Chapter 2
Challenges of Obtaining Evidence-Based Information Regarding Medications and Male Fertility

Abstract In the clinic, the existing literature is insufficient to counsel our infertile men on medication use. Most studies have flaws that limit their application to evidence-based practice. In this chapter, we discuss the limitations of the current literature and the challenges to designing more useful studies. Among the most important weaknesses of existing studies is lack of power; that is, too few men are included to draw conclusions about the existence and size of medication effects. Adequate power is particularly important when confirming an absence of medication effect. Bias is also a problem in most studies. Early studies were rarely randomized, placebo-controlled, or blinded; a common example is patients receiving different medication regimes based on the severity of their symptoms—making it impossible to attribute differences between treated and untreated men to the medications. Additional bias is introduced by failing to include other factors that influence the outcome in the experimental design. A uniform population amenable to randomization and placebo-control are experimental species, and useful information has been gained from these models. However, application to humans is limited by differences from other species in route of drug administration, absorption of the drug, concentration in the male genital tract tissues, and genital tract physiology. To a lesser degree, there is variation among individual men in their response to drugs. In addition, drugs in the same class may have different effects, limiting the applicability of data across drugs of a single class. Complicating matters further, a toxic medication may seem to improve fertility endpoints by improving a disease condition that diminishes fertility. Finally, drug interactions have not been studied, and actual fertility data (pregnancy/fecundity) in humans are rare. A healthy dose of skepticism is warranted when evaluating studies of medications and male reproductive health.

2.1 Experimental Design

For most drugs, there is a paucity of large, well-designed clinical trials evaluating effects on male fertility. The majority of human studies are small and observational, often retrospective, with inconsistency in study populations, doses, and endpoints. Although we may suspect that a pharmacologic agent has a negative impact, it is

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rare that this can be stated with certainty. Following are some important aspects of experimental design.

- Size and power: Limited clinical information is provided from underpowered studies (Ioannidis 2005; Meldrum and Su 2017). A prospective power analysis to determine the required number of study subjects is important for evaluating a medication's effects. This is critical for studies showing no effect of the medication. For example, if a decrease in testosterone level of 25% was considered clinically significant in the power analysis, an appropriately powered study allows the conclusion that it is unlikely that the drug causes testosterone to decrease by 25% or more. But the study is underpowered to comment on the potential for smaller testosterone changes in the population of treated men. Small sample size is also problematic when a statistically significant difference is determined, as the effect size can be overestimated (Wacholder et al. 2004; Meldrum and Su 2017). Thus, there may actually be a difference in testosterone level, as determined by the study, but it may only be 2% on average, instead of the 25% reported. The bottom line is that a high proportion of pharmacological studies are underpowered, and the results of an individual study of this type do little to inform evidence-based clinical practice.
- Randomization, placebo-control, and blinding: The gold standard for experimental design in clinical trials is a randomized, double-blinded, placebo-controlled trial (RDBPCT). For most medications, such studies have not been published for male fertility outcomes. It is not unusual to have medication effects detected that are later determined to result from bias introduced by population differences between treatment and control groups or by differences in the treatment of patients in the medication group versus the controls. Nevertheless, adequately powered, observational studies (e.g., cohort, case-control, and cross-sectional) are valuable and can sometimes provide more applicable clinical information than randomized, controlled trials (RCTs) because they may better reflect the patient population and/or the flexible dosing that is used in a clinical setting. Because such studies are more subject to bias, observational studies must be interpreted with caution.
- Lack of negative reports: There are fewer reports of drugs having no effect on male reproduction than reports of a positive or negative effect. This phenomenon, commonly known as publication bias, has been improving over time as the value of negative results is better appreciated (e.g., Lenson et al. 2017); however, there remain fewer reports of no drug effect, particularly in the older literature.
- Confounding: Sexual health and fertility are impacted by many confounding variables in addition to the medication under evaluation. Useful studies must control for a plethora of variables known to effect male reproduction, not the least of which is female sexual health and fertility. Medication studies have more clinical value if a representative population is studied and factors known to influence male fertility are considered in the experimental design. At a minimum, this includes age, smoking status, alcohol consumption, body mass index (BMI),

other disease conditions, other medications, reproductive tract anomalies (e.g., varicocele), and history of genital infection.

2.2 Species-Specificity and Reproductive Endpoints

Although there are studies in other species for all medications approved for human use, and recently reproductive endpoints have received more attention, species differ in their reproductive response to drugs. Different species are inherently dissimilar in reproductive physiology. There are also significant species differences in pharmacokinetics, including variation in absorption of medications, metabolic considerations, and concentration in the reproductive tract tissues. The dosages used in trials with experimental species are often high so that toxicity will be seen if present; however, that approach limits provision of clinically valuable information. Often, the dose-response curve for an exogenous chemical is non-linear and can be similar at low and high doses (Vandenberg et al. 2012), so a response may be missed at some doses.

In this volume, the human equivalent doses (HED) were calculated using human dosages found at FDA.gov or drugs.com, and the equivalent animal dose was based on differences in surface area among species as described by Reagan-Shaw et al. (2008). Pharmacokinetic data would be the most appropriate method for determining HED (Blanchard and Smoliga 2015); however, the data required are not readily available. The calculated value using body surface area is influenced by the weight of the experimental animal, which is often omitted from publications; in these cases, adult weights were estimated at 250 g for rats and 20 g for mice. The route of administration in humans is included in square brackets, indicating "all routes" if the human dose is equivalent for oral, intramuscular (IM), intravenous (IV), subcutaneous (SC), or metered dose inhaler (MDI) administration as indicated for humans. For drugs that are used at high doses to treat cancer, and lower doses for other conditions, HED were based on the lower dose that men of childbearing age might be taking chronically.

Endpoints measured after administration of pharmacological doses in an experimental species are unlikely to provide information useful for counseling patients. Nevertheless, such results can indicate drugs deserving clinical trials.

2.3 Variation in Effects of Drugs in the Same Class

In some cases, there are a variety of drugs in a given class, and data only exist for some of them. Included in the tables of this book are lists of comparable medications with little (e.g., case reports) or no data for male reproductive endpoints. Occasionally there is only one or a few drugs in a class that have reproductive toxicity, and those with scant data can represent alternative medications for use when

fertility is desired. In other cases, drugs with no published data have not been evaluated sufficiently and have unknown impact on male reproduction.

2.4 Few Studies with Live-Birth and Offspring Health as Outcomes

Although fertility and offspring health are our dominant interests, the outcomes used in most in vivo human studies look at endocrine or semen outcomes. Aside from the large literature questioning the relevance of semen analysis in evaluation of male fertility, there are also examples from the pharmacology literature that illustrate the challenges associated with reliance on these outcomes. In some studies, a negative effect on fertility is seen in the absence of reduced semen (or epididymal sperm in rodents) quality. Similarly, decreased semen quality is not necessarily associated with impaired fertility. Another challenge of using semen quality measures, and also reproductive hormone levels, to measure treatment outcomes is that these factors have large variability in fertile men and most are highly skewed in distribution (Cooper et al. 1991, 2010). Without adequate power and appropriate statistical techniques, effects of treatments can be difficult to detect. Generally, studies are underpowered to reach conclusions regarding a *lack* of medication effect. As such, the scarcity of reliable evidence for a fertility effect is profound when using changes in semen parameters or reproductive hormones as a surrogate for the effect on fertility or cause of male infertility. This is a significant limitation of reproductive pharmacotoxicology studies in men.

2.5 Individual Variation in Response

Not every individual responds comparably to medications. This can be due to demographic factors, drug interactions, other health conditions, environmental exposures, and differences in genetic predisposition. The most valuable information for counseling our patients is the proportion of men with fertility effects from a given medication. Instead, the literature commonly reports mean values for endpoints, even in cases of data that are not normally distributed (e.g., total sperm count; testosterone level), where nonparametric measures (e.g., medians) would be more appropriate. In most cases, we do not have the information required to inform evidence-based clinical practice. As with all medications, some individuals will have more severe adverse effects than others, and the mechanism for this is often obscure. No significance in mean values for a reproductive endpoint does not mean that there are no men suffering infertility due to the medication. Differences can also relate to clearance of the drug or the mechanism underlying the adverse reaction.

2.6 Illness Can Have Profound Effects on Male Reproductive Function

We now know that male infertility and poor semen quality are associated with reduced general health, many chronic illnesses, and even a shorter lifespan. As listed in Table 2.1, a medication that treats an illness can improve reproductive symptoms as the man's general health improves, while at the same time exerting a toxic effect on reproductive function. Four approaches have been used to separate the effects of disease from the effects of a medication: (1) Randomized, placebo-controlled trials of men being treated for the condition; (2) measuring outcomes before and after new administration of the drug; (3) measuring outcomes during drug exposure then after cessation of the drug; and (4) treating healthy individuals with the drug. In the latter case, information is provided on the effect of the drug alone, but this may not be as useful for making clinical decisions because it doesn't address what is happening in the patients who present with infertility while under treatment for a disease condition. RPCTs are not always possible for men with disease.

How an illness affects male reproduction can be related to the constitutional effects of the illness, like a chronic inflammatory state (e.g., fever, hypertension), or to destruction/functional effects on male reproductive tissues (e.g., BPH, genital tract infection). Molecular spermatogenic genetic predisposition can also be involved. Clearly, medications can play an important role in the entire multi-factorial process of reproduction.

2.7 Mechanism of Toxicity Is Often Obscure

The best information available about the comparative toxicities of required medications is important for reaching the goal of minimizing adverse drug reaction while enabling our patients to become fathers. Although there are hypotheses and models explaining the mechanism of drug toxicity in most cases, we are rarely certain, which hinders our ability to treat or manage medication-induced infertility.

2.8 Drug Interactions in Humans Have Not Been Studied

At best, studies are designed to look at the effect of a single drug, to compare multiple drugs, or to compare drug mixtures as is common for chemotherapeutic and antiviral regimens. Information about drug interactions is completely lacking. The result of poly-pharmacy, an increasing concern in medicine, is unknown. Generally younger patients in their reproductive years are taking fewer medications compared with older

Table 2.1 Medical conditions with negative reproductive effects in which medication benefit may mask its toxicity

Medical condition	Classes of medications	In vivo effect(s) of disease on sperm, semen quality, and fertility
BPH/LUTS	PDE5 inhibitors; α1-adrenergic antagonists; 5ARIs	Ejaculatory dysfunction; low semen volume or aspermia
Chronic pain	Opioids	Low T levels
Depression	Antidepressants	Ejaculatory dysfunction; no effect on semen quality
Epilepsy	Anticonvulsants	Endocrine abnormalities, poor semen quality, infertility
Genital tract infection	Antibiotics	Decreased semen quality and DNA fragmentation
HCV	Interferon-α/ribavirin	Low T levels; low free T levels, lower LH, FSH, inhibin b; low gonadotropin response to GnRH challenge; low testicular volume; poor semen quality; increased frequency of disomic and diploid sperm
HIV	NRIs, NNRIs, protease inhibitors, fusion inhibitors, and integrase inhibitors	Reduced semen quality related to stage and duration of disease; low free T levels
Hypertension	α2-Agonists, α-antagonists, β-blockers, calcium channel blockers, ACE inhibitors, diuretics	Ejaculatory dysfunction; poor semen quality
Metabolic syndrome; Type 2 DM	Metformin	Poor semen quality
Schizophrenia; bipolar mania	Antipsychotics, lithium	Increased prolactin and LH levels; decreased T; ejaculatory dysfunction; poor semen quality
Sickle cell disease	Folic acid, hydroxyurea, diphenhydramine, NSAIDS, opioids	Low total sperm count
Surgery	Opioids	Decreased T levels
Systemic inflammation (organ transplant, autoimmune disease; chronic inflammatory diseases including IBD)	Immunosuppressants	Decreased steroidogenesis; decreased spermatogenesis

5ARIs 5α-reductase inhibitors, *BPH* benign prostate hyperplasia, *CHF* congestive heart failure, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *IBD* inflammatory bowel disease, *LH* luteinizing hormone, *LUTS* lower urinary tract symptoms, *NNRIs* non-nucleoside reverse transcriptase inhibitors, *NRIs* nucleoside reverse transcriptase inhibitors, *PDE* phosphodiesterase, *T* testosterone

patients. However, the effect of multiple medications, that may or may not have other systemic effects and adverse reactions, could still have a role in male reproduction/spermatogenesis. We cannot forget that illness, especially chronic illness that affects men's health, may result in general compromise of reproduction along with the medications as mentioned above.

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