

## Article

# Ethical, legal, and regulatory issues regarding the study and use of medications in pregnant women

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## ABSTRACT

Despite the prevalence of off-label drug prescriptions for pregnant women, little attention is paid to the ethical, legal, and regulatory issues regarding this practice. This paper discusses some of these key issues relevant to the practice of off-label medication use by women during pregnancy.

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## INTRODUCTION

THE THALIDOMIDE TRAGEDY of the 1950s and 1960s is one of the most notorious cases of how dire the outcome can be when pregnant women consume a drug that is untested on pregnant women. While the FDA never approved thalidomide for use in the United States, it was marketed in other countries to treat nausea in pregnant women despite never having been tested for safety on this patient population. By the 1960s, it was banned because it was found to be a teratogen and caused serious limb birth defects in an estimated 8,000 to 12,000 babies.<sup>1</sup> Most of these babies were in West Germany, but there were also incidents of thalidomide-induced birth defects in Egypt, Belgium, Brazil, England, Israel, Sweden, Switzerland, and the U.S.<sup>2</sup> The thalidomide incident launched a shift into the modern era of pharmacovigilance — one in which not only efficacy, but adverse effects, are considered during regulatory review. It also left a legacy in the clinical realm, for now it is not uncommon for pregnant women to be undertreated by their physicians for medical problems due to fear of the unknown teratogenic effects of drugs. Despite these

unknown effects, drugs are still prescribed to treat pregnant women for medical conditions.

While the FDA may approve a drug for a specific indication, once the drug is approved for marketing, physicians can prescribe the drug for any reason, including for indications that are not approved by the FDA. Because of this, the lay public may not be aware that most of the drugs that are prescribed to pregnant women are not indicated for pregnant women nor are there studies to confirm the safety of a given drug during pregnancy. In 2000, a review of the Physicians' Desk Reference indicated that 40% of the drugs listed contained no advice at all regarding the use of the drug during pregnancy.<sup>3</sup> Of the drugs that did mention "pregnancy," less than half were classified in accordance with FDA pregnancy category ratings. Given how prevalent drug use is during pregnancy, there is very little information on long-term safety of drugs, much less information on the teratogenicity of most drugs.

Every year, more than 4 million women become pregnant and give birth.<sup>4</sup> Despite these numbers, pregnant women are a marginalized subpopulation of the adult population when it comes to clinical research and data. It is true that pregnant women do not bear the burden of being research subjects; but because of this, they have no benefit from the disproportionate amount of resources allocated to other groups in society. Unfortunately, pregnancy does not confer immunity from any of the chronic conditions that may affect a

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women who becomes pregnant including hypertension, diabetes, psychiatric conditions, autoimmune conditions, etc. Further, pregnant women are considered part of the immunocompromised population, making them (and their fetus) more vulnerable to infections that may need to be treated and supported with medications.

According to CDC Data & Statistics (2013), about 90% of women take at least one medication during their pregnancy (over-the-counter (OTC) and/or prescription). Regarding OTC medications, 65% of pregnant women take acetaminophen, 18% take ibuprofen, 15% take pseudoephedrine. In addition, 70% of women take at least one prescription medication during their pregnancy. With regard to prescription medications, 4.5% of women used an antidepressant before/during pregnancy, and 29.7% of women used antibiotics before/during pregnancy.<sup>5</sup> In addition to treating depression and infection, many pregnant women have health issues including heart disease, diabetes, psychiatric disorders, cholesterol, etc that may need to be controlled with medications.

According to Peters et al (2013), from 2000 to 2010, over 70% of FDA-approved medications had no published data on birth defect risks in humans and 98% had insufficient data to draw conclusions about the risk of birth defects. Despite the lack of published studies, many websites (which is where many women do their research) claim that certain medications are safe for pregnant women despite the lack of controlled studies to confirm safety.<sup>6</sup> According to Lyster et al (2001), only 12 drugs are approved and specifically indicated for pregnant women. All of these drugs that are approved for pregnancy are specifically for gestation and birth-related situations such as nausea, vomiting, preventing congenital malformation, and labor induction.<sup>7</sup> None of them are indicated to treat illnesses during pregnancy such as cancer, depression, hypertension, diabetes etc. When these medications are used during pregnancy, they are prescribed by a physician for off-label use and with no FDA-approved guidance to ascertain the safety of these medications for pregnant women.

There are divergent interests at stake in this issue, including the interests of the mother, the fetus, industry, prescribing physicians and society. Pregnant mothers may have chronic conditions that require medical treatment, and it's in their interest to know which medications are safe during pregnancy since they play a primary role in safeguarding the fetus. Physicians also have an interest in knowing which drugs are safe to prescribe to their patients to help them manage their medical needs during pregnancy. Industry has an interest to be profitable and bring safe and effective drugs to market. If drug companies were required to do clinical trials for pregnant women before approval because a pregnant woman might take the medication post market, this would

significantly add to the expense and time it takes to bring a drug to market. This may or may not be at odds with society's interests. On the one hand, society would benefit from knowing specific teratogenic data on a given drug because the social and monetary costs of children born with birth defects is high; however, society also would benefit from drugs being marketed at a relatively affordable price point. If every drug were required to be tested on pregnant women before being brought to market, this would significantly increase the cost of development which would be passed on to other members of society who may need the drug. On the other hand, an untested drug that is eventually found to harm fetuses when taken by pregnant women may be more vulnerable to lawsuits and litigation which would also drive up drug costs.

Pregnancy and birth are key, pivotal transition periods for women, families, and society; and safeguarding the health of mothers and babies is an important endeavor. The thalidomide tragedy, unfortunately, was not the last case in history in which a drug administered to pregnant women resulted in harm to the baby. Other drugs since thalidomide have been shown to have deleterious effects, sometimes many years after the drug was being marketed. One example that will be discussed later includes diethylstilbestrol (DES), taken by pregnant women to prevent miscarriage from 1943 to 1971. DES was shown to cause cancer in the daughters who were exposed to the drug in utero. Another example are the angiotensin-converting enzyme inhibitors used to treat hypertension. Women who used these drugs to treat hypertension in their 2<sup>nd</sup> and 3<sup>rd</sup> trimesters were more likely to give birth to babies with fatal neonatal renal issues.<sup>8</sup> In the case of valproic acid, use during pregnancy is associated with spina bifida as well as cardiac, craniofacial, skeletal, and limb defects.<sup>9</sup>

There are two major consequences that result from the inadequate safety data of drugs on pregnant women: 1) harmful drugs will injure babies and 2) uncertainty in the science may lead to judicial litigation. Every year, there are a number of babies who are born with birth defects with unknown cause. Given that many people seek to find a reason for why a tragedy occurs, drugs that were taken during the pregnancy may be the scapegoat in a lawsuit even if the drug did not cause the birth defect. This litigation effectively results in driving up the cost of the drug and may even result in the drug being taken off the market. It is not ideal for a jury of lay-people (with little scientific education) to make decisions of whether a drug is responsible for injury, especially since they often are basing these decisions on inadequate data. Even if a drug is confirmed to be harmful to a developing fetus, taking it off the market is not ideal when the drug is helping other population groups who do not include pregnant women. For example, thalidomide, despite its

notoriety as a teratogenic drug, is showing great promise as a therapeutic drug for AIDS and cancer.<sup>10</sup> Safety data is best ascertained in adequately-controlled studies so that a given drug can be confirmed or denied as safe for pregnant women. This would allow physicians to prescribe drugs with the appropriate knowledge of the real risks. However, obtaining safety data in pregnant humans is not without its ethical, legal, and regulatory complications — issues that will be discussed in this paper.

## REGULATORY ISSUES

The FDA requirements for pregnancy and lactation labeling is found in 21 CFR Part 201. The FDA Pregnancy Category System (established in 1979) categorizes drugs into 1 of 5 categories to guide doctors in prescribing drugs to their patients. In 1997, this system was further revised in an attempt to add more useful data so that a prescribing physician would have more clinically useful information. The following summarizes the current “ABCDX” system.

- Category A: Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus
- Category B: No evidence of risk in humans. Either animal study shows risk, but human findings do not; or, if no adequate human studies have been performed, animal findings are negative for risk.
- Category C: Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify potential risk.
- Category D: Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk
- Category X: Contraindicated in pregnancy. Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk, which clearly outweighs any possible benefit to the patient.

According to Boothby & Doering (2001) only 3 drugs are labeled as category A and they are thyroid hormones, folic acid, and prenatal vitamins.<sup>11</sup> Drugs that are labeled as Category X drugs are contraindicated in pregnancy due to an established link between their use and birth defects and include drugs like warfarin, live vaccines, iodides, diethylstilbestrol, and finasteride. Boothby & Doering (2001) discuss some of the major limitations of the current system including the lack of data on drug effects in pregnant women, overemphasis

on animal studies, lack of clinically practical interpretation of the “C” category of drugs (which account for more than 60% of the drugs in the Physicians’ Desk Reference), and high burden of proof required to assign drugs to the “A” category. The ABCDX system also oversimplifies other aspects of pregnancy and drug exposure including timing of when the drug is exposed (first trimester, second trimester, third trimester, etc) and does not take into account the importance of gestational age or organogenesis at 31-72 day of fetal life. The current system also does not account for changes in pharmacokinetics during pregnancy that would affect drug dosage, nor does it address the safety of the drug during breastfeeding.<sup>11</sup>

To note, in 1999 and 2008; the FDA proposed to revise the ABCDX pregnancy labeling system.<sup>12</sup> As of February 2011, the Final Rule is in the writing and clearing process and has not been adopted as of today to my knowledge. The proposed rule on Pregnancy and Lactation Labeling would eliminate the ABCDX system, and in its place have a narrative that includes standardized statements that would have a one-sentence risk conclusion. For example, “Human data do not indicate that Drug X increases the overall risk of structural anomalies” and state whether this is based on human or animal data.<sup>13</sup>

Prior to 1993, women were largely excluded from clinical trials altogether for fear that they may become pregnant and for other reasons which had the effect of making women grossly underrepresented in biomedical research.<sup>14</sup> According to Charo (1993), there are several reasons for this. The first is the inherent sexism bias in which the male body is considered the norm, while the woman’s body is considered more complicated than is necessary due to hormonal fluctuations and menstrual cycles — a “wildcard” because it would complicate studies to include them. The paradox of this is that the findings that are based on studying only men are then extrapolated to women as though they are the same. The second is that it makes more financial sense to exclude women because by studying just men, the data is more homogenous. If women and pregnant women were to be included, particularly in Phase 1 and Phase 2 clinical trials, the costs to bring a drug to market would significantly increase because the lack of homogenous data would require a larger study population to demonstrate efficacy. The third reason why pregnant women were excluded was that drug companies feared the liability if a drug caused harm to the fetus and resulted in birth defects.<sup>14</sup>

Despite the perceived complications of how drugs may affect a pregnant woman, there is industry guidance for how to proceed if a drug is discovered to be teratogenic. The FDA advises that a Risk Minimization Action Plan be developed for these drugs to minimize in utero

exposure. The FDA's guidance paper on RiskMAP suggests that RiskMAPs be designed to achieve specific objectives (such as pregnancy prevention). One such risk-management program in place is iPLEDGE, a distribution program for the drug Accutane designed to reduce the number of pregnant women taking the drug and reduce the number of unplanned pregnancies in women who are taking the drug.<sup>15</sup>

Due in part to the DES incident (which was experimentally prescribed to pregnant women to prevent miscarriage from 1943 to 1971) causing cancer in the daughters, in 1977 FDA disallowed fertile women from being enrolled in clinical trials in Pre-marketing Phase 1 and Phase 2 studies (studies that look for human dose-ranging and efficacy as well as teratogenic animal studies). Because of this, most drugs are approved without ever having been tested for their effects on pregnant women.<sup>14</sup>

In 1993 the FDA, realizing that there needed to be proper evaluation of drugs in women, changed some of its policies in an effort to include more women of child-bearing age in biomedical research. Prior to this change in policy, women with "childbearing potential" were excluded from early phase clinical trials. Because pregnant women are considered a vulnerable population, and because of the potential complications of study results of having pregnant women in trials; pregnant women are still, for the most part, systematically excluded from clinical trials.<sup>16</sup> The exclusion from clinical trials guarantees that fetuses won't be harmed by an experimental drug, but that ultimately leaves little guidance for how doctors are able to manage disease and illness in their pregnant patients. Though the FDA made changes to encourage women entering clinical trials, women who become pregnant while enrolled are typically dropped from studies. If pregnant women are so excluded from drug development studies, how *does* the scientific and medical community obtain knowledge on the safety of drugs on pregnant women? Most of the clinical research on a drug's effect on pregnant women are obtained in post-marketing or Phase 4 studies.<sup>17</sup>

The following diagrams the stages of clinical drug development.

**Premarketing: Phase 1, Phase 2, Phase 3**  
**Drug approved for marketing**  
**Postmarketing: Phase 4**

One program that attempts to collect safety data on a drug's effect on pregnant women is MEDWatch. According to Kessler (1993), many health professionals don't report adverse events associated with medications to the FDA. A clinical trial before a drug is marketed may have safety data for hundreds to thousands of patients,

but if there are serious adverse events that occur in one in 5000 or one in 10,000; these would be missed in those trials.<sup>18</sup> The other issue that can occur that is not addressed adequately in pre-market studies is the way a drug interacts with other drugs a patient may be taking. FDA actions can only work if physicians are actively reporting adverse effects. For example, in 1991, based on reports to FDA, the FDA was able to warn prescribing physicians about the dangers of using angiotensin-converting enzyme inhibitors during the second and third trimesters of pregnancy. The estimate is that only 1 % of serious adverse events are reported to the FDA.<sup>19</sup>

One reason for why the reporting is so low is that the culture of physicians reporting is not ingrained. The MedWatch program of FDA is an attempt to simplify the reporting process so that serious adverse events that are drug and medical device related can be appropriately reported in a timely way.

Another way that the effect of drugs on pregnant women is monitored is through pregnancy exposure registries. Pregnancy exposure registries are created to collect clinically relevant data that can be used on the product's labeling and to give healthcare providers useful information in treating patients during pregnancy.

FDA Pregnancy Exposure Registries are post-market, prospective, observational studies in which pregnant women enroll when they take a drug or vaccine before the outcome is known in order to obtain clinically relevant data for the drug's label. Although there are spontaneous reporting registries, there are limits because of recall bias, poor documentation, lack of control groups; so studies from exposure registries can help counteract these limitations. The FDA recommends (but does not require) a pregnancy exposure registry be established when the medical product is likely to be used during pregnancy, likely used by women of childbearing age, or it presents a special circumstance such as potential of the fetus being infected from a live, attenuated vaccines. Other cases where it may be important to establish a pregnancy exposure registry is if animal toxicology studies indicate toxic effects to the fetus based on pharmacological class, human case reports, or structure-activity relationships. In some cases, the FDA may require the company to conduct an exposure registry under an IND before approval.

## ETHICAL ISSUES

### JUSTICE

One major ethical principle relevant to the issue of pregnant women and research is the concept of justice, which refers to the principle of fairness. According to Faden

(2010), there are four issues of injustice with regard to pregnant women being excluded from clinical research. Being excluded from clinical research 1) denies pregnant women the benefits of participating in research, 2) results in pregnant women's interests being underrepresented, 3) results in pregnant women carrying a disproportionate burden from research findings, and 4) disrespects pregnant women.<sup>20</sup> Denying pregnant women the benefits of participating in research means that these individuals are denied the possibility of new therapies and technologies that could benefit them (such as the case with AIDS). The second issue is that pregnant women's interests are underrepresented. Biomedical research receives a lot of funding and in a just society, resources should be allocated in a proportionate way. Pregnant women's interests are underrepresented, and a disproportionate amount of funding goes to support other groups. Another issue of injustice occurs because pregnant women carry a disproportionate burden from the lack of knowledge. Physicians notoriously undertreat pregnant women for fear of causing harm because of the lack of research on effects of medications on pregnant women.<sup>16</sup>

## RESPECT FOR PERSONS

The issue of including pregnant women in trials include the question of respect for persons and respecting the autonomy of the pregnant woman giving consent. The question may also theoretically apply to the fetus and whether the fetus (who has diminished autonomy) and cannot give consent is entitled to certain protections. This is one reason that pregnant women and women of childbearing age were have been excluded from drug trials. While this protects the woman and fetus from the burdens of research, it also denies them the benefits that these two underrepresented populations would benefit from.

## AUTONOMY

Because the FDA prohibited formal testing of drugs on pregnant women (in Phase I and II) as a result of the DES incident and industry tends to not want the expense of formal testing of drugs on pregnant women in pre-market studies; the majority of the knowledge gained of the effects of drugs on pregnant women is gained in post-market studies. Since physicians are permitted to prescribe a drug for off-label use for pregnant women all pregnant women who consume medications are, in a sense, participating in an experiment. This violates the principle of autonomy because all pregnant women who

are taking a drug become un-consenting, post-market research subjects.

## LEGAL ISSUES

The litigious culture has contributed to the current state in which a pharmaceutical president once stated that "no one in his or her right mind would work on products for pregnant women because of enormous liability risks such work engenders."<sup>21</sup> A similar situation occurred with the vaccine industry where individuals who were injured by vaccines brought civil suits against vaccine manufacturers. In one case of a vaccine injury, the manufacturer was liable for a punitive amount at 200 times the annual revenue that the vaccine generated.<sup>21</sup> Not only does this work as a negative incentive for future and current manufacturers to produce vaccines, but it also makes the cost of these treatments more expensive as the cost of these lawsuits gets passed onto consumers. Nobody doubts that drugs can sometimes be responsible for serious adverse effects, and those who are severely injured should have some recourse and compensation; but legal liability over time hurts industry and results in fewer treatments being available for those who need them. In the case of the drug Bendectin, there were more than 300 lawsuits pending that claimed damages for injured babies.<sup>22</sup> Courts awarded punitive damages such that the drug manufacturer's insurance premiums soared to \$10 million annually, a mere \$3 million less than the annual revenue. After a Washington DC jury awarded \$750,000 to a family, Merrell Dow withdrew the drug from the market. The result of such lawsuits is that Merrell Dow withdrew the drug from the market not because Bendectin was scientifically shown to cause birth defects but because the lawsuits resulted in Merrell Dow's insurance premiums soaring to \$10 million annually, a mere \$3 million less than the annual revenue.<sup>21</sup> One unfortunate consequence of having cases go through the court system is that a jury's decision may not necessarily be based on scientific evidence since juries are not uncommonly made up of lay people. The FDA found, after an intensive 2-day review of available data, that there was no causal link between Bendectin and birth defects though they did admit that no drug can be proven to be absolutely safe for every pregnant woman under all circumstances. Based on this, many have criticized the judicial system because a safe and efficacious medication was taken off the market for business reasons, and those who may stand to benefit from the drug no longer have access to it. Lawsuits de-incentivize drug manufacturers from making medications for pregnant women since lawsuits can make insurance costs. Lawsuits also have the effect of overall de-incentivizing

pharmaceutical companies from producing treatments for pregnant women.

Another legal issue is the conflicting standards of common law with FDA regulations. Existing legal norms exist such as state liability laws often have a higher standard than FDA standards and regulations. For example, the Supreme Courts of New Jersey and Kansas found that FDA judgments can be reevaluated by the courts in the context of civil lawsuits.<sup>23</sup> Because of this, pharmaceutical companies can be liable for breaching state common law duties to warn of potential side effects based on evidence that FDA had found insufficient to warrant a warning. In this case, a pharmaceutical company may be in full compliance with FDA regulatory requirements but be found liable under local tort law.

No discussion of pregnancy and drug case law would be complete without a discussion of diethylstilbestrol (DES), a drug approved by the FDA to be marketed for preventing miscarriage from 1947 to 1971 on an experimental basis and warned of that. The drug was eventually linked to a rare form of vaginal and cervical cancer in the daughters of the women who took the drug after a latency period of 10-12 years. In the Supreme Court case of *Sindell v Abbot Laboratories*, the plaintiff, Judith Sindell was the daughter of a woman who took DES during pregnancy. She filed suit against 11 drug companies since it was unknown which manufacturer made the precise drug (as it was a fungible, brand-interchangeable drug) that her mother ingested. At the time Sindell's mother was pregnant, there were over 200 companies that manufactured DES. In this case, the court decided to uphold a kind of liability known as market share liability in which the defendants, because they were all involved in manufacturing a fungible product that harmed the plaintiff, were responsible for a percentage of the damages equal to their market share of the product at the time the product was used.<sup>23</sup>

In general, when patients are allegedly injured by pharmaceutical products, they bring civil charges against pharmaceutical companies rather than prescribing physicians even if the physician prescribed the drug for off-label use. One example of this is with "fen-phen." Fen-phen was a combination of fenfluramine and phentermine, each of which were separately approved by the FDA for short-term treatment of obesity. Physicians were prescribing this combination for longer periods than what was approved and for patients who were not truly obese.<sup>25</sup> Despite this alleged malpractice on the physicians' part, it is the drug manufacturers who were sued by plaintiffs who claim that their heart valves were damaged from the combination. While the case of fen-phen did not specifically involve pregnant women, the precedent it sets is relevant, because plaintiff attorneys argue that pharmaceutical companies need to more actively

discourage off-label prescribing. The problem here is that off-label prescribing is ubiquitous for pregnant women because there are so few drugs that are specifically indicated for pregnant women; and these situations further increase the difficulty of pregnant women receiving treatments.

## CONCLUSION AND CALL FOR ACTIONS

Currently, most of the burden and liability of alleged drug injury falls on pharmaceutical companies. Bearing all the burden of liability hurts industry, which eventually hurts consumers. In the case of pregnant women, there are fewer research dollars being allocated to develop treatment drugs that are safe during pregnancy and drugs that are developed become progressively more expensive to cover the cost of litigation. Given that physicians have a right to prescribe drugs for off-label use as supported by common law, tradition, and legislation; physicians should have more responsibility in ascertaining whether a drug is safe during pregnancy. One way to accomplish this would be to develop a mandatory reporting system to report when adverse effects occur, particularly for off-label use in pregnant women. Although physicians usually aren't conducting research, if they are prescribing drugs to pregnant women for off-label manner and the drug is NOT a "Category A" drug, the use of the drug is experimental in these cases, and informed consent should be obtained so the pregnant woman is made aware that the drug she is being prescribed has not had well-controlled studies confirming safety. Pregnancy exposure registries exist for some drugs, but unless the prescribing physician informs the patient of this, the patient may not be aware of these studies they can participate in. Physicians should be required to monitor whether a drug they prescribe to a pregnant woman for off-label use is being studied and inform the patient of this so she can enroll if she chooses. Since most drugs are not tested for safety in pregnant women before they are prescribed to pregnant women, it is inevitable that eventually, some drug will show some deleterious effects when taken during pregnancy. Mandatory reporting would alert regulatory bodies to the deleterious effects sooner, rather than later so that fewer babies are harmed.

In addition, consumers should have more access to information obtained in the regulatory process. There is an astonishing amount of opaqueness in the agencies that are meant to protect the public such as the FDA, and it leads to many consumers not trusting the regulatory process. While it's relatively easy to read about the ABCDX pregnancy category system, it's more difficult to ascertain what category a particular drug has

been labeled because it's not required on the drug insert nor is it easily found on the FDA website. The common sources that consumers may turn to give contradictory information. Further, it is interesting to note that the Center for Disease Control (CDC) publishes information that directly contradicts FDA information. For example, the CDC recommends that pregnant women take the pertussis vaccine for whooping cough. The CDC says the "(Tdap vaccine) is very safe for pregnant women and their babies," yet the FDA categorizes the Tdap vaccine as a "Category C" drug which means that potential benefits may warrant the use of the vaccine in pregnant women, but there are no well-controlled studies in humans.<sup>26,27</sup> The conflicting information makes it even more important that pregnant women have access to the primary data so they can make an informed decision about personal risk.

The medical literature and data should be more available to pregnant women so that patients can be empowered to take a role in making informed healthcare decisions and which medications, if any, to take while they are pregnant. While controlling Type I diabetes may be extremely important during pregnancy, other health conditions have considerably more "gray" area. An example of this would be in depression. There are numerous studies showing that untreated depression can result in worse outcomes in pregnant women than the side effects of treating depression, so the patient and doctor should be able to work together to see if the level of depression a pregnant woman is experiencing meets the threshold at which it would be more advantageous to treat with medications than not.<sup>27</sup> Like many diseases, there are risks and benefits to treating or untreated depression during pregnancy, and pregnant women should be able to discuss these risks and benefits with their physician to decide on the best course of action for her situation.

Finally, I would like to address the issue of autonomy, a concept I believe overrides all other ethical, legal, and regulatory issues. Whether a pregnant woman is a patient or research subject, she has the right to make decisions regarding her and her baby's health. Decisions must be made with knowledge of the known (and potentially unknown) risks and benefits of any treatment considered as well as the risks and benefits of no treatment. Patients ought to have the right to see the data if they request it. Researchers, regulators, and drug developers may use scientific data to draw their conclusions; but the conclusions that are drawn are normative, and not necessarily free from the influence of culture, politics, and economics. Every treatment, even those deemed "safe," have some risks, and consumers have the right to know where the margins of safety have been delineated and to decide whether those margins of safety are within their

threshold of tolerance. This is particularly important because "safe" is a highly equivocated term; so different studies, researchers, and doctors means different things when they describe something as "safe." Teratogenicity, stillbirth, and miscarriage appear to be the most common meaning when ascertaining whether a treatment is safe, but pregnant women may have a safety standard that is higher than simply not causing death and/or gross physical malformations and their right to should be honored.

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