

Effects of Pharmaceutical Medications on Male Fertility

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Abstract

The number of couples seeking consultation for infertility problems has steadily increased over the past decade, affecting 10%–15% of the sexually active population. Abnormal semen production, a male factor infertility (MFI), is thought to be the cause of up to 50% of all infertilities in developed countries. There are potentially many different causes of male infertility, including hormonal, anatomical, and secondary to exposure to exogenous substances. In many cases of MFI, a definitive cause for abnormalities is never identified. Recently, the research community has given greater attention to identifying causes of MFI ranging from genetic Y chromosome microdeletions to mechanisms of environmental damage on sperm production. Still evolving, is a clear understanding of how many pharmaceutical medications may cause MFI, which is often treatable and reversible. In this review we will outline the data regarding various pharmaceutical medications that have been investigated as possible causes of MFI.

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Introduction

Causes of male infertility: The number of couples seeking consultation for infertility problems has steadily increased over the past decade, affecting 10%–15% of the sexually active population (1, 2). MFI contributes to approximately 50% of all infertility (2–4). MFI may be generally diagnosed through an abnormal semen analysis (SA). While the SA has multiple measured parameters, the most important are abnormalities in sperm count, ranging from fewer than normal sperm (oligospermia) to undetectable sperm (azoospermia), sperm motility, a condition known as asthenospermia, and sperm morphology (5, 6). The relative importance of each of these parameters, among other measures of semen quality, are constantly a subject of debate within the fertility community (5, 7). A further complicating matter is the poor reproducibility of SA as an assessment tool for sperm quality and quantity. Indeed, data has shown that interjaculate coefficients of variation for sperm concentration and

motility are estimated to be as high as 44% and 15% respectively (8).

The causes of oligospermia or azoospermia can be divided into three distinct stages: Pre-Testicular, Testicular, and Post-Testicular, depending on the stage of spermatogenesis which is altered or impaired (9). Pre-testicular stage azoospermia results from the pituitary gland, part of the hypothalamic-pituitary-gonadal (HPG) axis, not producing proper hormones to stimulate the testes to produce sperm and is often due to an underlying endocrinologic abnormality (9).

Testicular stage azoospermia is a failure of testicular function and Post-Testicular azoospermia is due to physical causes such as obstruction (9). In the majority of MFI cases, a definitive cause for abnormalities is never identified (4). Pharmaceutical medications as well as recreational drugs have been documented to impact semen production at testicular stages (2, 10, 11). In addition, some medications impair ejaculation and erectile function, as

well as the ability to decrease libido (12). This review article will focus on the effects of certain pharmaceutical medications that may be associated with male infertility.

Anti-depressants: Depression is a common disorder with a lifetime prevalence of approximately 16% (13). Rising levels of depressive disorders have in turn led to an increase in the use of prescription antidepressants, with more than 253 million prescriptions on record for 2010, the second most among all medications in the United States (14). The underlying cause of depression is still being investigated but is thought to include an over-activity of the emotion processing regions of ventral limbic and underactivity of the dorsal prefrontal cortex (15). Antidepressant medications, specifically selective serotonin reuptake inhibitors (SSRIs), are currently the treatment of choice for individuals suffering from depression (16). SSRIs have been implicated as a source of MFI. However, as the use of SSRIs has increased in recent years, few studies have evaluated the effect of SSRIs on MFI. Further complicating the picture is the fact that some studies have linked depression alone, without the use of medications, to altered testosterone levels, which could conceivably contribute to MFI (17, 18). However, several other studies have failed to demonstrate such a correlation (17, 19, 20).

In 2006, researchers at Weill Cornell Medical College in New York published a case report that proposed a possible link between SSRIs and MFI (21). In 2010, the same group performed a retrospective study on thirty-five healthy male volunteers (22). The men were asked to provide semen samples at baseline and were then administered the drug paroxetine, an SSRI, for a period of five weeks. Results indicated that the key sperm parameters of volume, concentration, motility or morphology were not adversely affected during the trial period. However, sperm integrity DNA analysis showed that mean sperm DNA fragmentation was significantly greater (30.3%) in men after continued use of paroxetine when compared to the baseline (13.8%). Furthermore, self-reports from the subjects showed that 35% cited considerable changes in erectile function while 47% noted difficulties with ejaculation while taking paroxetine. Limitations of the study included a small sample size of healthy volunteers without baseline depression, a lack of placebo pill use in the control group, and the fact that fertility was not evaluated.

Another retrospective trial has demonstrated an association between SSRI use and decreased sperm motility (23). Evidence also shows that SSRIs have a spermicidal effect in vitro (24). One group has actually described SSRIs as an acutely helpful therapy to improve increased ejaculate volume in men taking Sildenafil (25). While there have been several small trials that link SSRIs to semen abnormalities, the authors could not identify a large trial that definitively link SSRIs to MFI as defined by inability to achieve pregnancy. As such, the data linking SSRIs to MFI are, at the present time, suggestive but not conclusive. A summary of the current evidence is offered in Table 1.

Calcium channel blockers: Calcium Channel Blockers (CCBs) are calcium ion antagonists. They block the movement of free calcium ions, which serve as important secondary messengers, between ion channels and ionophores. CCBs can have an effect on cardiac muscle, smooth muscle of blood vessels, and neurons (26, 27). CCBs are indicated as a therapy for various medical conditions including hypertension and heart failure (26, 27).

Since 1988, calcium antagonists have been shown to produce a dose-dependent reduction in sperm motility and viability in vitro (28). In one particular in vitro assay, the dose-dependent effect of Nifedipine, a CCB, was examined with regards to sperm morphology, motility, and phospholipid composition. The addition of the CCB resulted in significant inhibition of calcium ion uptake. The researchers also elucidated a clear dose-dependent and time-dependent effect of the calcium antagonist on sperm motility for different durations. Additionally, this study showed that exposure to the CCB resulted in structural changes in both the head and tail regions of sperm when evaluated by scanning electron microscope (29). Others have shown that CCB may inhibit the ability of sperm to bind to an egg by altering the lipid bilayer of the sperm plasma membrane (27).

Interestingly, researchers have also shown that calcium ions exert a paradoxical effect on human sperm motility, depending on the developmental stage of the sperm (30). Earlier in vitro experiments in non-human mammalian species had shown an increase in sperm motility with the addition of calcium ions, likely through the binding of calcium to a calmodulin-like protein. However, other experiments demonstrated that calcium chelators (EGTA and EDTA) as well as calcium

Table 1. The evidence for medication associated alterations in sperm and pregnancy potential

Medication Category	Medication	Case Report Evidence	In vitro evidence (Trial)	Clinical evidence (Trial)	Evidence for Semen Alteration	Evidence for Altered Pregnancy Potential	Studies
Anti-depressants							
	Paroxetine		+	+	+		22,24
	Citalopram	+	+		+		21,24
	Fluoxetine		+		+		24
	Sertraline	+	+		+		21,24
	Bupropion	+			+		21
	Combination SSRI			+	+		22
Calcium channel blockers							
	Diltiazem		+		+		28
	Nifedipine		+		+		29
	Non-Specified or Mixed CCB			+	+	+	27,32
Alpha-adrenergic blockers							
	Tamsulosin			+	+		33,34
	Alfuzosin			+	-		34,35
Anti-epilepsy							
	Phenytoin	+		+	-	-	39,40,41
	Carbamazepine	+		+	-	+	40,41,42
	Valproate			+	+	-	40,41,42,58
Anti-retroviral							
	HAART		+	+	+	-	45,48,51
	Saquinavir		+		+		50

This table outlines the evidence from the studies discussed in this review. Listed are medication categories and specific medications evaluated. The type of evidence is determined as either including a case report, in vitro, or clinical structure. The evidence is also determined to have evaluated the impact on fertility and change in sperm count or function. “+” denotes a “Yes” response, “-” denotes a “No” response. Blank spaces indicate no study evaluated this category among the reviewed articles

antagonists increased motility in human semen. One possible hypothesis for this effect was the triggering of a premature acrosome reaction in sperms before they underwent full capacitation and maturation (31).

In addition to the in vitro studies outlined above, there are also clinical trials that point to a link between CCBs and MFI. One small trial evaluating sperm from men taking CCB did not show decreased rates of oocyte fertilization when undergoing in vitro fertilization (IVF) without intracytoplasmic sperm injection (32). However, the pregnancy rate per transfer in embryos derived from men taking CCBs was only 17.4% (32). While significant data exists to suggest that CCBs may contribute to MFI, the authors could not identify a large prospective trial evaluating fertility outcomes among men taking CCBs. A summary of the current evidence is offered in Table 1.

Alpha-Adrenergic Blockers: Alpha-adrenergic blockers (AAB) are a class of medication most commonly used to treat Lower Urinary Tract Syndrome associated with Benign Prostatic Hyper-

plasia (BPH) (33). These drugs have a high affinity for alpha-adrenergic receptors in the smooth muscle cells of the lower urinary tract and blood vessels (33). AABs also have a high binding affinity for various other receptors including dopamine and serotonin (33).

The use of AABs has been shown to be associated with significant rates of antegrade ejaculation or even anejaculation (33, 34). As the process of male ejaculation encompasses a complex coordination of actions, this affect of AABs is thought to be secondary to the effect on dopamine and serotonin, among other mechanisms (34). The degree to which AABs may compromise the ejaculatory efficiency is substantial. One trial using a 5-day treatment with tamsulosin (an AAB) demonstrated that a measurable decrease in ejaculate volume may be seen in 90% of subjects following AABs use (33). Furthermore, the rate of anejaculation following AAB administration was as high as 30% (33). Additionally, AABs have been shown to also negatively impact semen parameters such as sperm concentration and motility (34).

However, other trials using AABs other than tamsulosin, such as alfuzosin, have not demonstrated deleterious effects on ejaculatory efficiency or altered semen parameters (35). While significant data exists to suggest that AABs, specifically tamsulosin, may contribute to MFI, the authors could not identify a large prospective trial evaluating fertility outcomes among men taking AABs. A summary of the current evidence is offered in Table 1.

Anti-epilepsy: Epilepsy is known to be associated with MFI. Epileptic males have been shown, in large studies, to have significantly lower fertility rates and greater risks of hyposexuality than the general population (36). Studies on anti-epileptic medications including carbamazepine, phenytoin and valproate have suggested specific drug-dependent side effects, including abnormal sperm morphology, reduced motility, lower sperm count, and reduced testicular volume. The most likely mechanism for these side effects is thought by some to be the interaction between anti-epileptic medications and sex hormones, interfering with normal HPG pathway functioning (37). However, many studies have been inconclusive whether these effects are symptoms of epilepsy itself or side effects of long-term administration of anti-epileptic medications (38, 39).

One case report published in 2005 described a patient suffering from infertility taking 400mg/day of carbamazepine with a semen analysis showing a normal sperm concentration but no motile sperm. One month after discontinuing his carbamazepine and starting phenytoin monotherapy, his semen parameters were found to be normal and his wife became pregnant within 6 months (40, 41). In a 2003 selective cohort study, researchers from Norway investigated the effect of carbamazepine and valproate on semen quality in a treatment arm for each medication and a control group receiving no medication. The study did show an increased rate of abnormalities in the tails of sperm in men taking valproate. These changes were not seen in men taking carbamazepine. Of note, there was no difference in fertility in any of the men, as defined by pregnancy, compared with the controls (42). While significant data exists to suggest that various antiepileptic medications may contribute to MFI, current data is inconsistent and precludes specific recommendations regarding individual medications. Furthermore, the well-described association between epilepsy and infertility presents a significant confounding variable

that the majority of studies have failed to eliminate. A summary of the current evidence is offered in table 1.

Anti-retrovirals: The treatment of human immunodeficiency virus (HIV) has transformed a once quickly lethal disease into a condition that, with proper treatment, may be compatible with a long lifespan (43, 44). As such, many individuals with well controlled HIV are increasingly interested in the possibility of pursuing parenthood. Therefore, an understanding of how medications used to treat HIV may impact MFI is warranted. The ability of HIV positive men to father children even with HIV seronegative women is now a reasonable proposition through IVF risk reduction programs that involve sperm washing to significantly reduce the risk of HIV transmission (45).

Early HIV infection is not thought to significantly impair semen parameters (46–48). However, some have evaluated if medications used to treat HIV infection could affect MFI. Highly active antiretroviral therapy (HAART) is provided to patients with HIV and, despite its tremendous reduction in HIV mortality, has been associated with a number of serious adverse side effects including neuropathy and lipodystrophy (49).

Numerous studies have evaluated the effect of HAART on sperm quality. One study showed that saquinavir, commonly used in HAART regimens, results in decreased sperm motility in vitro and negatively affects mechanisms that are essential to fertilization of an oocyte such as the acrosome reaction (50). A clinical study prospectively followed men starting HAART and demonstrated a 60% reduction in sperm motility over a period of 48 weeks (48). Other studies have shown similar results with reductions in ejaculate volume, increased rates of abnormal sperm morphology, and decreased sperm motility (51). However, despite these HAART associated semen abnormalities, centers following men undergoing HAART show high rates of ultimately achieving pregnancy (45). Regardless of the possible adverse effects of HAART on sperm quality, the health benefits of the treatment far outweigh any possible fertility benefit that could be associated with medication discontinuation. However, these studies may be helpful in counseling HIV positive men who wish to pursue parenthood. A summary of the current evidence is offered in table 1.

Miscellaneous medications: Data evaluating the effects of most medications on semen is lacking. However, the body of data available addressing

this topic is ever expanding. The effects of antibiotics on semen quality are largely untested. Many studies have documented the favorable impact of antibiotics on semen quality in the setting of testicular infection, particularly epididymitis (52–54). However, some emerging animal data have suggested that some antibiotics, such as tetracycline, may have an independent deleterious effect on semen quality when not given in the context of testicular infection (55). A substantial body of data shows a substantial deleterious effect, even in mild doses, of chemotherapeutic agents and radiation for the treatment of cancer on semen parameters (56–59). Specifically, alkylating agents, such as cyclophosphamide, have a particularly long lasting effect on spermatogenesis and may cause permanent oligo or azospermia (56). Therefore, current standard of care is to obtain a semen sample that is cryopreserved before initiation of chemotherapy for fertility preservation (57).

Additionally, exogenous medications that alter the hypothalamic pituitary gonadal axis may impact semen quality. Semen quality is known to be deleteriously affected, for example, with decreased levels of thyroid hormone or changes in prolactin concentration, which can be a side effect of multiple medications (60). Anabolic steroids, generally taken by individuals to increase muscle mass, have been well documented to lead to oligo or azospermia (61–63).

Recent research has also evaluated the impact of phosphodiesterase inhibitors used to treat male penile impotence, such as sildenafil, on semen quality. Many studies have found, in animal and human trials, increased motility and other semen parameter improvement with sildenafil (64–66). There is conflicting data regarding the effect of sildenafil on oocyte fertilization, however, with some studies documenting a negative effect and others finding no difference from placebo (67–70).

Discussion

Male factor infertility is a common cause of infertility. Only recently has more attention been given to the underlying causes of MFI including the association between semen parameters and certain medications. Establishing clear association between medications and MFI, however, is challenging on several levels.

Intra-sample variability is commonly reported

among all men who provide multiple sequential semen analyses (8). Furthermore, the number of days a man abstains from ejaculating prior to semen analysis may affect the results of the evaluation in terms of sperm concentration and sperm quality (71, 72). A myriad of other factors also may affect semen parameters including aging, stress, and even seasonal variation (73–75). Therefore, all the trials outlined in this review are inherently limited by these variations and would require relatively large sample sizes to minimize their impact. The majority of these studies, however, used relatively small sample sizes and, with few exceptions, failed to give specific details regarding the days of abstinence, age of subjects, and other factors that could certainly impact semen quality and quantity.

Another variable that can be modified by researchers to a large extent is time. The entire process of spermatogenesis can last anywhere between 70–75 days. However, the most crucial final stage between the transition of spermatids to motile spermatozoa requires about 2 weeks for completion (76, 77). With this knowledge in mind, it is important that any effect of medications on semen quality be measured after significant time has elapsed since administration. Therefore, it is possible that events even several months prior to the ejaculate sample could affect semen quality and quantity. Additionally, these studies generally did not evaluate different doses of medications tested, precluding the ability to determine if there is a dose-dependent relationship between the drug in question and the SA parameters. These factors confound the ability to establish a firm cause and effect relationship between a suboptimal SA and exposure to specific medications.

A further limitation of many of these studies is the lack of determining if an alteration documented in semen quality or quantity translates into a tangible deleterious effect on the ability to achieve pregnancy or is correlated to possible birth defects in the offspring produced. The vast majority of the studies reviewed rather focused solely on semen parameters as the sole endpoint. Without establishing if these medications confer a decreased fertility rate, labeling a medication as having an effect on MFI per se seems premature.

Another drawback from many clinical trials discussed as mentioned earlier is the absence of a placebo medication or a control group. Most often, researchers compared collected samples to

normal WHO criteria for healthy males. Even though the WHO criteria likely serves as a fair representation for normal male characteristics, the absence of a control group increases the likelihood of ignoring an important confounding variable in a certain trial. As such, to eliminate any chance of bias and provide more certainty to the results, researchers should seek to limit confounding variables to the best of their capabilities.

Despite these design limitations, the literature does suggest that certain medications may, in fact, prove detrimental to male reproductive potential. Specifically, there is good data that SSRIs, CCBs, certain AABs, and HAART medications certainly could contribute to MFI. However, many men still father healthy children even while taking medications. Therefore, as the detrimental effects of these medications were never universally observed, counseling men taking these medications should include discussing the risk that the medications may, but also may not, pose to their reproductive health. In many instances, the detrimental aspects of these drugs on semen parameters is likely outweighed by the significant medical benefit conferred to one taking the medications, especially in life-extending treatments such as HAART.

The classes of pharmaceutical medications discussed in this paper are limited, largely due to the relative lack of research that has been done in this field. The association between MFI and exposure to pharmaceutical compounds has only recently been explored and is a subject sure to generate more research and discussion in the years to come. Indeed, SA certainly does not evaluate many of the parameters of sperm that may impact MFI such as an intact acrosome reaction [8]. Future exploration into this field must relate the affects that medications may or may not have, not only on semen parameters, but also on the ability to actually father a child.

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