## Title
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## Journal
The Lancet Diabetes & Endocrinology, 5(3)

## ISSN
2213-8587

## Authors
Piotrowska, Katarzyna
Wang, Christina
Swerdloff, Ronald S
et al.

## Publication Date
2017-03-01

## DOI
10.1016/s2213-8587(16)00034-6

Peer reviewed

HHS Public Access

Author manuscript

*Lancet Diabetes Endocrinol*. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

*Lancet Diabetes Endocrinol*. 2017 March ; 5(3): 214–223. doi:10.1016/S2213-8587(16)00034-6.

# Male hormonal contraception: hope and promise

**Katarzyna Piotrowska, MD**, **Christina Wang, MD**, **Ronald S. Swerdloff, MD**, and **Peter Y. Liu, MBBS (Hons I), PhD, FRACP***

Division of Endocrinology, Department of Medicine, Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute (LA BioMed) Torrance, CA 90509

## Abstract

Family planning is a shared responsibility, but currently available male-directed methods are either not easily reversible (vasectomy) or not sufficiently effective (condom). Despite this, approximately 20% of couples using a contraceptive method worldwide, and up to 80% in some countries, choose a male-directed method. Male hormonal contraception (MHC) is acceptable and highly effective, with perfect use failure rates of 0.6% (95% confidence interval 0.3–1.1%) provided sperm concentration are maintained below 1 M/mL. Upon cessation of MHC, sperm quality fully recovers in a predictable manner resulting in pregnancies and live births. Spontaneous miscarriage and fetal malformation rates overlap that observed in the general population. Short-term adverse events, namely acne, night sweats, increased weight and altered mood and libido are recognized, but are generally mild. Further optimization of specific androgen-progestin regimens followed by Phase 3 studies of lead combinations is still required for successful development of an approved MHC and to determine long term adverse effects.

### Keywords

Contraception; male; recovery; suppression; semen; androgen; progestin

## 1. Introduction

Finding a partner and starting a family are common human desires. These desires are constrained by the need to space and limit pregnancies according to personal and financial

*Corresponding author: Peter Y. Liu, FRACP, PhD, Division of Endocrinology, Department of Medicine, Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute (LA BioMed) at Harbor-UCLA, Medical Center, Torrance, CA 90509, Ph: 310-222-1867, Fax: 310-533-0627, pliu@labiomed.org.

**Author Contributions**

KP co-wrote the first draft of the manuscript, performed the literature search and tabulated some of the data.
CW reviewed and provided intellectual input to the manuscript.
RSS reviewed and provided intellectual input to the manuscript.
PYL co-wrote the first draft of the manuscript, performed the literature search, tabulated some of the data and performed the statistical analysis. He is corresponding author.
All authors reviewed and agree for the final manuscript to be submitted.

**Declaration of Interests**

KP and PYL declare no conflicts of interests. CW received research support from Clarus Therapeutics, Lipocine, Prolor and Besins Healthcare International and is a consultant for Lipocine and TesoRX. RSS received research support from AbbVie and Clarus Therapeutics, Lipocine, Prolor and Besins Healthcare International and is a consultant for Anatres, Clarus Therapeutics, Lipocine and Novartis.

circumstances. Allowing both men and women to share family planning responsibilities by increasing contraceptive choices would promote important, but still largely unmet individual and societal needs, such as ameliorating the number of elective terminations for unplanned pregnancies and reducing overpopulation [2]. Promising candidate non-hormonal male-directed approaches have been identified [3,4], but pivotal trials in humans that would be necessary for drug or device registration are lacking: table 1. In contrast, more than 2000 men have already been exposed to over 2000 person-years of male hormonal contraception (MHC, consisting of androgens with or without progestins) to assess contraceptive efficacy: table 2. Furthermore, testosterone has been marketed for 6 decades after first being synthesized 8 decades ago, and is increasingly prescribed throughout the developed world [5,6]. Vast clinical experience relevant for understanding the safety of testosterone therapy is therefore available. Nevertheless, concerns arising from the Women's Health Initiative study regarding the safety of hormonal therapies in general seems to be hampering product development of MHC by industry [7,8]. Accordingly, this review of male-directed contraceptive methods will focus on recent advances in MHC as well as new generic information regarding the safety of exogenous hormone exposure in men for non-contraceptive purposes. The hope is that this review will promote male-directed contraceptive drug development.

An ideal male-directed contraceptive method should be safe, rapidly and uniformly effective (i.e. usable by all men) and rapidly and uniformly reversible. In contrast, the two currently available male-directed methods are not widely acceptable because vasectomies are not easily or uniformly reversible and condoms have limited user efficacy. Despite this, many couples already choose a male-directed method, although considerable regional and national variability in usage exists [9]. Recently completed studies confirm the effectiveness, reversibility and short-term safety of MHC, which promises many advantages over existing methods [1,10–12]. These androgen-progestin treatment regimens reduce sperm output and induce a predictable degree of infertility by exploiting the negative feedback suppression of pituitary gonadotropin secretion by sex hormones [3,13,14]. The inhibition of ovulation by combined estrogen-progestin contraceptives uses an analogous mechanism; this approach is widely utilized by women because multiple delivery systems (transdermal patches, oral pills, transvaginal rings, intramuscular injections and subcutaneous implants), drug and dose combinations are available to broaden choice. MHC may also fulfill many of the requirements for an ideal male-directed contraception method and the hope is that a range of treatment options will become available to satisfy differing needs and preferences of couples.

### 2.1 MHC is acceptable to many couples, but there is marked geographical variability

Multiple surveys of diverse populations worldwide [15–18] show that at least one quarter of men, and in some countries many more, would consider using a male hormonal contraceptive. Women would trust their specific partner to be responsible for personal contraceptive needs, but not any man in general [9]. Amongst actual volunteers participating in clinical trials of MHC, intramuscular injections every 1–3 months [19,20], subcutaneous implants every 3 months [21] or transdermal gels applied every day [22,23] would be acceptable treatment regimens. These complementary data from potential users contemplating a

theoretical product, and actual participants in a clinical trial of a specific MHC, show that MHC is acceptable to men and their partners.

In order to understand current male-directed contraceptive use throughout the world, we examined the most recent complete national data collected since 2010 by the United Nations [24]. Data meeting these criteria were available for 66 nations from Africa and the Middle East, Asia-Pacific, Europe and South America, but were not available from North America. However, findings are consistent with pre-2010 data from North American countries. In aggregate, male-directed methods (male sterilization, condom, withdrawal) were utilized by about 10% of all couples surveyed, but this ranged from 0 to 50% in individual countries. Amongst couples that were actually using a contraceptive method, about 20%, and up to 80% in some countries, were relying on a male-directed method. More research is needed to understand why marked regional variability exists, whether these differences are due to cultural, religious or other attitudes, and whether such attitudes can be changed. Nevertheless, a large group of couples already rely on existing male-directed methods, despite such methods being far from ideal. Many additional couples would presumably utilize a male-directed method that was more effective, convenient and reversible. Societal changes as well as drug development may both be needed to increase usage as oral mode of delivery and higher income and education have been associated with higher acceptability of a theoretical MHC [18]. Reliably understanding the factors that influence acceptability may require such methods to first become available.

### 2.2 MHC induces predictable contraception

In contrast with the situation in women where hormonal method either prevents, or does not prevent ovulation, contraceptive effectiveness with MHC depends on the degree to which spermatogenesis is suppressed [25–27]. The clinical assessment of spermatogenesis continues to depend upon semen analysis, a widely recognized surrogate measure of male fecundity [27]. Accordingly, contraceptive failure (i.e. pregnancy) rates of 0.6 (95% confidence interval CI 0.09–2.7) % can be expected if sperm concentrations are consistently suppressed to no more than 1 M/mL, whereas failure rates of 1.4 (0.4–3.7) % occur with a threshold of 3 M/mL [25,26]. Based on these data and recognizing that both paternity and actual sperm concentration at the time of conception can only be assumed [12], expert opinion recommends a sperm concentration threshold of 1 M/mL as suitable for reliable contraception [28,29]. Specific delivery, dose and drug combination influences the degree of suppression of sperm output, and each regimen must therefore be individually evaluated for sperm suppression in preparation for contraceptive efficacy studies. Over 3000 person years of androgens alone or in combination with progestins has been administered to assess sperm quality or contraceptive efficacy [1,10–12]. Multiple androgen-progestin drug combinations have been studied [3,14], but together comprise less than one-fifth of the total hormone exposure [1,10–12]. The vast majority of these studies have utilized testosterone, although two other androgens, 7-alpha-methyl-19-nortestosterone and dimethandrolone undecanoate, are also being evaluated [30,31]. Few androgens alone, or combination androgen-progestin regimens have actually been evaluated for contraceptive efficacy.

Initial proof of concept studies showed that short-acting testosterone therapy is a highly effective contraceptive (i.e. prevents pregnancies) and profoundly suppresses spermatogenesis through negative feedback inhibition of gonadotropins [25,32]: table 2. Contraceptive efficacy has since been confirmed via a longer-acting testosterone regimen [12,33], over a longer duration of time [12], and with an androgen-progestin combination [34]: table 2. Individual large scale studies show contraceptive failure rates of 0.8–2.3%, with upper 95% limits of 1.8–4.5%: table 2. Pooling data from studies which suppressed sperm count to no more than 1 M/mL and calculating Poisson confidence limits, yields a contraceptive failure rate of 0.6 (0.3–1.1)%. This compares favorably with the use of the oral contraceptive pill by women in the first year [35–37]. In fact, modern female hormonal methods, which utilize lower doses, report 12 month failure rates of 7% [36]. Nevertheless, available MHC efficacy data are limited by relatively low overall exposure, especially for androgen-progestin combinations: table 2. A recent large-scale study of over 100 person years of combined androgen-progestin exposure has been conducted and shows profound suppression of spermatogenesis to a threshold of 1 M/mL during which very few pregnancies occurred [38,39]. However final results are still pending.

### 2.3 Optimizing MHC to increase the rate and extent of sperm output suppression

We performed an integrated analysis of individual participant data of all then-available studies to examine rates of suppression of sperm output to concentrations compatible with reliable contraception (< 1 M/mL) [10]. By 3 and 6 months, 50% and 85% of men, respectively, adequately suppressed sperm output [10]. However, this analysis included many exploratory MHC regimens where drug dose and frequency had not yet been optimized. Accordingly, restricting the analysis to contraceptive efficacy studies where regimen optimization has already occurred should yield more realistic estimates. These show that only 96% of men did suppress sperm output to a threshold of 1 M/mL by 6 months: table 2. Of historical interest, 75% of men suppressed sperm output to a threshold of azoospermia by 6 months (table 2).

Modern large-scale optimized androgen and androgen-progestin combinations report adequate suppression in 80–95%, not 50%, of men by about 3 months [11,12,33,34]: table 2. This reduction in sperm output is comparable to the disappearance of sperm after vasectomy [40]. The distinction regarding androgen alone versus androgen-progestin combinations is important because progestin co-administration enhances both the rate and extent of sperm output suppression by up to two fold [10]: table 3. Furthermore, individual progestins differ in properties related to the binding and activation of progesteroneand other steroidreceptors, in anovulatory potency and the ability to support pregnancy in women [41]. It is therefore likely that there are certain progestins which will be more effective in spermatogenic suppression than others, but current studies in men are underpowered to prove this distinction [10]. Accordingly, it remains plausible that a fully optimized androgen-progestin combination could be universally applied to all men within a practical timeframe.

Optimization of this regimen may also involve varying the dose of testosterone. In humans, a higher total dose of administered testosterone is associated with a higher proportion of men with inadequate suppression of sperm output during MHC [10,42,43] and higher baseline

endogenous testosterone is also associated with slower suppression [10]: table 3. However, there are few data directly comparing testosterone dosages within the same study, although the few available data do support this contention [44]. Nevertheless, once the testosterone-dependent feedback inhibition of gonadotropic secretion reaches its limit, increasing the testosterone dose will increase intratesticular testosterone levels. These very low concentrations of intratesticular testosterone are sufficient to maintain spermatogenesis, at least in rodents and primates [45–47]. In fact, there is no definable dose of testosterone that would both maintain sexual function and also suppress gonadotropins without simultaneously activating spermatogenesis in rodents [48]. Whether these considerations are relevant in humans is not directly known. If relevant, further suppression of intratesticular testosterone by direct inhibition of steroidogenesis may be required, and proof of principle in humans has been demonstrated using a nonspecific inhibitor of steroidogenesis [49]. Drugs which inhibit 17 beta-hydroxysteroid dehydrogenase type 3 enzyme, which catalyzes the final step of testosterone biosynthesis, would specifically reduce testicular steroidogenesis. Direct proof of principle studies in humans are required.

Further optimization may require dose adjustment or titration. Although high dose testosterone therapy may reduce the eventual nonsuppression rate (see previous paragraph), initial high dose testosterone therapy may be required to first induce rapid suppression of sperm output, which could then be followed by dose reduction for maintenance of sperm output to concentrations compatible with reliable contraception (< 1 M/mL). Whether this proposed regimen can actually decrease the rate of sperm rebound where sperm output increases to rates that are not compatible with reliable contraception (≥ 1M/mL) observed in many large studies [11,12,25] will require direct verification. Alternate dose preparations of established androgen-progestins, akin to the low and high dose oral contraceptive pill for women, may also be necessary.

Another regimen optimization approach is to investigate novel androgens, particularly non-injectable formulations which seem to have greater acceptability (see Section 2.1). One such androgen is dimethandrolone undecanoate (7alpha, 11beta-methyl-19-nortestosterone), which like other 19-nortestosterone derivatives binds to both androgen and progesterone receptors [31]. This orally bioavailable androgen is 4-fold more potent than testosterone and about half as potent as progesterone, for their respective cognate receptors. However, it is not aromatized and hence bone, metabolic and sexual health needs to be carefully assessed [50,51]. Another promising approach is the use of combined transdermal androgen and progestin gels [52,53].

It is also possible that MHC may not universally suppress sperm output adequately in all men even after drug and dose optimization. Methods to predict non-suppression would then become important: table 3. Caucasian ethnicity, progestin co-administration and higher testosterone dose are important predictors of non-suppression. Higher BMI also predicts less complete suppression, but the effect size is small and may not be clinically relevant [10]. Other factors, such as drug levels and lower LH [54], or biomarkers of testicular function such as insulin like 3 [55], may ultimately prove to be useful in identifying these individuals, but require verification in larger cohorts: table 3. Although younger age, lower baseline testosterone and lower initial sperm concentration are all associated with faster

spermatogenic suppression, the independent effect sizes of these parameters are relatively small [10]. Pharmacogenetic approaches may explain the large and opposing ethnic differences in the rate and extent of spermatogenic suppression observed between Caucasian and Asian men [10,56,57], and ultimately unveil methods to identify or ameliorate nonsuppression.

### 2.4 Alternative approaches

An alternate approach if predicting non-suppression was impossible would be to verify adequate suppression in all men before MHC methods were relied upon. The inconvenience would be minimal with sensitive home semen testing kits (e.g. SpermCheck Vasectomy ®). Such methods are already FDA approved and currently many couples confirm near azoospermia post-vasectomy before ceasing other contraceptive methods [58]. These techniques can be used to assess male infertility [59] and even more sensitive fluorescent methods are being developed for home use [60].

It may not be possible to apply rapid onset male contraception for methods that target processes which occur early during spermatogenesis since the spermatogenic cycle is about 70 days. Other agents that directly and rapidly reduce sperm output or function (eg Table 1) could be initially co-administered and then progressively withdrawn to allow the maintenance of sperm output to concentrations compatible with reliable contraception (< 1 M/mL) by hormonal methods alone. This approach might be both advantageous for cost and safety. GnRH antagonists or direct inhibitors of testicular steroidogenesis have been used in this context, with limited success [3]. Targeting non-hormonal mechanisms of action could be synergistic, and particularly advantageous if later stages of spermatogenesis were suppressed.

### 2.5 MHC methods are reversible

We performed an integrated analysis of individual participant data of all then-available studies and demonstrated that it is realistic to expect full recovery of spermatogenesis to levels consistent with normal male fertility (20 M/mL) for all men ceasing hormonal male contraceptive regimens [1]. Sperm concentrations of only 13–15 M/mL are associated with normal male fertility [27]. Non-recovery of sperm output has only been reported twice and in both cases there was an explanatory intercurrent and unrelated sterilizing process, specifically myotonic dystrophy in one man [34] and epididymitis in another [12]. Highly predictable recovery of spermatogenesis (to concentrations of 20 M/mL) following cessation of MHC has been verified: 67%, 90% and 100% of all men would be expected to recover by 6, 12 and 24 months, respectively [1]. Various covariables influence the rate but not the extent of recovery: table 3. Of these variables, only treatment duration has a clinically important effect. Two large studies published subsequently to the integrated analysis verify the main conclusions [11,12]. In the first study [12], 855 men received up to 30 months of androgen therapy, representing 12–18 months longer exposure than any previous contraceptive efficacy study: table 4. As predicted, the median time to recover to a sperm output of 20 M/mL was 7.6 [12], which is longer than the median recovery time of 3.4 (95%CI 3.2–3.5) months calculated from all previous studies [1]. The rate of recovery of sperm output following cessation of MHC in this study was also entirely consistent with our previous analyses: all except 17 men had recovered by 12 months, and by 15 months one man had a

sperm concentration of 13 M/mL and the other presumably never recovered due to intercurrent epididymitis [12]. In the other study [11], 354 men received 42–44 weeks of combined androgen-progestin therapy after which the median recovery time was 3.7 months and by 16 months all evaluable men had recovered. Together these new data confirm our earlier analyses showing that it is reasonable to expect full recovery of spermatogenesis to levels consistent with normal male fertility and that the rate of recovery is dependent upon treatment duration.

One limitation is that MHC studies of more than 30 months treatment duration do not exist, and may not be available without post-marketing surveillance. Systematic studies of eugonadal men treated with androgens beyond 30 months for non-contraceptive purposes also do not exist. Amongst anabolic steroid abusers sperm quality tends to recover spontaneously within 4–12 months and the expectation is that the hypogonadotropic hypogonadism is fully reversible [61]. Another limitation is that few data are available for men of African or Hispanic origin, so longer treatment studies in more diverse populations of men are required. Many factors that predict slower initial suppression of sperm output also predict faster recovery of sperm output, suggesting that these processes are interlinked: table 3. If true, individuals with subnormal sperm concentrations at baseline would be expected to have faster but not more complete suppression, and delayed recovery to 20 M/mL. A preliminary study examining men with baseline sperm concentration of 8 ± 6 (mean ±SD) M/mL confirmed that the extent of suppression is not different, and showed recovery back to individual baseline sperm concentrations, but did not address the rate of suppression or recovery to 20 M/mL [62]. Future research verifying this possibility is required.

In order to further verify recovery of fertility, we examined pregnancies and their outcomes: table 4. A limitation of this analysis was that many couples were likely using other forms of contraception after cessation of MHC if parenthood was still not desired. Nevertheless, 51 pregnancies resulting in 32 live births occurred after cessation of MHC and all individuals known to be actively seeking parenthood were reported to be able to do so: table 4. These data provide reassurance that the recovery of sperm concentration, motility and morphology which we previously documented [1], translates into actual live births.

### 2.6 MHC methods do not increase fetal risk

We examined pregnancy outcomes occurring during or after MHC treatment to assess fetal risk: table 4. There were 112 pregnancies in total, resulting in 45 live births, 7 spontaneous abortions, 17 induced abortions and 1 congenital malformation, and 42 unknown pregnancy outcomes. We calculate spontaneous miscarriage rates of 6% (95%CI 3–12%) and 11% (95%CI 6–18%) assuming no or proportionate miscarriage rates amongst pregnancies with unknown outcomes, respectively. These miscarriage rates overlap with spontaneous abortion rates of 8–20% in the general population [63].

The aggregate congenital malformation rate was 0.9% (95%CI 0.0–4.9%) and 1.8% (95%CI 0.0–6.3%), assuming no or proportionate miscarriage rates amongst pregnancies with unknown outcomes, respectively. In this setting, the upper CI of 4.9% is probably realistic because it is reasonable to assume that no, or almost no, congenital malformations occurred in the unknown group. This is because serious adverse events, of which fetal malformations

is one category, were individually reported in all contraceptive efficacy studies and should have been reported to study investigators by the participant. Accordingly, these data are also consistent with the 4% congenital malformation rate that occurs during spontaneous pregnancies [64] and after artificial reproductive technologies [65]. Nevertheless, there is insufficient power to conclusively exclude the possibility that congenital malformation rates could be increased by MHC, even when all studies are aggregated. Structural data in humans however, do suggest that fetal malformations arising from exposure of the developing spermatozoa to a hostile environment should not occur since the integrity of the blood-testis barrier is preserved following 18 weeks of androgen-progestin MHC exposure [66].

### 2.7 Short-term side effects of MHC methods are now defined in a large placebo-controlled trial

Adverse events that led to more than one subject discontinuation in one or multiple contraceptive efficacy studies [12,25,32–34] are tabulated: table 5. When compared with a recently completed placebo-controlled androgen-progestin MHC trial, altered mood and libido as well as acne, weight gain and night sweats were statistically more prevalent than those treated with placebo [11]. Notably, 93% of men on active treatment, but also by 81% of men on placebo therapy self-reported adverse events. Many factors, particularly biochemical factors, were judged to be clinically irrelevant. The inclusion of placebo controls had never previously been attempted, and would not have been ethically justifiable in any of the contraceptive efficacy studies as unwanted pregnancies would have occurred. Postmarketing surveillance will be needed to properly assess infrequently occurring adverse effects.

Men receiving active treatment had twice the frequency of complaints (20% versus 8%, on average for mood and libidinal changes, weight gain, acne and night sweats) than those receiving placebo [11]: table 4. Although these adverse events were generally mild, they were sometimes of sufficient intensity to lead to subject discontinuation, and statistically more prevalent than in the placebo group. In women, mood related side effects of estrogen-progestin contraceptives have been attributed to the use of gestagens [67,68], but population-based epidemiological data actually show less depression and suicidality [69,70]. Whether these data are relevant in men is not known. Across the duration of therapy, HDL cholesterol fell by about 10% and in proportion with total cholesterol and none of the lipid changes in any treatment or placebo group were statistically significant. The magnitude of the reported changes was consistent with many MHC studies and the clinical relevance of these minor lipid changes is uncertain particularly since reverse cholesterol transport may actually be beneficial.

Although this placebo controlled trial was a major methodological advance, the treatment regimen itself probably did not maintain adequate suppression of gonadotropins or spermatogenesis. An alternate progestin (see **Section 2.3**), delivery system, or doses of androgen or progestin could well have resulted in more or different adverse events. Ultimately, postmarketing surveillance of specific androgen-progestin regimens will be required.

### 2.8 Long-term cardiovascular and prostate risks of MHC

Examining the long-term adverse cardiovascular or prostate effects of MHC will also likely require phase 4 studies. A recent systematic review was unable to make conclusions regarding the relationship between testosterone and prostate cancer due to contradictory findings arising from different study designs, definitions and methodologies [71]. However it was concluded that the preponderance of studies suggest that exogenous testosterone in men with a prostate cancer history poses little if any risk [71]. Furthermore, testosterone therapy does not seem to increase the risk of developing high-grade prostate cancer [72]. In this study, 50,000 men were systematically identified with high-grade prostate cancer from population-based cancer registries and linked to Medicare records to ascertain preceding testosterone use during the previous 5 years. This carefully adjusted population-based, but non-randomized, study provides the strongest reassurance to date that testosterone use does not lead to high-grade prostate cancer [72]. However, all of these men had prostate cancer diagnosed after the age of 70, whereas the target population for MHC is much younger. Whether longer lifetime exposure and/or earlier age of first exposure to androgens alters the risk of prostate cancer simply is not known, and a definitive randomized study examining prostate cancer incidence would require large numbers and long follow up since prostate cancer is very uncommon in young men.

Nevertheless, recent data of prostate epithelium gene expression from 30 young men without known prostate disease provide some reassurance of prostate safety [73]. Global and androgen-regulated gene expression did not differ despite expected differences in intraprostatic dihydrotestosterone, testosterone and androstenedione with 10 weeks of treated prototype MHC therapy: testosterone, testosterone with depot medroxyprogesterone acetate, testosterone with dutasteride or placebo therapy [73]. Testosterone with dutasteride mimics an androgen that is minimally 5 alpha reduced, such as 7-alpha-methyl-19-nortestosterone and dimethandrolone undecanoate [30,31]. Concerns regarding prostate growth due to 5 alpha reduction of androgens in the prostate gland would also be negated by the use of such androgens.

Similarly, lower urinary tract symptoms in middle-aged or older men do not appear to be worsened by testosterone therapy [74,75]. Nevertheless, concern remains. How MHC might influence lower urinary tract symptoms in younger men requires further evaluation.

Large nonrandomized observational studies comparing those treated with those not treated with testosterone report reduced [76,77], as well as increased [78] mortality with testosterone therapy. Cardiovascular events may also be reduced [77], increased [78,79] or not changed [80]. Methods to match those treated with those untreated differed amongst these studies and may have contributed to these contradictory findings. Nevertheless, lack of randomization renders definitive assessment impossible. For example, another study showed that testosterone was more often prescribed prior to a non-fatal myocardial infarction than afterwards, from which the authors concluded that testosterone therapy may cause non-fatal myocardial infarction [79]. This conclusion is particularly problematic since it is likely that many prescribers are reluctant to continue testosterone immediately following acute myocardial infarction.

The findings from randomized controlled trials are equally contradictory. Two reports published in the same year deserve particular attention [81,82]. Both studies were similarly powered (209 and 274 men randomized), recruited the same men (frail men over the age of 65 with a baseline testosterone concentration of less than 12 nmol/L), and treated them identically (for 6 months with transdermal testosterone gel which was dose-titrated to maintain comparable eugonadal testosterone concentrations). Nevertheless, one study reported an excess of cardiovascular events and was terminated [81], whereas the other slightly larger study did not [82]. The most parsimonious explanation is that if the effect of testosterone on cardiovascular events in frail older men were robust (i.e. not due to chance), then both studies should have yielded identical results. Other explanations include differences in adjudication of cardiovascular events and possibly differences in the degree of frailty between the study populations and in the aggressiveness of dose titration. Furthermore, these putative testosterone induced cardiovascular events are unlikely to be due to progression of atherosclerosis per se, both because the duration of therapy was relatively short and also because atherosclerosis progression was not demonstrated in a recent study that was adequately powered to do so [83]. In this study, 308 relatively healthy men over the age of 60 were randomized to receive titrated testosterone or placebo gel for 3 years. Testosterone therapy did not increase common carotid artery intima media thickness, coronary calcification or cardiovascular events [83]. To add to the confusion, meta-analyses of randomized placebo controlled trials including the two studies outlined above have also yielded contradictory results. The first reported that testosterone therapy increased cardiovascular events [84], but a subsequent more comprehensive metaanalysis which included more studies [85] did not. Another limitation is that the majority of the studies included in both metaanalyses were performed in older men.

How these data concerning cardiovascular safety relate to younger men is not known. A definitive randomized study examining cardiovascular events would require large numbers and long follow up since cardiovascular disease is uncommon in young men.

## 3. Conclusions and Next Steps

There has been significant progress in documenting the effectiveness, reversibility and short-term safety of MHC. Further regimen optimization of lead compounds is required before Phase 3 registration studies can be contemplated. Uncertainty remains regarding long-term cardiovascular and prostate effects, but data in older populations show no clear signal for harm and surrogate endpoints suggest safety. Male-directed methods are already being relied upon by many couples, despite the limitations of currently available methods. From a drug or device registration perspective, MHC remains closest to approval, although non-hormonal methods could potentially be combined with hormonal methods in the future. Ultimately, the market will decide whether better methods are needed, at what cost and to what degree of safety. Definitive assessment of cardiovascular and prostate risk, and acceptability will likely require postmarketing surveillance and assessment. Societal as well as drug development will both be needed to maximize acceptability. In the meantime, uniform reporting of contraceptive efficacy studies to include detailed information regarding suppression and recovery of sperm output, pregnancies, pregnancy outcomes (particularly fetal abnormality) to allow integrated aggregation of data is required to better delineate unanswered questions

regarding nonuniform suppression, recovery of fertility and fetal risk. Such harmonization could be executed by the hormonal male contraception summit group. Continuing research into androgen therapy in the older man to assess prostate and cardiovascular safety will inform safety concerns in the younger population, but research examining short-term appropriately selected surrogate markers of prostate and cardiovascular safety using lead androgen-progestin formulations in the MHC target population of young men is still required. Community advocacy to better understand contraceptive priorities amongst couples will be needed to convince industry and government agencies of the hope and promise of male hormonal contraception.

Over 50 years have passed since the oral contraceptive pill became readily available. Developing a single universally applicable female-directed hormonal method with absolutely no adverse effects was not necessary. Instead, it has been increasingly recognized that providing a range of different options is more important because no single method can realistically be ideal for every couple. Indeed, certain women should not use female hormonal methods at all due to previous occurrences of breast cancer, thromboembolism, migraine headaches or older age. The hope and promise of male hormonal contraception is that equally effective male-directed methods will also become available, broadening choice.

## Acknowledgments

This review was supported by the Endocrinology, Metabolism and Nutrition Training Grant T32 DK007571, the National Center for Advancing Translational Sciences through UCLA CTSI Grant UL1TR000124, Contraceptive Clinical Trials Network HHSN275201300024I and R01 HL124211, and research funds from Los Angeles Biomedical Research Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funding sources had no role in the writing of the manuscript or the decision to submit it for publication.

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## Search Strategy and Method

Studies where men were treated with an androgen or androgen-progestin regimen for at least 3 months were initially identified by PubMed search using search terms “androgen” or “testosterone” in combination with “contraception”. We focused on studies published in the last 10 years to provide an update that was subsequent to our earlier comprehensive subject-level meta-analysis which already included all studies which met these search criteria up to that time [1]. We also searched the reference lists of articles identified by this search strategy to find additional studies which met the original search criteria

We obtained information regarding contemporaneous national contraceptive use from the United Nations (accessed 9/28/2015): http://www.un.org/en/development/desa/population/publications/dataset/contraception/wcu2015/Data/UNPD_WCU2015_CP_Country%20Data%20Survey-Based.xlsx

We also queried clinical trial registries (https://clinicaltrials.gov and http://www.who.int/ictrp/en) to search for contemporaneous studies of potential hormonal and non-hormonal contraceptive methods (accessed 9/28/2015).

Statistical analyses were performed using Statistical Analysis System genmod and freq procedures to calculate aggregate point and asymptotic 95% confidence limits for Poisson events and proportions, respectively (version 9.3; SAS Institute, Inc., Cary, NC).

## Table 1

Non-hormonal male contraception

| Drug | Target | Mechanism | Adverse Event | Clinical Trials |
|---|---|---|---|---|
| | ***Testis*** | | | |
| Gossypol | Exact target unknown (presumed seminiferous tubules) | Inhibition of spermatogenesis and sperm motility through oxidative stress | Irreversible Infertility in up to 20%; Dose dependent hypokalemia | Yes |
| Triptolide | Exact target unknown (presumed seminiferous tubules) | Unknown | Irreversible infertility | Yes |
| Indenopyridine enantiomers and derivatives (CDB 4022), l-CDB 4022, l-RTI-4587-073) | Exact target unknown (presumed Sertoli cell) | Unknown | Species dependent irreversible Infertility | No |
| Lonidamine Derivatives (H2-gamendazole and Adjudin) | Apical ectoplasmic specialization (Sertoli-Germ cell junction) | Disruption of Sertoli-Germ Cell Junction preventing sperm maturation | Liver Inflammation, Muscle Atrophy, Infertility. | No |
| JQ1 | Testis specific bromodomain | Impairs chromatin remodeling during spermatogenesis | None in mice | No |
| BMS 189453 | Retinoic Acid Receptor α, β g antagonist | Blocks spermatogonial differentiation | None noted at low doses. | No |
| BMS 189532 and 195614 | Retinoic Acid Receptor α antagonist | Blocks spermatogonial differentiation | None noted | No |
| WIN 18,446 (BDAD) | Aldehyde Dehydrogenase 1a2 (ALDH1a2) inhibitor preventing conversion of Retinaldehyde (vitamin A) to Retinoic Acid | Blocks spermatogonial differentiation through suppression of Stra8 expression | Impairs liver aldehyde dehydrogenase resulting in Disulfiram like reaction with alcohol | Yes |
| | ***Epididymis*** | | | |
| None | HE6 (G protein coupled receptor) | Defect of reabsorption of testicular fluids in epididymal ductules | Unknown | No |
| None | CRISP-1 glycoprotein (secreted by epididymal epithelium) | Suppresses sperm capacitation and inhibits sperm-egg fusion in rats and mammals | Unknown | No |
| | ***Sperm Motility and Sperm Egg Fusion*** | | | |
| None | EPPIN: epididymal protease inhibitor; | binding of semen coagulation protein (semenogelin 1) which impairs sperm motility | Unpredictable irreversible infertility; Variable immune response | No |
| N-Butyldeoxynojiri mycin (Miglustat) | Glycophospholipid Biosynthesis Inhibitor (mice only) | Impairs sperm motility | No effect on sperm in man; GI symptoms and Weight loss | Yes |
| HC-056456 | CatSpers: Ca permeable ion channels | Mutation or defect of CatSper genes prevent sperm hyperactivation/ Reduced Sperm Motility | No other phenotype reported in knockout mice | No |
| S-3-chlorolactaldehyde | Glyceraldehyde-3-Phosphate dehydrogenase-S (Gapdhs): Sperm specific glycolysis (GAPD2 human specific homolog of GAPDS) | Inhibits sperm specific glycolysis | Many | No |

**Table 2**

Contraceptive efficacy of MHC regimens

| Regimen | N Enrolled | Sperm Conc^ (M/mL) | N (%)Failed to suppress^^ | Median time to enter efficacy (months) | N Entered Efficacy | Maximum Treatment Duration (months) | Pregnancies During Efficacy n (%) | Exposure person year | Failure rate/100 couple yr |
|---|---|---|---|---|---|---|---|---|---|
| *a* TE [32] | 271 | 0 | 68 (25) | < 6 | 157 | 18 | 1 (0.6) | 123.8 | 0.8 (0.02 – 4.5) |
| *b* TU [12] | 1045 | 1 | 43 (5) | 3.6 | 855 | 30 | 9 (1.1) | 1554.1 | 1.1 (0.4 – 1.8) |
| *c* T implant [34] | 55 | 1 | 2 (4) | 1.8 | 51 | 18 | 0 (0.0) | 35.5 | 0 (0.0 – 8.0) |
| *a* TE [25] | 399 | 3* | Not reported* | 2.2 | 349 | 18 | 11 (3.1) | 279.9 | 1.4 (0.4 – 3.7) |
| *b* TU [33] | 308 | 3 | 9 (3) | 2–3 | 296 | 12 | 1 (0.3) | 143 | 2.3 (0.5 – 4.2) |
| Total (0, 1, 3) | 2078 | 0, 1, 3 | 122 (7) | | 1708 | 12–30 | 22 (1.3) | 2136.3 | 1.0 (0.7 – 1.6) ¶ |
| Total (0, 1) | 1371 | 0, 1 | 113 (8) | | 1063 | 18–30 | 10 (0.9) | 1713.4 | 0.6 (0.3 – 1.1) ¶ |
| Total (1) | 1100 | 1 | 45 (4) | | 906 | 18–30 | 9 (1.0) | 1589.6 | 0.6 (0.3 – 1.1) ¶ |

^ Sperm concentration required to enter efficacy;

^^ Failed to suppress to sperm concentration required to enter efficacy by 6 months

*a* testosterone enanthate 200 mg/week;

*b* testosterone undecanoate 500 mg/month (with 1000 mg loading dose);

*c* testosterone implant 800 mg every 4 months with DMAP 300 mg every 3 months

* Original threshold was 5 M/mL, but data shown here is for those who suppressed to no more than 3 M/mL

¶ Studies pooled and 95% Poisson confidence limits calculated using SAS 9.3 (Cary, NC).

## Table 3

Predictors of suppression and recovery of sperm output

| | Slower Suppression | Less complete suppression | Faster recovery |
|---|---|---|---|
| **Age** | Older * | - | Older * |
| **Race** | Asian * | Caucasian * | Asian * |
| **BMI** | - | Higher * | - |
| **Drug** | No progestin Coadministration * | No progestin coadministration *<br>Higher effective testosterone dose * | Shorter acting testosterone formulation * |
| **Treatment duration** | - | - | Shorter * |
| **Baseline sperm concentration** | Higher * | - | Higher * |
| **Baseline testosterone concentration** | Higher * | - | - |
| **Baseline LH concentration** | - | Lower ^ | Lower * |
| **Other** | - | Higher drug concentrations ^<br>Higher insulin like 3 ^ | Faster initial suppression of sperm output * |

* Factors from [1,10]

^ Factors from [54,55], requiring replication in larger studies

**Table 4**

Pregnancy outcomes during and after MHC

| | | Pregnancies | | | | | | | | | | | | Recovery of Sperm Output | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Regimen** | **n Enrolled** | **Pregnancies During Treatment (n)** | **Pregnancy Outcome^** | | | | | **Pregnancies After Treatment (n)** | **Pregnancy Outcome^** | | | | | **Known Pregnancies During and After Treatment (n)** | **Maximum Treatment Duration (months)** | **Median time to Recovery 20 M/mL (months)** |
| | | | **LB** | **SA** | **IA** | **UK** | **CM** | | **LB** | **SA** | **IA** | **UK** | **CM** | | | |
| *a* TE [32] | 271 | 10 | 3 | 0 | 6 | 1 | 0 | 10* | 4 | 1 | 2 | 3 | 0 | 20 | 18 | 3.7 |
| *b* TU [12] | 1045 | 28 | 0 | 0 | 0 | 28 | 0 | Not Reported | - | - | - | - | - | 28 | 30 | 7.6 |
| *c* T implant [34] | 55 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 3 | 1 | 0 | | 1¥ | 5 | 18 | 5.0 |
| *a* TE [25] | 399 | 19 | 10 | 4 | 5 | 0 | 0 | 33 | 25 | 1 | 4 | 3 | 0 | 52 | 18 | 2.3 |
| *b* TU [33] | 308 | 4 | 0 | 0 | 0 | 4 | 0 | 3 | 0 | 0 | 0 | 3 | 0 | 7 | 12 | 2–3 |
| Total (n) | 2078 | 61 | 13 | 4 | 11 | 33 | 0 | 51 | 32 | 3 | 6 | 9 | 1 | 112 | N/A | N/A |

^ LB = live birth; SA = spontaneous abortion; IA = induced abortions; UK = unknown; CM = congenital malformation

*a* testosterone enanthate 200 mg/week;

*b* testosterone undecanoate 500 mg/month (with 1000 mg loading dose);

*c* testosterone implant 800 mg every 4 months with DMAP 300 mg every 3 months

* Excludes pregnancy by a man other than the partner

¥ Includes one set of twins. One of the twins born with Vater Anomalad, which was thought to be unrelated to the study drug.

**Table 5**

Short-term adverse effects of MHC

- Acne*
- Night sweats*
- Increased weight*
- Altered mood (including depression, anger, mood swings, irritability)*
- Altered libido (increased or decreased)*
- Fatigue/Lethargy
- Reduced testis size
- Drug-delivery related (eg. Pain from injection site, severe coughing after injection, skin rash/facial swelling after injection)
- Hypertension^
- Polycythemia^
- Hyperlipidemia^
- Abnormal Liver Function^

*Adverse effects verified in a placebo-controlled trial [11]

^No clinically relevant difference between active and placebo groups [11]