Assessing safety in hormonal male contraception: a critical appraisal of adverse events reported in a male contraceptive trial

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ABSTRACT

Introduction There is unmet need for male contraceptive options, but a recent injectable combination male contraceptive trial was terminated early due to adverse events (AEs).

Methods We examined the frequency of reported AEs by male research participants compared with AEs reported in prescribing information of approved female hormonal contraceptive methods. Published data from trials of the top five most-used female hormonal contraceptives, supplemented by contemporary contraceptive research, were compared with the frequency of AEs reported in a male injectable hormonal contraceptive trial.

Results We observed similar frequencies of AEs reported by users of male contraceptives compared with those reported by female users. Among quantitatively comparable AEs, compared with men, women reported experiencing higher frequencies of headaches, pelvic pain, and weight gain and similar frequencies of decreased libido. Compared with women, men reported experiencing higher frequencies of acne and mood changes. Men discontinued participation due to AEs at a lower frequency than women.

Conclusions Female hormonal methods generally have similar frequencies of AEs to those reported in a recent male hormonal contraceptive trial, and male users had lower rates of discontinuation due to AEs. There were fewer serious AEs of the male contraceptive than reported in contemporary female trials which resulted in FDA licensure. This suggests there may be implicit bias in the scientific community regarding the level of acceptable risk for users of male contraceptive methods.

Key messages

- A 2016 study on an injectable combination male hormonal contraceptive was terminated early due to adverse events (AEs).
- AEs reported during a male contraceptive research trial are reported at seemingly similar frequencies to those reported for women during hormonal contraceptive trials.
- We observed different standards for acceptable AEs for male and female contraceptives, which may lead to slower product development for male contraception.

INTRODUCTION

Men have unmet need for modern contraceptive options. Today, men have two contraceptive choices: condoms and vasectomy. Condoms have a high failure rate (13% with typical use[1]) while vasectomy is a permanent, surgical method and is not reliably reversible. In comparison, all female hormonal contraceptive options combined have a 6% to 8% failure rate, with long-acting reversible female contraceptives at 99% efficacy.[1] No new methods of male contraception have come to market in almost a century.

Current hormonal research into male contraception has focused on the administration of an androgen, which results in markedly decreased sperm counts after 3–4 months; after hormone discontinuation, sperm counts return to pretreatment levels.[2] Weekly testosterone injections tested by the WHO in 1996 provided effective contraception for 98% of male participants, with no serious treatment-related adverse events (AEs).[3] The low acceptability of weekly injections led to explorations into a daily pill; however, there has been difficulty in developing a

daily dosage of an oral androgen that can completely suppress spermatogenesis while avoiding androgenic effects. Contemporary studies suggest that the combination of an androgen and a progestogen (progestin) to improve tolerability has potential to become a successful long-acting male contraceptive.[4–7] Despite 22 years elapsing since male hormonal contraception was shown to be effective in a clinical trial, there remains no male hormonal contraceptive in the market.

Recently, an injectable male contraceptive, 1000 mg testosterone undecanoate and 200 mg norethisterone enanthate, was studied in a phase II trial in 10 study sites between 2008 and 2012.[8] Three hundred and twenty male participants received an injection every 8 weeks until sperm counts dropped to less than 1 million sperm per millilitre of ejaculate. With a failure rate of 1.57 per 100 users (95% CI 0.59 to 4.14), the contraceptive effectively and reversibly suppressed spermatogenesis in 95% of the participants; however, the study was terminated early following a recommendation by an external safety review by WHO. Though details were not disclosed, the committee said the termination of the study was due to their review of AEs, specifically mood changes, depression, pain at injection site, and increased libido.[8]

As male contraceptive studies progress and regulatory agencies are faced with risk–benefit assessments, there is need for a critical appraisal of how AE risk is determined for men using contraception. AEs experienced by female contraceptive users are assessed in terms of the physical risks of pregnancy and childbirth; because this risk–benefit equation cannot be applied to men, an unprecedented risk analysis for male users must be established in order to work towards regulatory approval. In view of this ethical dilemma, we gathered evidence to explore the differences in documented AEs in male compared with female contraceptives. Published data from the injectable male contraceptive trial and representative female contraceptive methods were compared in order to assess reported AEs.

METHODS

We compiled data on AEs associated with the five most commonly used female reversible hormonal contraceptive methods from 2006 to 2010: combined oral contraception (COC), levonorgestrel-releasing intrauterine system (LNG-IUS), progestogen-only injectable, combined transdermal system, and combined vaginal ring, as determined by a report using data from the National Survey of Family Growth, 2006–2010.[9] We also examined AEs reported in the approval of the first female contraceptive pill in 1960, which set the precedent for risk–benefit analysis in approval of female hormonal contraceptives.

The data on female hormonal contraceptives were collected from published prescribing information from each method's leading brands, as determined by reports using data from the National Survey of Family Growth, 2006–2010.[9 10] For COCs, we reported data from Ortho Tri-Cyclen Lo: norgestimate/ethinylestradiol (EE),[11] Yasmin: drospirenone/EE,[12] Yaz: drospirenone/EE[13] and Ortho Tri-Cyclen: norgestimate/EE[14] - the top four most-used COC brands in the United States from 2006 to 2010.[10] For the IUS, we used data from Mirena: levonorgestrel-releasing.[15] For the injection, we used data from Depo-Provera: medroxyprogesterone acetate.[16] For the vaginal ring, we used data from NuvaRing: etonogestrel/EE.[17] Finally, for the transdermal system, we used data from Ortho Evra: norelgestromin/EE.[18] For each of these contraceptives, we report AEs as reported by Food and Drug Administration (FDA)-approved prescribing information, found under subsection 6.1: Clinical Trial Experience. The most contemporary prescribing information for each method was used, each being most recently revised in 2019 except for Ortho Evra, for which the most recently revised data available are from 2017. We assumed that these clinical trials were conducted appropriately, since they led to FDA approval of their respective contraceptives.

Data on the first female contraceptive approved by the FDA, the COC Enovid, were collected from a 1959 report of efficacy.[19] AEs of the injectable combination male contraceptive were collected directly from clinical trial data.[8]Reviewed AEs are those that were asssessed as being possibly, probably, or definitely related to the study products and that were reported by atleast 2% of male particpants.

The goal of this analysis was to understand the AEs of female hormonal contraceptives as reported in studies that led to FDA approval, not to review all AEs for contraceptives. Through understanding AE reporting for female contraceptives in trials leading to licensure, we can start to compare how this process is working for male contraceptives.

We grouped the AEs as described by each study. Some AEs were similar between men and women, such as weight gain or mood changes. Some AEs were reported differently for men and women. We aggregated the following AEs under the category of pelvic pain: abdominal pain/tenderness discomfort, pelvic pain/tenderness/discomfort and testicular pain/discomfort. Based on the definition used in the FDA-approved prescribing information, the following AEs are included under the category of mood changes for female users: mood swings, depression, depressed mood, and affect lability. Of the mood-related AEs reported in the male clinical trials, depression, emotional disorders, hostility, aggression, affective disorder, and mood swings are included in 'mood changes'.

To evaluate the scope of discontinuation of female methods, we collected additional data on discontinuation due to AEs, reported by a population-based study that provided a larger scope and sample size than data available from the prescribing information.[9]

In this review, the terms women/female refer to any person born with female sex organs and man/male refer to any person born with male sex organs.

Patient and public involvement

No patients were involved in this research.

RESULTS

We reviewed 12 reports, detailing seven AEs quantifiably comparable between sexes. There were 320 men evaluated in the single 2016 WHO study,[8] while a range of 830 to 45 021 women were evaluated in the trials from which we compiled data.

Acne

Male participants reported acne more frequently than users of female contraceptives (table 1). This is as expected, as estrogen-containing contraceptives reduce acne and are prescribed for acne treatment, while acne is a known AE of exogenous androgens. A range of 1% to 8% of users (dose-dependent) of testosterone gel 1% (AndroGel) experience acne as an AE.[20]

Changes in libido

Men reported a decrease in libido at a similar frequency to users of female contraceptives today, while women from the 1959 trials reported decreases in libido at about four times the frequency (table 1).

Men reported an increase in libido at a higher frequency than women in the 1959 trials (table 1). There were no reports of libido increase among modern female hormonal contraceptive users.

Pelvic pain

The frequency of pelvic pain experienced by men was less frequent than users of female contraceptives (table 1).

Weight gain

The frequency of men experiencing weight gain was less frequent than women today. Women in the 1959 trials reported more weight gain by over 14-fold. This is likely attributable to the greater concentration of estrogen in the 1959 COC than in today's COCs (table 1).

Mood changes

Male participants reported mood changes at a greater frequency to users of female contraceptives using data from prescribing information (table 1).

While depression, hostility, aggression, affective disorder, and mood swings were reported in fewer than 5% of men, respectively, 16.9% of men reported emotional disorders; however, the lack of differentiation between mood swings, emotional disorders, and affective disorders renders them difficult to compare to previously reported AEs by women.

Headache

Male participants reported experiencing headaches less frequently than female users of hormonal contraception did (table 1).

Discontinuation and acceptability

Women discontinued trials of hormonal contraceptives due to AEs at higher frequencies than men discontinued the 2016 WHO trial due to AEs (table 2).

Additionally, 81.7% of male participants reported they would use a contraceptive similar to the male injectable combination method, were it available on the market.[8]

Adverse Events exclusive to men

Gynaecomastia (5.6%) was reported by men and is not experienced by women, due to biological differences. Additionally, the following AEs reported by men are not events that women on hormonal contraceptives have significantly reported: injection site pain (23.1%), increased libido (38.1%), night sweats (2.8%), irritability (2.8%), increased appetite (5.0%), hyperhidrosis (5.3%) and musculoskeletal pain and myalgia (20.7%).

Adverse Events exclusive to women

Commonly reported AEs by women but not men include abdominal pain, sore breasts, nausea/vomiting, changes in premenstrual syndrome, vaginal discharge, alternation of menstrual bleeding patterns, vulvovaginitis, back pain, and dysmenorrhea (table 3).

When Enovid was first approved in 1960, the most common problems encountered by users were irregular menstruation, scanty or absent menses, weight change, headaches, nausea and other gastrointestinal disturbances.[19] Self-reported changes in libido were reported by 42% of the participants.[19] Across four separate trials, 28.2%–41.8% of participants using Enovid dropped out due to AEs.[19]

Serious AEs

A variety of serious AEs, such as deep vein thrombosis, pulmonary embolism, and cervical dysplasia, were reported for contemporary female contraceptives (table 4); these serious AEs are consistent with clinical use of female hormonal contraception over the years, especially COCs.[21] In the 2016 male injectable contraceptive clinical trials, out of a total of 320 participants, there were 14 serious AEs, 10 of which were assessed as not related to the study regimen. There was one death from suicide, assessed as not related to the study. There was one case of depression, assessed to be probably related, and there was one case of intentional paracetamol overdose and one case of tachycardia with paroxysmal atrial fibrillation, both assessed to be possibly related.

DISCUSSION

This critical appraisal of AEs in contraceptive trials reveals what appears to be similar AE frequency in most categories for female contraceptive trial participants and male contraceptive trial participants. With the exceptions of increased acne, mood changes, and increased libido, all comparable AEs reported on the

Table 1 Percentage of people who reported different adverse events on the male injectable combination contraceptive, the female combined oral contraceptive, the female intrauterine system, the female vaginal ring, the female injection, the female transdermal system, and combined oral contraception during the 1956 trial

		AE frequency (%)			
Adverse Event	**Contraceptive**	**Men**	**Women**	**Sample size (n)**	**Publication**
Acne	Injectable combination male contraceptive	45.9		320	Behre et al 2016[8]
	COC		5.1	1723	Ortho Tri-Cyclen Lo[11]
	IUS		6.8*	5091	Mirena[15]
	Vaginal ring		2.4	2501	NuvaRing[17]
	Transdermal System		2.9	3322	Ortho Evra[18]
	Injection		1.2	>3900	Depo-Provera[16]
Libido decrease	Injectable combination male contraceptive	4.1		320	Behre et al 2016[8]
	COC (1959)		22	830	Pincus et al 1959[19]
	Vaginal ring		2	2501	NuvaRing[17]
	Injection		5.5	>3900	Depo-Provera[16]
Libido increase	Injectable combination male contraceptive	38.1		320	Behre et al 2016[8]
	COC (1959)		20	830	Pincus et al 1959[19]
Pelvic pain	Injectable combination male contraceptive	1.9		320	Behre et al 2016[8]
	COC		5.6	4826	Ortho Tri-Cyclen[14]
	COC		9.2	1723	Ortho Tri-Cyclen Lo[11]
	IUS		22.6*	5091	Mirena[15]
	Vaginal ring		7.2	2501	NuvaRing[17]
	Transdermal system		8.1	3322	Ortho Evra[18]
	Injection		11.2	>3900	Depo-Provera[16]
Weight gain	Injectable combination male contraceptive	3.8		320	Behre et al 2016[8]
	COC (1959)		55	830	Pincus et al 1959[19]
	COC		2.4	1723	Ortho Tri-Cyclen Lo[11]
	Vaginal ring		4.9	2501	NuvaRing[17]
	Transdermal system		2.7	3322	Ortho Evra[18]
	Injection		37.7	>3900	Depo-Provera[16]
Mood changes	Injectable combination male contraceptive	31.7		320	Behre et al 2016[8]
	COC		2.2	1056	Yaz[13]
	COC		2.3	2837	Yasmin[12]
	COC		3.8	4826	Ortho Tri-Cyclen[14]
	COC		7.6	1723	Ortho Tri-Cyclen Lo[11]
	IUS		6.4*	5091	Mirena[15]
	Injection		1.5	>3900	Depo-Provera[16]
	Vaginal ring		6.4	2501	NuvaRing[17]
	Transdermal system		6.3	3322	Ortho Evra[18]
Headache	Injectable combination male contraceptive	5.3		320	Behre et al 2016[8]
	COC		6.7	1056	Yaz[13]
	COC		10.7	2837	Yasmin[12]
	COC		33.6	4826	Ortho Tri-Cyclen[14]
	COC		30.5	1723	Ortho Tri-Cyclen Lo[11]
	IUS		16.3*	5091	Mirena[15]
	Vaginal ring		11.2	2501	NuvaRing[17]
	Transdermal system		21.0	3322	Ortho Evra[18]

*Crude incidence per person-years.
AE, adverse event; COC, combined oral contraceptive; IUS, intrauterine system.

Table 2 Percentage of total users who discontinued their contraceptive method either during clinical trials or everyday use, specifically due to adverse events (AEs) or worries about possible AEs.*

Contraceptive	Discontinuation due to AEs (%)			
	Men	Women	Sample size (n)	Publication
Injectable combination male contraceptive	6.25		320	Behre et al 2016[8]
Depo-provera injection		36.6	12 529	Daniels et al 2013[9]
Transdermal system		25.8	5631	Daniels et al 2013[9]
COC		22.71	45 021	Daniels et al 2013[9]
COC		6.0	1056	Yaz[13]
COC		6.7	2837	Yasmin[12]
COC		4.0	1723	Ortho Tri Cyclen-Lo[11]
Vaginal ring		13	2501	NuvaRing[17]

*The data on discontinuation from everyday use was measured over a 4-year period in the United States.
AE, adverse event; COC, combined oral contraceptive.

male injectable contraceptive were either similar to or less frequent than the same events experienced by women on a broad array of hormonal contraceptives.

Adverse Event analysis

Emotional disorders were the main reported AE in the male contraceptive clinical trial. Mood changes, an area of concern for all hormonal treatments, were experienced by a greater frequency of men; however, not represented in table 1, recent population-level data from Denmark show that female hormonal contraceptive use can result in up to an 80% relative increase in risk of depression.[22]

Notably, 95% of emotional disorders in the male contraceptive trial were rated 'mild,' and few led to discontinuation.[8] Other adverse events commonly reported in the male clinical trial, such as myalgia and injection site pain, are difficult to compare to female effects seen in contraceptive trials. However, while quantifiable data on insertion/injection site pain of applicable female contraceptives were not found, it

Table 3 Percentage of women who reported specific adverse events during clinical trials of hormonal contraceptive methods

AE	Contraceptive	AE frequency (%)	Sample size (n)	Publication
Sore breasts	COC	8.3	2837	Yasmin[12]
	COC	3.8	2501	NuvaRing[17]
	IUS	8.5*	5091	Mirena[15]
	Injection	2.8	>3900	Depo-Provera[16]
Nausea/vomiting	COC	4.5	2837	Yasmin[12]
	COC	16.3	1723	Ortho Tri-Cyclen Lo[11]
	Injection	3.3	>3900	Depo-Provera[16]
	Transdermal system	16.6	3322	Ortho Evra[18]
	Vaginal ring	5.9	2501	NuvaRing[17]
Changes in premenstrual syndrome	COC	13.2	2837	Yasmin[12]
Vaginal discharge	IUS	14.9*	5091	Mirena[15]
	Vaginal ring	5.7	2501	NuvaRing[17]
Alteration of menstrual bleeding patterns	IUS	31.9*	5091	Mirena[15]
Vulvovaginitis	IUS	10.5*	5091	Mirena[15]
Back pain	IUS	7.9*	5091	Mirena[15]
Dysmenorrhea	Vaginal ring	3.5	2501	NuvaRing[17]
	COC	6.4*	5091	Mirena[15]
	Injection	1.7	>3900	Depo-Provera[16]
	Transdermal system	7.8	3322	Ortho Evra[18]

*Crude incidence per person-years.
AE, adverse event; COC, combined oral contraceptive; IUS, intrauterine system.

Table 4 Serious adverse events reported by FDA-approved prescribing information of contemporary hormonal female contraceptives and those assessed to be possibly or probably related to the male injectable contraceptive.*

Contraceptive	Reported serious AEs	Publication
COC	Depression, pulmonary embolism, toxic skin eruption, uterine leiomyoma	Yasmin[12]
COC	Migraine, cervical dysplasia	Yaz[13]
COC	Carcinoma of the cervix in situ, cervical dysplasia	Ortho Tri-Cyclen Lo[11]
COC	Breast cancer, carcinoma of the cervix in situ, hypertension, migraine	Ortho Tri-Cyclen[14]
IUS	Group A streptococcal sepsis	Mirena[15]
Vaginal ring	Deep vein thrombosis, anxiety, cholelithiasis, vomiting	NuvaRing[17]
Male injectable combination contraceptive	Depression, intentional paracetamol overdose, tachycardia with paroxysmal atrial fibrillation	Behre et al 2016[8]

*The number of female participants that reported each adverse event was not reported.
AE, adverse event; COC, combined oral contraceptive; FDA, Food and Drug Administration; IUS, intrauterine system.

is understood that pain, bleeding and dizziness are common side effects of IUS insertion.[15]

Serious Adverse Events

With regard to serious AEs, death, typically from thrombotic events, is the most severe AE reported in association with female contraception. A 2019 systematic review suggests at least 300–400 women die annually from venous thrombosis due to hormonal contraception.[23] Death has not been reported as a correlated event in any male contraceptive efficacy studies. Notably, however, there was one death by suicide, classified as unrelated, and one suicide attempt (paracetamol overdose), classified as possibly related, in the 2016 injectable male contraceptive study.[8]

Limitations

Due to study heterogeneity, we cannot be certain that trial populations were similar prior to entering the trial. This prevents us from comparing any of the AEs; however; these heterogeneous trial populations were each used to achieve FDA approval. This provides valuable context in understanding how AEs are interpreted and ultimately deemed safe enough to receive FDA approval.

Additionally, the disproportionally smaller sample size of male contraceptive users compared with female users widens the confidence interval for all data on male contraception and hinders our ability to understand potential risk of AEs at the population level. However, reviewing data on AEs side-by-side provides a tool to understanding the reality of AE frequency, and its regulatory assessment, across different contraceptive methods.

An improved framework for evaluation of male contraception that assesses AEs in conjunction with a placebo group could produce a better understanding of AE correlation, avoiding potential ecological fallacies, and resulting in a more equal application of patient safety.

Risk analysis

Discussion of female methods has always occurred within a shared understanding that unsought pregnancy can harm and even kill women. In the approval of the first COC, regulators considered the risks of abortion and childbirth as factors in their approval decision for the contraceptive.[24] Additionally, psychological harms can be accounted for and used in risk determination. For example, while 5.4% of female users report mood changes, including depression, as an AE of their hormonal contraception (table 1), that is still lower than the 20%–22% of women who may experience maternal or postpartum depression.[25] The risk of the contraceptive can thus be deemed less severe than the risk that would exist if the contraceptive were not approved. We report that current male contraceptives under study would be more effective than any methods already available to men (condoms), and further have been shown to be highly acceptable to participants. Therefore, it may be premature to conclude that risk of AEs outweigh any potential benefits. The same risk analysis that is applied to women cannot be extended to men, who cannot physically get pregnant; however, a framework for evaluating the risks and benefits of male partners is an approaching ethical dilemma that regulators must contend with. Male contraceptives are often evaluated at an individual level, which does not account for benefits seen at the family level. For example, a common scenario of male contraceptive demand comes from male partners of women with health problems for whom hormonal contraception is medically contraindicated.[26] In that scenario, the contraceptive benefit is for the family as well as for the man. When viewed through this lens, it is rational to understand why men would be willing to accept some risk of AEs for contraception that benefits their family situation.

Further, safety assessments of male contraceptive methods limited to AEs neglect the counterfactual, namely that, similarly to women, unintended pregnancy can cause harm to men. Various studies have demonstrated the presence of postpartum depression in men.[27] It is possible that the effects of paternal postpartum depression, particularly when a pregnancy is unintended or unwanted, will outweigh the risks of contraceptive use. Understood in this framework, the possible benefits of a male contraception might outweigh the possible risks. Unfortunately, there is a critical lack of research specifically on the mental and other health adverse effects of unintended pregnancies on fathers. A 2018

study demonstrated that prenatal motivation to have a child significantly predicted postpartum depression symptoms, both maternally and paternally, however, the frequency at which symptoms occur in fathers remains unstudied.[28] At present, we are unable to quantify the negative consequences of a woman's pregnancy on their male partners. Better data on paternal postpartum depression and paternal consequences of undesired pregnancy would enable a more equitable analysis of AEs, and would also allow us to describe potential male health benefits of male contraception.

CONCLUSIONS

Our data show that although there were concerning AEs of the injectable male contraceptive, placed in the context of other current contraceptive technology it appears that this method is promising and could have a place in the method mix even if there are AEs to be managed. AEs are expected and managed for women using hormonal contraception; however, the same basis of acceptability has not been applied to men. The acceptability of AEs for approved female contraceptive methods, compared with a very low tolerance of AEs for male methods, does show gender bias. This bias assigns contraceptive responsibility to women, normalises female discomfort and pain associated with reproductive health, and fails to consider mental health consequences of ill-timed pregnancy for men as well as women. Despite a long history of AEs, female contraceptives are widely demanded, used and supported. Regulatory bodies have granted women the right to choose whether the risks associated with contraception outweigh the risks of unplanned pregnancy. A disturbing paradigm seems to be developing where male contraceptive methods are perceived, even before creation, to be unlikely to achieve regulatory approval and unlikely to attract pharmaceutical investment if the method has even minimal safety concerns.[29 30] As numerous male contraceptive methods are under development, the data reviewed here remind us that female contraception has been acceptable to regulators and consumers despite a nuanced balance of risks and benefits. Regulatory, pharmaceutical and research actors should work to extend to men the same choice to assess risks and benefits of contraception.

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