Pharmacoethics and Pregnancy: Overcoming the drug orphan stigma

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Abstract

There is paucity of evidence to support clinical decision making and counseling related to medication use in pregnancy. Despite multiple efforts from legislative bodies and advocacy groups, the inclusion of pregnant women in clinical drug trials assessing efficacy and safety remains scarce. Pregnancy can be complicated by multiple co-morbidities that require pharmacological intervention; these interventions primarily target the pregnant women but also sometimes have secondary effects for the fetus. The U.S. Food and Drug Administration has issued multiple guidance documents on incorporating pregnant women in clinical trials to aid pharmaceutical companies in designing a protocol to ensure safety and adherence to ethical standards. Advances in pediatric pharmacology studies provide lessons for researchers on the best practice of designing clinical trials with inclusion of patients from special populations. In this review, we present the status of pregnant women in clinical trials, highlighting the ethical stigma and possible future directives.

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Abstract

There is paucity of evidence to support clinical decision making and counseling related to medication use in pregnancy. Despite multiple efforts from legislative bodies and advocacy groups, the inclusion of pregnant women in clinical drug trials assessing efficacy and safety remains scarce. Pregnancy can be complicated by multiple co-morbidities that require pharmacological intervention; these interventions primarily target the pregnant women but also sometimes have secondary effects for the fetus. The U.S. Food and Drug Administration has issued multiple guidance documents on incorporating pregnant women in clinical trials to aid pharmaceutical companies in designing a protocol to ensure safety and adherence to ethical standards. Advances in pediatric pharmacology studies provide lessons for researchers on the best practice of designing clinical trials with inclusion of patients from special populations. In this review, we present the status of pregnant women in clinical trials, highlighting the ethical stigma and possible future directives.

Introduction

Pregnant women are poorly represented in clinical drug trials. Around 80% of pregnant women receive medication during pregnancy, most of which are used in an off-label manner and lack information on potential teratogenicity [1]. In fact, from 2000 to 2010, the U.S. Food and Drug Administration (FDA) approved 172 new drugs, 98% of which lack data on teratogenicity and 73% had no data on safety for use during pregnancy [2]. Many women with pre-existing conditions such as asthma, chronic hypertension, and diabetes might be taking medication prior to conception. In addition, the physiologic changes in pregnancy can exacerbate existing medical conditions or induce new medical conditions that require treatment. This highlights the importance of the availability of safety data on drugs prescribed during pregnancy. To complicate matters further, the doses of drugs used during pregnancy are extrapolated from clinical drug investigations performed in men and non-pregnant women and/or from animal models, raising questions about the pharmacokinetics and pharmacodynamics of these drugs during the different stages of pregnancy [3].

One of the landmark events in obstetric pharmacology was the thalidomide disaster that occurred in the 1960s. This drug, used for morning sickness in pregnant women, was found to be teratogenic, causing devastating skeletal deformities in prenatally exposed fetuses [4]. Another drug, diethylstilbestrol, a synthetic estrogen, was initially prescribed to women with threatened pregnancy loss and then was marketed as routine for prophylaxis of possible pregnancy loss for all pregnancies during the 1950s [5]. Twenty years later after continued and extensive use, a small study showed an increased risk of clear cell carcinoma of the vagina in females born to diethylstilbestrol-exposed pregnant women among other comorbidities before regulatory action was taken to curtail its use [6]. Historically, after the thalidomide and diethylstilbestrol negative outcomes, the US FDA has excluded pregnant women from phase 1 and phase 2 trials in 1977 over concerns for the safety of administering drugs in pregnancy, after which the pharmaceutical companies extended this exclusion into phase 3 and phase 4 [7]. These examples among many others underscore the importance of risk and benefit assessment of medication use during pregnancy. However, the current evidence to support this assessment is sparse. In this review, we aim to highlight a) the need for inclusion of pregnant women in clinical trials, b) what legislative actions were taken to curtail obstacles for their inclusion, and c) possible solutions for clinical pharmacology researchers.

The Ethical Dilemma across history

Prioritizing protection of the fetus was an important factor that prevented pregnant women to participate in clinical drug trials. Several federal regulations now request clarification on inclusion criteria by defining whether the fetus or the pregnant woman are being targeted, and whether the study aims to highlight

therapeutic or non-therapeutic outcomes [8]. In 1974, after the devastating thalidomide disaster, congress asked the newly established National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to make recommendations for the conduct of research involving pregnant women and fetuses (Federal regulations at subpart B of 45 CFR 46) [9]. Dr. Kelsey, who was the primary reviewer of the thalidomide application assigned by the FDA, delayed the approval of thalidomide over concerns of adverse effects and the drug was never approved in the United States [10]. The aim of the recommendations thus was to protect the fetus from unnecessary harm. More than twenty years later and after much deliberation, the wording was changed in 2001 to include a more proscriptive approach; stating that pregnant women or fetuses may be involved in research if all of 10 conditions are met **(Table 1)** . In 2002, a registry for reporting adverse effects was established. In 2004, the FDA developed the guidance on pharmacokinetic (PK) studies in pregnancy, and, in 2005, guidance was provided on clinical lactation studies and pregnancy [11]. In 2009, the Second Wave Initiative was launched aiming to systematically address the knowledge gap on treatment of pregnant women in a collaborative manner [12]. The FDA has also addressed drug labeling to include risk summary and clinical consideration in an effort to improve patient care decision and counseling under the Pregnancy and Lactation Labeling Rule (PLLR) [7]. This was first proposed in 2008 with the revised version put in action in 2014. While much has been done to support the moral imperative of including pregnant women, much more needs to be done to ensure that we provide pregnant women with beneficence, autonomy, and justice.

Pitfalls of Maternal Physiology and Placental Transfer

Substantial changes in maternal physiology complicate the extrapolation of the safety profile and dosing of drugs. Changes in the cardiovascular, renal, and gastrointestinal systems affect the absorption, distribution and excretion of certain drugs given to the pregnant woman during pregnancy [13]. There is no doubt that drug pharmacokinetics are different in pregnancy and non-pregnant state and, ideally, drug properties should be studied in every trimester and in the postpartum period. However, these trials are challenging to conduct, and the information is scarce, which is why researchers often rely on opportunistic studies in which patient are already receiving the therapeutic agent in question [14, 15]. In addition to that, the placenta was thought to be an impenetrable barrier that protected the fetus from harmful agents including medication. However, after the thalidomide incident, challenges have been unearthed to explore mechanisms of transfer of compounds across the lipid membrane [16]. Several mechanisms have been proposed to explain the drug transfer across the placenta including simple diffusion, facilitated diffusion, pinocytosis, and active transport. Ongoing research is crucial in identifying potential drugs that follow the trajectory of maternal to fetal transfer, and the molecular characteristics of compounds. Uncharged lipophilic drugs tend to transfer readily [17], whereas size does not usually limit transfer as most drugs have a molecular weight of less than 500 Daltons [18].Insulin and enoxaparin are two examples of drug transfers that are limited due to size [19, 20]. Human placental drug transfer studies are often limited to drugs given near time of delivery. This limitation to study design led to development of ex vivo perfused human placental models which represented a non-invasive and effective method of studying transplacental transfer [21].

Importance of data on drugs for pregnant women

Physician Counseling

Counseling is a key concept in any patient encounter, particularly when it comes to initiate new therapies during pregnancy as it helps consolidate a patient-centered practice. In fact, informing patients about the indication, dosage, regimen, side effect(s) and alternatives can improve adherence and limit therapeutic failure, or help to recognize adverse effects that otherwise might result in unnecessary diagnostic tests and hospitalization [22]. It is imperative for providers during the prenatal visit to obtain a thorough history about medical problems and medications used to treat them, and to screen for herbal medicine use in pregnancy which is particularly important as the use of complementary and alternative medicine is high globally [23]. Some women might have stopped taking their medications prior to the first visit with a provider after finding out they are pregnant. This action can sometimes lead to deleterious consequences. For example, women treated with SSRIs for depression who have discontinued the medication of fear of fetal concern may have

relapses and suicidal ideation [24]. On the other hand, counseling may help prevent unnecessary pregnancy termination because of perceived high fetal risk not knowing the accurate extent of the risk in question due to lack of proper information [25].

During the counseling, the provider must also distinguish between teratogenicity which entails structural abnormalities to the fetus in the first trimester and fetotoxicity referring to functional damage later in pregnancy [26]. While the teratogenicity profile of some drugs has been established through prior animal studies, detecting fetotoxicity requires more research particularly as some effects pertaining to neurodevelopment might not be evident until childhood. Women prefer to seek information about medication use in pregnancy directly from their healthcare providers. However, the challenge arises when there is lack of evidence-based data to appropriately display a risk-benefit assessment for the patient to decide [22, 27]. Database such as LactMed®[28] and Reprotox®[29] are some of the common resources utilized by clinicians when counseling patients, but these databases can often give inconclusive recommendations given the paucity of evidence available.

Treating life-threatening diseases and those associated with morbidities

There is a considerable increase in maternal comorbidity including obesity, hyperlipidemia, diabetes, and hypertension in recent years worldwide. Many of these comorbid conditions have been linked to higher rates of pregnancy-related morbidity and mortality [30]. Asthma for example can be common in pregnancy and in some cases worsens due to physiological changes. In one study, it has been shown that there has been a reduction in prescriptions of asthma medication during the first trimester of pregnancy [31, 32]. However, it is important to control asthma symptoms during pregnancy despite the safety profile of some medications used. Uncontrolled asthma can lead to complications including preeclampsia, preterm delivery and low birth weight [33]. This is a compelling example where risks of uncontrolled asthma outweigh potential risks of neonatal fetotoxicity from exposure. Another example are oral steroids like prednisone. Prior observational studies have reported cleft lip and cleft palate when prednisone was used early in pregnancy but those results were not consistent over time [34].**Table 2** highlights controversial medications that need additional counseling given their possible or known adverse effects on the fetus. There is much controversy in interpreting population-based studies and animal studies when it comes to teratogenicity and fetotoxicity. Some drugs that showed adverse effects in animal models were not matched when studying human population and vice versa. Statins, which are now being investigated as potential drugs to prevent preeclampsia have been previously contraindicated in pregnancy. However, a recent meta-analysis including 16 human studies showed no relationship between statins and teratogenicity [35]. More recently, the FDA has requested removal of the contraindication of statins in pregnancy [36].

Improving the infrastructure of research seems to be something that would benefit the moral imperative to incorporate pregnant women into clinical drug trials. Pharmacoepidemiologic studies are limited by the fact that often disease and severity are related to exposure and adverse outcome and that systematic bias is not usually accounted for when the pharmacologic exposure or the disease itself was the cause of fetotoxicity. For example, autoimmune diseases like rheumatoid arthritis, inflammatory bowel disease or lupus might exacerbate during pregnancy. In these diseases it has been noted that there is an increased risk of low birth weight, preterm birth and associated morbidities with current treatment options, but whether this is in an effect of the treatment per se or the disease itself is hard to decipher [37-39].

The effect of the regulatory bodies on clinical trials in pregnancy

Pregnant women have previously been categorized as a "vulnerable population' with special consideration enforced by regulatory bodies when including them in research. The American College of Obstetrics and Gynecology instead recommended that pregnant women be categorized under "scientifically complex," and recently the Common Rule, the federal policy for the protection of human subjects, has been revised in 2019 to remove pregnant women from the vulnerable population category [40]. However, despite that, some institutional review boards (IRB) may still feel reluctant given that there is no practical guide to address the risk and benefits of enrolling pregnant women into clinical trials [41]. Two important steps to curtail this is

to involve experts in the field of maternal-fetal medicine and obstetrics pharmacology in board meetings and to require justification for exclusion of pregnant women and that this justification may be questioned during review [42]. IRB interpretation of the regulatory process has some flaws [11], particularly when it comes to the wording of "minimal risk of the fetus." When submitting to the IRB of the academic institution or other regulatory bodies, researchers may present preclinical and animal studies corroborating the risk to the fetus, but with concern that these studies are evaluated by the IRB regulatory staff and due to the dearth of available data may not be sufficiently supportive or convincing[11]. For that reason, there is wide agreement to clarify regulations for enrolling pregnant women in trials and develop practical guidelines that can be universally implemented [15].

The FDA previously had regulatory rules in place that restricted inclusion of pregnant women in clinical trials, citing that woman should only be included if there is direct benefit to the woman or fetus with minimal risk or if risk is solely related to the intervention in question [43]. In their revised guideline in 2018, they have recommended excluding pregnant women from phase 1 and phase 2 trials and allow enrollment later. Federal regulations require investigators to consider the interest of the pregnant woman and fetus, raising the ethical question of whether the fetus is considered a patient. One argument involves a dependent moral status to be deemed on the fetus, which is based on the expectation of whether the fetus is to achieve the moral status of becoming a child and a person [44]. It is only when the pregnant woman considered the previable fetus a patient and therefore invoke the dependent moral status, then the healthcare provider and patient should have a thorough discussion about the beneficence of protecting the fetus from harm.

Pharmaceutical companies have long feared including pregnant women in clinical trials even during the phase 3 and phase 4 of the process. In response to that, the FDA has issued a guidance for industries to better design clinical trials. It highlights emphasis on pharmacokinetic and pharmacodynamic studies of drugs in pregnant women, particularly if that population is to benefit from the drug. In addition, in 2002, the FDA also issued a guidance on reporting adverse effects of medication in pregnancy and that surveillance should not be limited to the post-marketing phase. The recent events of the COVID-19 pandemic have highlighted the deficiency and reluctance posed on including pregnant women in trials. In a recent analysis, it has been shown that pregnant women have been excluded from the therapeutic clinical trials involving the COVID-19 infection, despite most medications used showing low or non-significant safety concerns, except for remdesivir [45]. This only increases the concerns that despite guidance and call to action initiatives, there is no legal framework to enforce its implementation.

Extrapolating innovations from pediatric clinical trials

While neonates and children have been lumped with pregnant women under the umbrella of vulnerable populations, numerous advances have led to success in conducting pediatric clinical trials [46]. Quality of clinical data in pediatrics has stemmed from the fact that investigators tend to include multiple drugs in a single protocol, extensive pharmacokinetic and pharmacodynamic modeling and incorporation of multiple sites [47]. As for legislative processes, the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) contributed to the development of drug trials in the pediatric population. The BPCA provided incentive for drug development and PREA enforces pediatric studies to be conducted of medication that would help the health of children. Incentives included exclusive marketing by manufacturers for an additional six month for conducting pediatric-focused studies, which can translate to up to 500 million dollars in revenue for each drug [48]. Unfortunately, these do not yet apply to the pregnant population.

Recent innovations in clinical trial design allowed the development and use of population-based pharmacokinetic and pharmacodynamic modeling to better understand the mechanism of drugs within the physiologic milieu [49, 50]. These advances will likely help optimize selected drug doses and understand interaction with tissues in an attempt to minimize unwanted adverse effects to the fetus. These models have been described by Mendes and Zhang [49, 50]. Population pharmacokinetics-pharmacodynamics studies have been used in pediatric clinical trials and have been found to be very helpful as they incorporate drug properties, physiologic variables, and target tissues to determine effect [51]. Despite its success in pediatric populations, its use in the pregnant population seems underutilized.

A multi-disciplinary collaboration is necessary to optimally design and conduct clinical drug trials in pregnant women. For example, if a rheumatologist wishes to conduct a trial on effective treatment of rheumatoid arthritis flare and include pregnant women, a collaboration with maternal-fetal medicine and neonatology specialists should be considered to optimize outcome of the study and avoid adverse effect of treatment or disease on the fetus.

A complex twist: treating the fetus through the pregnant woman

Some fetal conditions are treated through transplacental transfer of drugs adding a complex layer on the safety of drugs. While the drug is administered to the pregnant woman and has known maternal side effects, the primary indication is to treat the underlying fetal condition. One important condition is fetal arrythmia (i.e. supraventricular tachycardia) in which studies have shown benefit in administering digoxin, sotalol, and flecainide among other antiarrhythmic medications [52]. In this unique circumstance often added maternal monitoring by electrocardiogram is advised to balance maternal/fetal well-being. Another example is prevention of congenital toxoplasmosis. Spiramycin, a well-known macrolide, has shown to decrease transmission of toxoplasmosis in a seropositive pregnant woman by 60%. Due to its chemical properties, it tends to concentrate in the placenta and rarely transfer to the fetus mitigating adverse effects and fetotoxicity [53].

Conclusion

The Belmont Report originally published in 1979 enforces the adherence to the basic ethical principles in research including beneficence, justice, and respect to persons. We need a call to action by all stakeholders (i.e. legislative agencies, pharmaceutical companies, funders and academic researchers) to prioritize including pregnant women in clinical trials. It helps not only make a better risk-benefit assessment, but also help prevent adverse effects in the fetus or the pregnant woman when it is medically needed to give medications. We should strengthen the pregnant woman's autonomy to be able to participate in clinical trials if she wishes and that this should not be a predicament; at the same time monitoring for fetotoxicity should be standardized and required in clinical research. If pregnant women are not included in future drug research studies, they will lag behind in terms of receiving benefits of therapeutic advancement compared to the general population. Learning from pediatric drug advances, clinical research involving pregnant women has a promising road ahead.

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Table 1. The ten requirements for inclusion of pregnant women in clinical trials outlined by the FDA [43]

1	Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, includi
2	The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the
3	Any risk is the least possible for achieving the objectives of the research;
4	If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to
5	If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and
6	Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably for
7	For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisio
8	No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9	Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to
10	Individuals engaged in the research will have no part in determining the viability of a neonate.

Table 2. Some medications with controversial use in pregnancy

Medication	Condition
Amitriptyline	Major depressive disorder; Migraine prophylaxis
Lithium	Bipolar disorder
Paroxetine; Fluoxetine	Major Depressive Disorder
Prednisone	Inflammatory conditions including rheumatoid arthritis, lupus nephritis, inflammatory bowel disea
Statins	Dyslipidemia
Warfarin	Thromboprophylaxis in patients with mechanical heart valve

Figure 1. Timeline of advancements in policy making towards drug trials in pregnancy