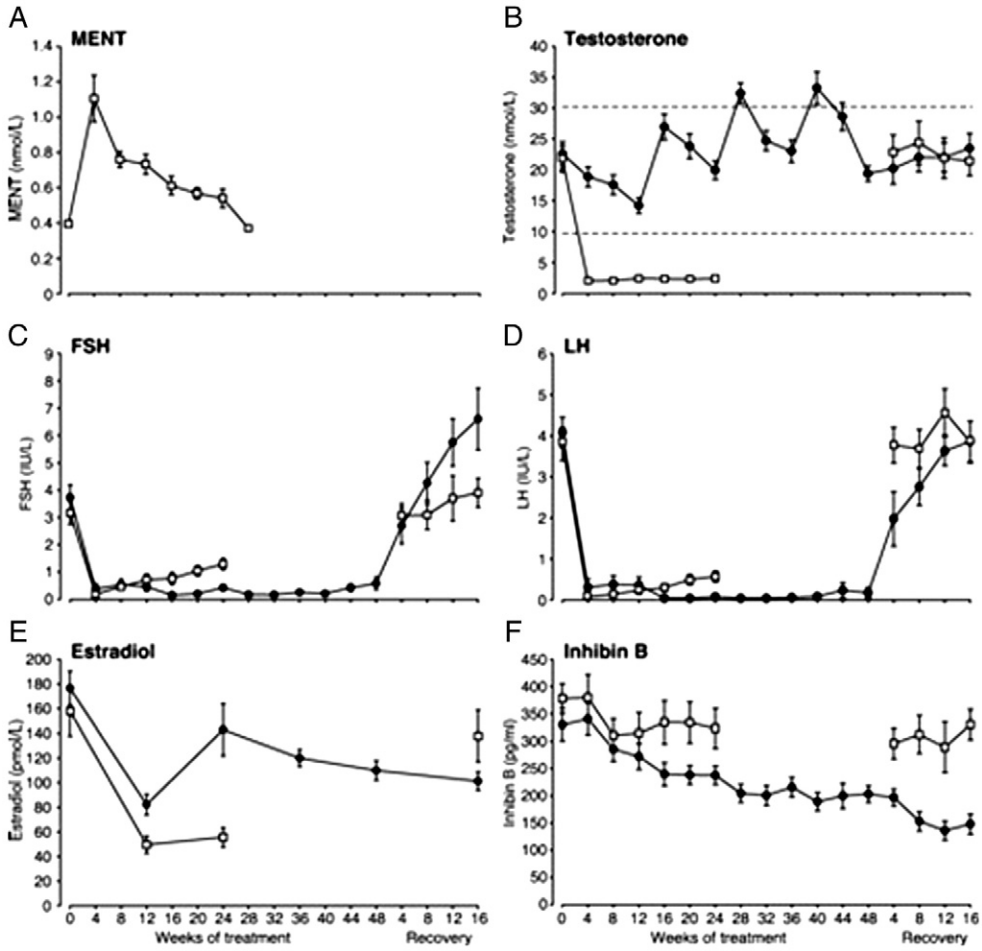

Fig. 3. Serum hormone concentrations in men receiving two etonogestrel implants either with testosterone (closed circles) or MENT implants (open circles). (Reprinted with permission from Ref [46]).

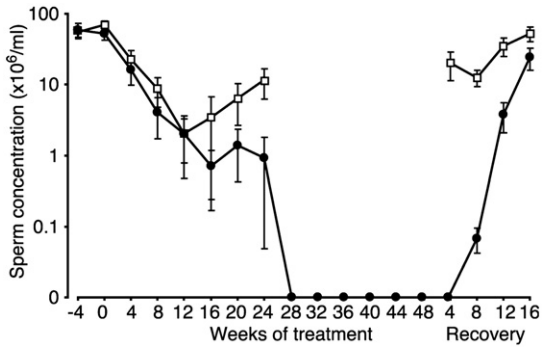

Fig. 4. Sperm concentrations in 29 men receiving 2 etonogestrel implants either with testosterone (closed circles) or MENT implants (open circles). (Reprinted with permission from Ref [46]).

prompted a complete revamping of the manufacturing process. The new prototype implants based on different elastomer technology showed more sustained and higher levels during long-term release rate studies. These new implants will be manufactured for testing in further trials.

5. Outlook

As this article shows, neither the development of MENT^R in particular nor hormonal male contraception research in general has yet resulted in a product ready for licensing and application. However, the occasion of the 100th meeting of the Population Council's International Committee on Contraception Research provides an opportunity to pause and take stock of the 40-year history of research in hormonal male contraception.

Although the principle of hormonal male contraception has been proven, it appears to be extremely difficult to work out details of the steroid combination to be used and to bring it to the consumer. Without the input of the pharmaceutical industry, it will be impossible to complete the final steps in this development. However, the reluctance of the pharmaceutical industry to enter the field of male contraception has been additionally reinforced by the WHO decision to suspend the TU/NETE efficacy study. A concentrated effort by investigators, donor organizations and politicians will be required to bring industry back into the field or to take the lead in such development.

Although opinion polls among possible consumers indicate willingness to use such methods and despite the keen interest of the media in male contraception, there is no strong urge on the part of society to develop male contraceptives. Research for female contraceptives before the arrival of the "pill" was driven by large segments of the female population fighting for gender equality and freedom from reproductive burdens. Although many men would now be willing to use a hormonal male contraceptive, there is no real force behind this intention. Men (and women) are not taking to the streets to rally for male contraception. There is a decisive gender difference between men and women in the perception of contraception. For women, contraception means personally avoiding pregnancy with all its medical, social and economic implications, including the threat of death from childbearing. In contrast, for men, contraception is more a rational issue regarding respect for the partner and avoiding financial, social and legal obligations of fatherhood. However, the time can be foreseen when even this rational approach may result in a popular demand for male contraception, be it for the purpose of sharing responsibility for family planning by both sexes, be it for a contribution to reduce overpopulation and maintain an ecological balance or be it for men's desire to regain reproductive power, a motive not so acceptable to advocacy groups. Until this time comes, the endurance and perseverance of organizations such as the Population Council are of utmost importance to maintain the field of male contraception research be it on an underpowered level due to lack of sufficient funding.

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