



# Pregnant Women Get Sick Too: Why Pregnant Women Require Meaningful Access to Clinical Research

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PREGNANT WOMEN GET SICK TOO:  
WHY PREGNANT WOMEN REQUIRE MEANINGFUL ACCESS  
TO CLINICAL RESEARCH

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Harvard Law School Class of 2010

Food and Drug Law Course Paper

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I authorize this paper to be included in Professor Peter Hutt's  
Electronic Book of Student Papers.

## ABSTRACT

Clinical research in pregnant women is controversial, so much so that is almost universally avoided by the pharmaceutical industry and heavily restricted by the Department of Health and Human Services in the regulations governing IRB approval of clinical studies. Many would argue that the risks to the fetus justify pregnant women's restricted access to clinical drug. I respond that these perceived risks are the result of misplaced, exaggerated fears about drug safety, tort liability, and speculative concerns about pregnant women's potent conflicts of interest with their fetus. I further assert that for the vast majority of pregnant women who do use medications during pregnancy, the psychological and medical consequences of not knowing whether their medications are safe and effective are far worse than the hazards of allowing those women to participate freely in clinical trials.

Section I of this paper identifies the problem of women's present inability to make informed decisions about medication during pregnancy, and the need for clinical drug testing to rectify that problem.

Section II argues that the current predominant method of assessing drug safety for pregnant women and their fetuses via post-market registries is inadequate, and advocates for clinical trials instead.

Section III outlines the history government regulation of pregnant women's drug-use and other medical decisions and the discriminatory assumptions inherent about women that are conveyed through the government's actions. I then discuss the Department of Health and Human Services regulation on pregnant women's participation in clinical research. I critique the government's restrictive approach on a policy level and also through a constitutional law lens. I

conclude that on a policy level, the current regulations inappropriately perpetuate stereotypes that pregnant women are irresponsible, mentally unsound, incapable of acting in their and their child's best interests, and otherwise in special need of paternalistic restrictions on their freedom. On the constitutional question, I conclude that while a Due Process challenge to the legislation is unlikely to prevail, there is a considerable possibility that the regulations could be held to violate the Equal Protection Clause of the Constitution.

Section IV provides a counterargument to industry claims that clinical research in pregnant subjects is impracticable because of the threat of litigation. I respond that under current tort law, the industry faces far greater exposure to liability than they would have if they conducted research on pregnancy safety, because their routine failure to conduct adequate experimentation in pregnant women can give rise to strict liability for their failure to warn and failure to test.

Section V proposes and compares various legal mechanisms and incentives that may accomplish better industry inclusion of pregnant women in clinical trials. The three mechanisms I examine are government-run or subsidized studies, FDA labeling requirements, or outright requirements of pregnancy testing as a condition of IRB or FDA approval.

## I. The Problem of Inadequate Drug Safety Information for Pregnant Women

Less than 1% of drugs listed in the *Physicians Desk Reference*, the go-to source for prescribing information for many doctors, have been found safe after testing in pregnant women.<sup>1</sup> This means that for more than 99% of drugs, women lack the basic clinically-proven safety assurances that men enjoy for all FDA approved drugs. Once you factor in animal testing and post-market data, the information available proves, but only slightly; we still lack adequate information to determine the safety for use in pregnancy of 91% of drugs approved by the FDA.<sup>2</sup> Of the limited information that we do know, almost all of it comes from data assembled after a drug has been approved by the FDA and after it has entered the market.<sup>3</sup>

This dearth of information would be less shocking if drug use by pregnant women were less ubiquitous. Each year, 10% of women between the ages of 15 and 44 in the United States become pregnant.<sup>4</sup> Of those women, 60% will use a prescription medication and 93% will use an over-the-counter medication during pregnancy.<sup>5</sup> With so many pregnant women taking therapeutic drugs during pregnancy, it is astonishing to learn that so few of those drugs contain the safety information pregnant women need to make an informed choice about their medical treatment. If scientific information about the health risks of medications in pregnancy were

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<sup>1</sup> Rita Rubin, *Pregnant with Fears Drug Registries Help Women Stay Informed*, USA TODAY, Mar. 21, 2000, at A1.

<sup>2</sup> DAWN A. MARCUS & PHILIP A. BAIN, *EFFECTIVE MIGRAINE TREATMENT IN PREGNANT AND LACTATING WOMEN: A PRACTICAL GUIDE* 35 (2009).

<sup>3</sup> Caitlin S. Buhimschi & Carl P. Weiner, *Medications in Pregnancy and Lactation: Part 1. Teratology*, 113 *OBSTETRICS & GYNECOLOGY* 166, 168 (2009); *cf.* PETER RUBIN & MARGARET RAMSAY, *PRESCRIBING IN PREGNANCY* 2 (4th ed. 2008) (50% of pregnant women will use a prescription medication other than prescribed vitamins or dietary supplements).

<sup>4</sup> U.S. DEPT. HEALTH AND HUM. SERVS., FOOD AND DRUG ADMIN., CTR. DRUG EVAL. RES. (CDER), *GUIDANCE FOR INDUSTRY, GUIDANCE FOR INDUSTRY: ESTABLISHING PREGNANCY EXPOSURE REGISTRIES* 5 (2002).

<sup>5</sup> MARCUS & BAIN, *supra* note 2, at 30; *compare* MIKE SAMUELS & NANCY SAMUELS, *NEW WELL PREGNANCY BOOK* 134 (1996) (in Scotland, 97% of pregnant women take prescription drugs at some point during their pregnancy and 65% take over-the-counter drugs).

available, it is likely even more pregnant women would use even more drugs. Pregnant women routinely abstain from taking new medications during pregnancy because of the potential for unknown risks to the fetus, no matter how those drugs are needed to treat or ameliorate the pregnant women's medical conditions. Women also cease taking their existing medications for chronic medications like allergy or hypertension drugs, and women endure diseases they encounter during pregnancy without antibiotics or pain relievers.<sup>6</sup>

As one FDA spokesperson put it: "Pregnant women are actually the last orphans when it comes to drug information."<sup>7</sup> I would go further than this and contend that all women who could become pregnant are orphaned by the lack information available on drug effects in pregnancy. Adding to the problem is the fact that at least half of all pregnancies are unplanned.<sup>8</sup> Many women inadvertently expose their fetus to drugs that they were using before they realized that they were pregnant.<sup>9</sup> Consequently, nonpregnant women also need information about the pregnancy risks of their medications so they can decide whether they need to take added precautions to avoid becoming pregnant while using the drug.

Without knowledge about whether a particular medication is safe for use in pregnancy, a woman who has inadvertently taken the drug in the first weeks of her pregnancy is faced with terrifying uncertainty. She may decide to terminate the pregnancy to avoid to possibility of birth

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<sup>6</sup> Even ibuprofen and other common NSAIDs which are provided over the counter have been shown to cause fetal kidney failure and heart abnormalities if taken in the later stages of pregnancy. Buhimschi & Weiner, *supra* note 3, at 168.

<sup>7</sup> Francesca Lunzer Kritz, *Ending Guesswork on Drugs in Pregnancy; FDA Seeks Better Safety Data for Women and Their Doctors*, WASH. POST, Feb. 26, 2002, at F1.

<sup>8</sup> CDER, PREGNANCY REGISTRIES, *supra* note 4, at 5.

<sup>9</sup> U.S. DEPT. HEALTH AND HUM. SERVS., FOOD AND DRUG ADMIN., CTR. DRUG EVAL. RES. (CDER), REVIEWER GUIDANCE: EVALUATING THE RISK OF DRUG EXPOSURE IN HUMAN PREGNANCIES 3 (2005).

defects, which in turn can cause unnecessary emotional trauma if the drug is in fact safe.<sup>10</sup> If she continues the pregnancy, her lack of knowledge can cause her undue worry and stress even if the drug ultimately proves safe.<sup>11</sup> This stress can be significant; one study found that hearing that a drug taken while pregnant could be unsafe caused higher levels of stress in pregnant women than a major financial crisis, being sued, sexual dysfunction, premature delivery, hospitalization lasting over a month, or their husband/partner becoming unemployed over the course of the pregnancy.<sup>12</sup> Other studies have shown that stress itself is a teratogen, that is, a substance that irreversibly alters the growth, structure, or function of a gestating embryo or fetus.<sup>13</sup> Women who experience elevated levels of stress during pregnancy are more likely to have underweight and premature babies, and those infants are more likely to be born with physiological malformations such as heart defects and cleft lip or cleft palate disorders.<sup>14</sup>

The frequent uncertainty about drugs' teratogenic potential has led to widespread overestimation of the risks.<sup>15</sup> One study surveying pregnant women found that, on average, they estimated the risk of major birth defects for certain non-teratogenic drugs to be 24%—approximately the same risk as Thalidomide.<sup>16</sup> Compounding the problem, the heavily-publicized teratogens Thalidomide and DES caused limb malformations and cancer, two of the most severe kinds of birth defects that can result from maternal drug use. This creates the false

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<sup>10</sup> MARCUS & BAIN, *supra* note 2, at 32; *see also* Toby L. Schonfeld et al., *iPLEDGE Allegiance to the Pill: Evaluation of Year 1 of a Birth Defect Prevention and Monitoring System*, 37 J. L. MED. & ETHICS 104, 109 (2009).

<sup>11</sup> *Id.* (“unfounded patient fears and stress may result in substantial maternal stress and anxiety and even consideration of pregnancy termination”).

<sup>12</sup> SAMUELS & SAMUELS, *supra* note 5, at 147–48.

<sup>13</sup> Buhimschi & Weiner, *supra* note 3, at 167.

<sup>14</sup> MARCUS & BAIN, *supra* note 2, at 32.

<sup>15</sup> *See* INSTITUTE OF MEDICINE, WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES VOLUME 1 182 (Anna C. Mastroianni, Ruth Faden, and Daniel Federman eds., 1994).

<sup>16</sup> CDER, EVALUATING THE RISK, *supra* note 9, at 3.

perception not only that drug teratogenicity is common, but that teratogens cause devastating harm to the developing fetus. Yet or the vast majority of known teratogens the effects are usually minor, such as low birth weight or preterm delivery, which are common disorders<sup>17</sup> unlikely to have any long-term effects on a child's development. Not all drugs even cross the placenta, and for many that do, the placenta filters out much of the drug so that the fetus is only exposed to a vastly reduced dose of the medication.<sup>18</sup> Thus when a pregnant women takes a drug, it does not necessarily mean that the drug will ever enter the fetus' bloodstream. Nevertheless, the myth drugs are always incredibly dangerous during pregnancy is pervasive in our society.

The tragic consequence overestimating drug risk during pregnancy is that many women are unnecessarily discouraged from taking safe medicines that would benefit them. Many doctors specifically counsel women to avoid taking all medications during pregnancy unless absolutely necessary.<sup>19</sup> On top of this many drug labels expressly warn women to stop taking the drug if they become pregnant even where there is no indication that the drug has any teratogenic potential.<sup>20</sup> Drug companies include these unfounded warnings as a precaution to shield themselves from lawsuits, but the warnings can cause pregnant women who read them to needlessly avoid safe medications.

The FDA even requires that for any over-the-counter drug that is absorbed systemically, even if it is proven safe for pregnancy, the label must warn in bold type, “**If pregnant or**

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<sup>17</sup> Low birth rate occurs in one out of every twelve births and pre-term labor occurs in one of eight. CDER, EVALUATING THE RISK, *supra* note 9, at 4.

<sup>18</sup> See Caitlin S. Buhimschi & Carl P. Weiner, *Medications in Pregnancy and Lactation: Part 2. Drugs with Minimal or Unknown Human Teratogenic Effect*, 113 OBSTETRICS & GYNECOLOGY 417, 423–24, 428 (2009) (noting that less than 10% of certain antibiotics, asthma medication and corticosteroids cross the placenta).

<sup>19</sup> SAMUELS & SAMUELS, *supra* note 5, at 136; Rubin, *supra* note 1, at A1.

<sup>20</sup> Rubin, *supra* note 1, at A1; see also Buhimschi & Weiner, *supra* note 188, at 427 (commenting that the allergy medicine, Zyrtec, claims on its label that it should not be used in pregnancy because it is unsafe for the fetus even though human studies indicate that it is safe).



**breastfeeding, ask a healthcare professional before use.”<sup>21</sup>** Although this does not warn of any specific danger to the woman or her fetus, it does imply that there is some cause for concern about the drug’s safety. At a minimum this causes pregnant women to incur the added burden and expense of arranging a doctor’s visit to use an over-the-counter medication, something that no nonpregnant individual ever has to do. At worst it can cause so much undue fear that women will avoid taking the medication altogether. In essence, the labeling requirement transforms an over-the-counter medicine into a prescription medicine for pregnant women, depriving them of the convenience and expectations of safety that all other adults enjoy for over-the-counter treatments.

A woman with a dangerous condition during pregnancy has a terrible choice between forgoing treatment, taking a drug with known teratogenic effects, or experimenting on herself and her fetus with drugs for which no human data is available. Although animal data might inform her decision, experts routinely stress that animal data is particularly unreliable as a predictor of human fetal risk.<sup>22</sup> Consequently, favorable animal data might induce a woman to try a drug, only to find out later her fetus has been harmed. The inverse is also true: evidence of teratogenic effects in animals might deter a woman even though human studies, if conducted, would show that the drug is safe for human pregnancies. The latter is especially likely, given

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<sup>21</sup> 21 C.F.R. § 201.63(a).

<sup>22</sup> See, e.g., Howard A. Denemark, *Improving Litigation Against Drug Manufacturers for Failure to Warn Against Possible Side Effects: Keeping Dubious Lawsuits from Driving Good Drugs Off the Market*, 40 CASE W. RES. L. REV. 413, 435 (1990) (observing that extensive animal testing of Thalidomide in high doses did not reveal any teratogenic potential even though a single dose in humans can cause birth defects, and that other drugs are teratogenic in animals but not in humans); Bernard A. Schwetz et al., *Monitoring Problems in Teratology*, in SCIENTIFIC CONSIDERATIONS IN MONITORING AND EVALUATION TOXICOLOGICAL RESEARCH 179, 179 (E. Gralla ed. 1981) (“[e]xtrapolation from animal data to humans is difficult with the best of data and is very risky with poor data.”).

that women are so vehemently discouraged from taking drugs by their doctors and the drug company's labels.

The dangers for women who forgo taking drugs to treat their medical conditions while pregnant are very real. While taking drugs can potentially harm a fetus, *not* taking needed drugs will almost certainly harm the mother.<sup>23</sup> Consider, for example, mental illness during pregnancy. Approximately 500,000 pregnant women each year are diagnosed a form of mental illness.<sup>24</sup> More than two thirds of pregnant women exhibit symptoms of depression, and one third of pregnant women will take a psychiatric medication at some point during their pregnancy.<sup>25</sup> The high prevalence of psychiatric conditions during pregnancy is unsurprising, given that women are twice as likely as men to experience depression.<sup>26</sup>

Pregnant women with depression and bipolar disorders experience an increased incidence of low birth weights, inconsolable crying once the baby is born, and postnatal complications that result in hospitalization of the infant.<sup>27</sup> Depression in pregnant women is also correlated with increased stress levels, excessive weight gain, smoking, and alcohol and drug use, all of which harm the fetus independent of the mental disease's direct effects.<sup>28</sup> In the long-term, children of women whose depression was untreated during pregnancy are more likely to develop psychiatric problems of their own, including suicide, than children whose mothers took medication for their

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<sup>23</sup> Susan Epstein, *Tort Reform to Ensure the Inclusion of Fertile Women in Early Phases of Commercial Drug Research*, 3 U. CHI. L. SCH. ROUNDTABLE 355, 365 (1996).

<sup>24</sup> Am. Congress Obstetricians & Gynecologists, *ACOG Practice Bulletin: Use of Psychiatric Medications During Pregnancy and Lactation*, 92 CLINICAL MGMT. GUIDELINES FOR OBSTETRICIAN-GYNECOLOGISTS 1, 1 (Apr. 2008).

<sup>25</sup> *Id.* at 5.

<sup>26</sup> *Id.* at 4.

<sup>27</sup> Am. Congress Obstetricians & Gynecologists, *supra* note 24, at 2, 5.

<sup>28</sup> Am Congress Obstetricians & Gynecologists, *supra* note 24, at 5.

illness.<sup>29</sup> Even mild anxiety disorders produce increased rates of fetal distress, miscarriage, preterm delivery, forceps deliveries, and slowed mental development in the child for years after birth.<sup>30</sup> Schizophrenia causes all of the above, plus an increased risk of maternal hemorrhaging and unexplained infant death.<sup>31</sup> Fetal risk aside, untreated mental can seriously harm the mother. In one especially tragic case, a woman who chose to forgo her anti-depressant regimen during pregnancy and breastfeeding because of uncertainty about the drug's safety threw herself and her newborn baby in front of a train.<sup>32</sup> While it may be tempting to dismiss this as a rare occurrence, suicide is the leading cause of maternal death in the United Kingdom, accounting for 15% of all maternal deaths.<sup>33</sup> On top of all of this, a woman who suffers from mental illness and stops taking her medication during pregnancy must cope with experiencing the mental disease itself, which is no small burden to bear.

Yet in spite of the dangers of prevalence of mental disease in pregnancy, approximately 70% of psychiatric medications are still classified as Category B or C drugs by the FDA,<sup>34</sup> meaning there are “no adequate or well-controlled studies in pregnant women.”<sup>35</sup> The remaining 30% of psychiatric drugs are all category D or X drugs, meaning that either human studies or

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<sup>29</sup> *Id.* at 6.

<sup>30</sup> *Id.* at 2, 6.

<sup>31</sup> *Id.*

<sup>32</sup> Kritz, *supra* note 7, at F1.

<sup>33</sup> RUBIN & RAMSAY, *supra* note 3, at 115.

<sup>34</sup> *See id.* at 2–4.

<sup>35</sup> 21 C.F.R. § 201.57(c)(9)(i). The FDA currently categorizes drugs into one of five groups based on pregnancy risk. Category A drugs have been shown by adequate human studies to have no demonstrated risk to the fetus. Category B drugs are drugs for which animal studies fail to demonstrate a risk, but for which there are no adequate or well-controlled human studies. Category C drugs are drugs for which animal studies suggest a possible risk to the fetus, but for which there are no adequate or well-controlled human studies. Category D drugs are drugs for which post-market use in humans or human studies have demonstrated fetal risk, but the benefits of the drug outweigh those risks. Category X drugs are drugs for which post-market use in humans or human studies have demonstrated fetal risk, and the benefits of the drug do not outweigh those risks. *Id.*

post-market use by humans have revealed that the drug poses teratogenic risks to the fetus.<sup>36</sup> Thus despite the overwhelming prevalence of mental disease in pregnant women, pregnant women have no options that they know are safe. Either they must take a dangerous drug, take no drug at all and suffer from their illness, or try a category B or C drug without knowing whether or not it is safe.

Asthma is another common disease that can have terrible effects of a woman and her fetus if she refuses medication with uncertain pregnancy risk. Women with asthma are more likely to develop pregnancy-related hypertension and gestational diabetes.<sup>37</sup> Offspring of women with diabetes are five times more likely to be stillborn and three times as likely to die within the first month after birth.<sup>38</sup> Diabetes also doubles the risk of major birth defects.<sup>39</sup> Asthma is also especially treacherous in pregnancy because women require 20% more oxygen than they do when not pregnant, and asthma attacks can deprive a fetus of oxygen.<sup>40</sup> In spite of this, one doctor observed that: “Many asthmatics experience worsening of their symptoms during pregnancy simply because they have stopped or reduced their usual medications due to fears (their own or those of their doctors) about their safety.”<sup>41</sup>

For other conditions, like epilepsy, ceasing medication during pregnancy is not an option. Even a single grand mal seizure can cause a miscarriage.<sup>42</sup> Seizures can also cause a woman to fall or have a car accident, posing additional serious risks for grave harm.<sup>43</sup> Anti-viral

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<sup>36</sup> Am Congress Obstetricians & Gynecologists, *supra* note 24, at 2–4.

<sup>37</sup> RUBIN & RAMSAY, *supra* note 3, at 170.

<sup>38</sup> *Id.* at 150.

<sup>39</sup> *Id.*

<sup>40</sup> *Id.* at 169.

<sup>41</sup> *Id.* at 170.

<sup>42</sup> Patricia Guthrie, *Medicine and pregnancy risk: Seeking answers*, ATLANTA JOURNAL-CONSTITUTION, Dec. 10, 2002, at C1.

<sup>43</sup> SAMUELS & SAMUELS, *supra* note 5, at 126–27; Rubin, *supra* note 1, at A1.

medications used to treat AIDS are also absolutely necessary to prevent disease progression in the mother and can at the same time significantly reduce the chances of transmitting HIV to the fetus.

Moreover pregnancy can often give rise to the very conditions that require treatment or exacerbate preexisting medical conditions. Many women develop cardiovascular disease for the first time in pregnancy.<sup>44</sup> This can occur either because of pregnancy-specific conditions like pre-eclampsia, or because changes in the woman's body such as increased blood pressure can precipitate the onset of cardiovascular illness.<sup>45</sup> Pregnancy also increases the likelihood of urinary tract infections, which in turn cause premature labor and low birth weight.<sup>46</sup> Additionally, digestive problems like constipation, diarrhea, acid reflux, and heartburn are commonly more frequent during pregnancy, and can all cause adverse effects on the fetal development.<sup>47</sup> For instance, diarrhea and vomiting cause dehydration that reduces amniotic fluid, which leads to preterm labor and limb deformities.<sup>48</sup> Vomiting also disrupts the pregnant woman's daily life; over half of employed pregnant women have to take off time from work due to morning sickness, and almost all were unable to cook food for themselves and/or their families<sup>49</sup>.

While it is true that testing drugs with unknown pregnancy risk in clinical trial subjects could put their fetuses at risk, the truth is that fetuses are already experiencing the same risk on an incredibly widespread scale, without any of the benefits of monitoring and guidance that

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<sup>44</sup> RUBIN & RAMSAY, *supra* note 3, at 77.

<sup>45</sup> *Id.*

<sup>46</sup> *Id.* at 36, 48–49.

<sup>47</sup> *Id.* at 17–23.

<sup>48</sup> *See id.*

<sup>49</sup> Caroline Smith et al., *The Impact of Nausea and Vomiting on Women: A Burden in Early Pregnancy*, 40 AUST. & NEW ZEALAND J. OBSTETRICS & GYNECOLOGY 397,399–400 (2000)

come from supervision in a clinical trial setting. Women who take drugs without having adequate knowledge of their safety are forced to gamble with their health and with the health of their fetus. They become their own researchers and their own research subjects. And as Dr. Sandy Kweder, former co-chairwoman of the FDA's pregnancy labeling task force once said, "It's wrong for every patient to be her own experiment."<sup>50</sup>

Also, for many of the drugs for which we lack adequate safety information, no animal teratology studies were conducted. If animal tests or in vitro studies on embryos are conducted as a prerequisite for human trials, we would have much better guidance as to whether those drugs are safe enough to test in a clinical population of pregnant woman. We can further gain some sense of the potential fetal risks of a new drug by comparing the drug's chemical structure to known teratogens.<sup>51</sup>

Furthermore, there is also strong evidence to suggest that the average risk of fetal effects among most drugs is fairly small. Only 3–5% of all pregnancies currently result in birth defects despite widespread use of prescription and nonprescription use of medications by pregnant women.<sup>52</sup> Of the 3–5% of children born birth defects, only 1% have abnormalities that are attributed to drugs taken during pregnancy.<sup>53</sup> It cannot rightly be said that testing drugs in pregnant women is too inherently dangerous to fetus to be ethically justified, when all evidence indicates that the risk of serious birth defects from medications is extremely minute.

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<sup>50</sup> Marilyn Kennedy Melia, *A New RX for Healthier Pregnancies*, CHI. TRIBUNE, Jan 21, 2004, at C1.

<sup>51</sup> See INSTITUTE OF MEDICINE, *supra* note 15, at 184–85. This is a proven method in other contexts, as researchers frequently perform structural comparisons of new drugs to known carcinogens to predict potential cancer risk before testing the drug in a clinical population. *Id.* at 185.

<sup>52</sup> See, e.g., Janice K. Bush, *The Industry Perspective on the Inclusion of Women in Clinical Trials*, 69 ACAD. MED. 708, 710 (1994).

<sup>53</sup> INSTITUTE OF MEDICINE, *supra* note 15, at 178; SAMUELS & SAMUELS, *supra* note 5, at 124–25.

Finally, even if information is available about the *safety* of a particular drug for use in pregnant women, there may be no way for a woman and her doctor to assess its *effectiveness* at the recommended dose. The recommended dose for a drug in nonpregnant adults may differ from a pregnant woman's needs. Pregnancy changes a woman's blood flow, blood oxygen content, body fat composition, water content and overall weight, all of which can affect how drugs are absorbed by a pregnant woman's body.<sup>54</sup> The placenta has also been shown to interfere with the rate that a drug is metabolized by the pregnant woman.<sup>55</sup> This could be because the drugs are being metabolized by the fetus, or it could be that the placenta, which averages two pounds in weight, is absorbing the medicine like any other organ.<sup>56</sup> Together these changes can render the standard dose for the drug either ineffective or an overdose. For example, one study found that the concentration of ampicillin, a common antibiotic, in pregnant women's bloodstreams was half the amount in nonpregnant persons who were given the same dose of the drug.<sup>57</sup> Without tailored studies in pregnant woman, dosing information available to doctors may be meaningless as applied to a pregnant patient. Just as children need tailored dosing because of their size,<sup>58</sup> pregnant adults have physiological differences that also necessitate targeted studies to determine the appropriate dose of any given medication.

Opponents of pregnancy testing argue that pregnancy is not the only factor that can generate differences in the safety and effectiveness of drugs.<sup>59</sup> Race, blood type, diet, physical

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<sup>54</sup> U.S. DEPT. HEALTH AND HUM. SERVS., FOOD AND DRUG ADMIN., CTR. DRUG EVAL. RES. (CDER), GUIDANCE FOR INDUSTRY: PHARMOKINETICS IN PREGNANCY—STUDY DESIGN, DATA ANALYSIS, AND IMPACT ON DOSING AND LABELING 3 (2004).

<sup>55</sup> Guthrie, *supra* note 42, at C1.

<sup>56</sup> *Id.*

<sup>57</sup> RUBIN & RAMSAY, *supra* note 3, at 37.

<sup>58</sup> See EVAN DERENZO & JOEL MOSS, WRITING CLINICAL RESEARCH PROTOCOLS: ETHICAL CONSIDERATIONS 80 (2006)

<sup>59</sup> Bush, *supra* note 52, at 709.

fitness, nutrition, psychological factors, medical history and other factors can all have an effect on a drug's safety and effectiveness, just as pregnancy can.<sup>60</sup> In order to achieve a truly representative clinical trial population and ensure that a particular drug is safe and effective in *all* persons, you would have to test the drug in test subjects that exhibit variation in all of the aforementioned factors. As one industry spokesperson put it, “[c]learly, pharmaceutical firms cannot test for every one of these [factors] before a drug is marketed.”<sup>61</sup>

Yet pregnancy is different from these other variables. Because there are unlimited possible variations in diet, you would need to test in as many different research as there are different possible diets. Pregnancy on the other hand causes predictable, consistent differences in body structure and function that can be extrapolated from a small test subject group to the entire class of pregnant women. Another reason pregnancy is different from other variables is that, a fetus exposed to a drug is at a uniquely critical stage in its physical development, meaning that drugs can have especially drastic and life-altering effects on organ formation that are unlikely to occur in a fully developed human being. Furthermore, pregnancy is not a lifestyle choice like tobacco use, diet or exercise. It a condition necessary for the survival of the human species. The social importance of pregnancy sets it apart from other human behaviors and makes it especially deserving of reasonable accommodations by pharmaceutical companies to ensure that women are able to be safe and healthy while pregnant.

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<sup>60</sup> *Id.* at 711.

<sup>61</sup> *Id.* at 709.



## II. The Inadequacy of Pregnancy Registries as a Substitute for Clinical Trials

Much of our available information on drug teratogenicity comes from pregnancy registries.<sup>62</sup> A pregnancy registry usually consists of a telephone hotline or web resource that pregnant women and obstetricians can access to report their pregnancy outcomes after using a drug. A registry differs from clinical trials in significant ways, perhaps the most significant being that they only ever begin to gather data after a drug has been marketed to, purchased by, and used by pregnant women who had no way of knowing the drugs' risks before taking them. Some would assert that the absence of clinical studies is not a real problem because registries and surveillance studies can substitute for traditional clinical trials in assessing drug safety. I argue that registries have shortcomings compared to traditional clinical trials that render them largely unreliable and unhelpful as a source of information for pregnant women and their doctors.

Registries are typically operated by the individual drug's manufacturers.<sup>63</sup> Some independent groups also conduct registries, but these are often oriented toward a particular medical condition rather than a particular drug.<sup>64</sup> The fact that drug manufacturers manage the registries for their own drugs creates an opportunity for bias to influence results. Unlike controlled clinical trials conducted by manufacturers where any bias is largely offset by the oversight of FDA approval, registries are conducted voluntarily by drug manufacturers without any FDA input or minimum requirements for reliability.

One example of where the potential for bias and lack of oversight can cause misleading results is during the recruitment process. Pharmaceutical companies may selectively recruit women whose preliminary testing (such as prenatal screening) detected no abnormalities in order

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<sup>62</sup> Buhimschi & Weiner, *supra* note 3, at 166.

<sup>63</sup> *Id.* at 168.

<sup>64</sup> *Resources for Better Drug Safety Information*, WASH. POST, Feb. 26, 2002, at F7.

to artificially dilute any negative outcomes.<sup>65</sup> The FDA has discouraged this practice, but simultaneously made clear that its statements were not binding on the industry.<sup>66</sup> Another area where bias can come into place is on the question of when, if ever, registry data should be made public. Registry data is routinely kept secret until the manufacturer concludes that the results are statistically solid. Depending on rate at which women volunteer their information, this can take several years, or may never occur.<sup>67</sup> However, there are no set requirements for when, if ever, a registry operator must disclose the registry data, and thus manufacturers have an opportunity and an incentive to game the system. If early reports to the registry are all positive, they can stop accepting volunteers and report the results promptly, even if a statistically significant sample size has not been reached, or if not enough follow-up has occurred to see if abnormalities emerged later in the pregnancy. This early positive data will allow drug companies to gain pregnant customers. On the flip side, if early reports are negative, the manufacturer can delay reporting the results for a long period of time or even indefinitely while they continue to profit from pregnant purchasers of the drug.

A further problem is with registries is that their existence is not required to be reported on drug labels, so doctors and women must proactively ferret out the information on a case by case basis.<sup>68</sup> Some registries post their results online, but others provide it only upon request.<sup>69</sup> Some will only send information to a qualified physician.<sup>70</sup> Although this may not pose an obstacle for some women, others will inevitably forgo obtaining the information rather than go through the

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<sup>65</sup> CDER, PREGNANCY REGISTRIES, *supra* note 4, at 9.

<sup>66</sup> *Id.* at 1, 9.

<sup>67</sup> Rubin, *supra* note 1, at A1.

<sup>68</sup> For a discussion of a proposed FDA rule that would require such labeling, *see infra* Part IV.B.

<sup>69</sup> *Resources for Better Drug Safety Information*, *supra* note 64, at F7.

<sup>70</sup> *Id.*

administrative hassle and expense of arranging separate appointment with their doctor to obtain the requested registry information once it arrives.

In cases where a patient does not know about a registry, it is up to the doctors to research registry information before prescribing a drug to a pregnant or pregnable woman. Relying on individual doctors' abilities to compile this scattered, often unpublished data for every drug is entirely impractical and unrealistic. Even if the data from registries were reliable, which, for reasons discussed below, it is not, doctors are simply unlikely to be able to keep abreast of the information and keep their patients informed. One study involving nearly 500,000 pregnant women showed that doctors only discussed potential pregnancy risks of medications with the patient 47-48% of the time when prescribing, even when studies showed high-risk for teratogenic effects.<sup>71</sup>

Registries also routinely suffer from low levels of participation. This weakens the usefulness of their information by making it difficult to detect whether there is a statistically significant difference between the rate of birth defects when using the drugs and the rate of birth defects in the general population. The reasons for low participation in pregnancy registries are manifold. Since registries often wait for volunteers to contact them rather than proactively seeking out users of the drug, they only accumulate data if a pregnant woman or her doctor independently chooses to report to the registry. A doctor or patient who has reservations about data privacy, or who is simply uninformed or unmotivated is unlikely to volunteer. Women may also be too embarrassed to report to registries if they deviated from their doctor's advice or a

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<sup>71</sup> *Advice lacking for risky drugs; Doctors aren't warning women when medicine can cause birth defects*, GRAND RAPIDS PRESS, Sept. 30, 2007, at A10.

drug label warning not to use the medicine during pregnancy.<sup>72</sup> Clinical studies on the other hand, often actively recruit participants and can therefore encourage participation in ways that a passive registry cannot.

A second reason participation in registries may be low is that if a drug has multiple registries (for example, one founded by the drug manufacturer and the other by a nonprofit organization) women may only contact one of the registries. The competing registries will divide the pool of eligible participants between them and will each have lower numbers of participating women as a result.

A third reason for low participation is more subtle. Doctors and patients may only think to seek out a registry after an abnormality is detected. Women with uneventful pregnancies and healthy infants may not give a second thought to medication that they used in pregnancy. Also, waiting to report until abnormalities are observable by ultrasound, at birth, or at a later point, causes a delay which can be weeks, months, even years after the abnormality initially formed. If an obstetrician is reporting to the registry on behalf of a patient, he or she will only be able to report drug effects that are observable before or at the time of birth, because the obstetrician will likely have no contact with the infant after the birth.<sup>73</sup> If a problem is not observed until later in the child's life, the mother and the child's pediatrician might be less likely to make the connection between the drug and the defect because the pediatrician might not have access to the mother's prescription history during pregnancy and might not think to ask. Given the lapse of time, the doctor also would be less likely to suspect that a child's condition is caused by maternal drug exposure rather than an environmental source. Thus many incidences of drug-related

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<sup>72</sup> See Ami E. Doshi, *The Cost of Clear Skin: Balancing the Social and Safety Costs of iPLEDGE with the Efficacy of Accutane (Isotretinoin)*, 37 *Seton Hall Law Review* 625, 659 (2007).

<sup>73</sup> Rubin, *supra* note 1, at A1.

abnormalities that are not immediately apparent to the naked eye at birth could go unreported. If the mother were a participant in a clinical trial, however, researchers as part of the informed consent process would surely counsel her to notify them if the child had any abnormal medical conditions that she became aware of only after the trial ended.

There is another, related problem with relying on detection of abnormalities as a basis for reporting to registries. Birth defects can be masked by miscarriages, because a woman's obstetrician is highly unlikely to autopsy a miscarried fetus to look for developmental abnormalities. Since a significant number of pregnancies (20-30%) spontaneously abort, a woman outside of a clinical setting might have no reason to suspect her miscarriage was the result of a teratogen rather than natural causes. A clinical researcher on the other hand would be able to investigate if there is a higher-than-normal rate of miscarriage among the test subjects that could be attributable to the drug, and also whether a fetus showed any signs of abnormal organ development prior to the miscarriage.

Furthermore, a mother who takes a particular drug for which safety in pregnancy is unknown may have no reason to suspect that her child harbors some unseen birth defect that is not immediately apparent to the naked eye. Her child's medical condition would go untreated during the intervening time between the formation of the abnormality and its detection by his pediatrician, which could be months or even years after birth. In a clinical setting, however, researchers would be more likely to perform specialized screening tests that would increase the likelihood that any problems are caught early and treated. For example, ultrasound equipment is capable of performing a complete and thorough scan of a fetus that can successfully detect organ

abnormalities in 90% of fetuses after the first 12–14 weeks of pregnancy.<sup>74</sup> Yet most obstetricians still wait until the end of the second trimester to perform a complete fetal anomaly scan.<sup>75</sup> This delay in ordinary obstetric practice is significant for two reasons. First, if a woman begins taking drugs in her second trimester and the obstetrician’s subsequent scan reveals abnormalities, the woman would have no way of knowing whether those abnormalities predated the drug use. Thus her report of birth defects to the registry could be a false positive indication of teratogenicity when in reality the drug had no effect. A researcher in a clinical trial, however, would certainly know to scan the fetus prior to administering a drug, and so would be able to know of any pre-existing fetal conditions going into the drug trial.

Another flaw with registries is that they do not necessarily identify *when* during the pregnancy a birth defect originated. A clinical trial in pregnant humans could be structured, as many animal trials are,<sup>76</sup> to identify the timing of any teratogenic effects. This structure consists of dividing the test subjects into the three segments: the first group is tested during conception and the early stages of pregnancy, the second group is tested during organogenesis,<sup>77</sup> and the third group is tested during the third trimester and lactation to account for the different kinds of abnormalities that are specific to these distinct developmental periods. A registry however, is unlikely to conflate participants who took the drugs at different stages in their pregnancies. It is, of course, possible that a registry might only contain entries from women who all took the

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<sup>74</sup> See RUBIN & RAMSAY, *supra* note 3, at 4–6. The technology can even operate successfully to detect fetal abnormalities before the end of the first trimester, but then the detection success rate is only 50–60%. *Id.* at 6.

<sup>75</sup> *Id.* at 6.

<sup>76</sup> See Bush, *supra* note 52, at 710.

<sup>77</sup> Organogenesis is the period during which the fetus develops internal organs. In humans this begins between the third and eighth weeks and continues for the most part until the third trimester.

medication at the exact same stage in their pregnancy, but there is certainly no guarantee that this will happen.

The timing of the drug exposure is vitally important, because a drug may be entirely harmless if administered during the early stages of pregnancy and yet cause birth defects when used in the second or third trimester, or vice versa.<sup>78</sup> Women who only need drugs for part of their pregnancy, or a woman took a drug during the first few weeks of pregnancy before they knew they were pregnant, might be unduly alarmed by a registry that discloses the drug causes birth defects without revealing what time periods during pregnancy the drug is dangerous. This is especially troubling given that abortion is only constitutionally unrestricted in the first trimester, so a woman who is worried about an unintentional exposure at the start of her pregnancy may have very little time to make a decision whether to carry the fetus to term. Since the registry will most likely not tell her specifically whether first trimester exposure to the medicine is harmful, and since any defects are unlikely to be observable by ultrasound in the first trimester, her difficult decision will almost certainly be uninformed. Clinical trials would remedy this by identifying the timing, not just the incidence, of fetal abnormalities.

Registries also do not necessarily control for factors that could be contributing causes to an observed birth defect, such as environmental toxicants, family history or other prescription drugs. Because women who report incidents to registries do not have conventional researcher-subject relationships with the drug companies conducting the registries, those companies may not have complete access to the women's medical records. Even if a registry operator did attempt to collect information about a woman's medical and environmental background, they

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<sup>78</sup> See, e.g., Buhimschi & Weiner, *supra* note 3, at 168 (“Many potent human teratogens act during very specific developmental stages.”); Bush, *supra* note 52, at 710–11 (A “misunderstanding regarding pregnancy and drug testing is that the first trimester is the only one that is of concern . . . for some particular drugs, the damage occurs after the first trimester.”).

may not know which questions to ask, and the women may not be familiar enough with their full medical history to supply complete answers.

The postmarket nature of registries and the way in which they are conducted make them poor substitutes for clinical research. Due to their secrecy and inaccessibility, pregnant women and their doctors may not have access to the information they generate. Any information they are able to obtain from registries is probably unreliable and not likely to be independently corroborated through peer review. As the FDA itself noted, “pregnancy exposure registries are limited to screening for major teratogens on the level of thalidomide,” and are not helpful for identifying subtler, more “modest risks.”<sup>79</sup> Because of the many innate flaws in registries, they do not and cannot provide pregnant women with the information they need to evaluate the risks and benefits of their medication.

### III. The Role of the Government in Pregnant Women’s Exclusion from Clinical Trials

#### A. Policy Objections to DHHS Current Regulations in the Context of the Flawed History of Government Overzealousness in Limiting Pregnant Women’s Rights

This section of the paper articulates the view that pregnant women are presently treated as exceptional cases under the law in ways that impose atypical limitations on their freedom. Pregnant women are routinely characterized as having a special conflict of interest that other parents do not share vis a vis their offspring that justifies additional governmental intrusions into pregnant women’s autonomy. The below examples of involuntary treatment orders and pregnant substance abusers illustrate that this characterization is overblown. They show how discriminatory stereotypes about proper maternal behavior lead the government to unreasonably assume pregnant women pose a special risk to their fetuses and to consequently intrude on

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<sup>79</sup> CDER, EVALUATING THE RISK, *supra* note 9, at 16.



pregnant women's rights. I use these examples to illustrate how the Department of Health and Human Services (DHHS) regulations on pregnant women's participation in clinical trials constitute a similar unjustified overreaction to the perceived exceptional threat that pregnant women pose to the wellbeing of their fetuses. I argue that the DHHS regulation should be abolished because it perpetuates the same unrealistic negative stereotypes about pregnant women as the discriminatory practices of involuntary cesarean orders and treatment of pregnant substance abusers. The regulations are also especially restrictive ways that are likely to overdeter researchers who wish to conduct trials involving pregnant women.

i. Pregnancy Exceptionalism in Involuntary Treatment Orders

One extreme example of pregnancy exceptionalism in the law is the practice of involuntary treatment orders for cesarean operations. These occur when a physician believes that a cesarean is safer for the fetus than vaginal delivery and seeks a court order to compel a woman to submit to surgery against her will. The substance of these orders is unprecedented. No court has ever ruled that a parent be forced to undergo surgery (such as an organ transplant or blood transfusion) to save their dying child<sup>80</sup>, yet courts are willing to order a highly invasive abdominal surgery to reduce a risk to a fetus from a vaginal birth. This perplexingly gives a potential child whose survival is dependent on its maternal host greater protection than a living child with a wholly separate existence from its mother.

Though physicians rarely seek involuntary treatment orders, when they do judges are surprisingly willing to grant them. Between 1987 and 2006, a stunning 86% of involuntary treatment orders sought by doctors against their pregnant patients were granted.<sup>81</sup> The procedure

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<sup>80</sup> Laura M. Purdy, *Are Pregnant Women Fetal Containers*, in *BIOETHICS: AN ANTHOLOGY* 67 (Helga Kuhse & Peter Singer eds., 2006)

<sup>81</sup> Purdy, *supra* note 80, at 67.

involved in obtaining such orders is also atypical in alarming ways. In the vast majority of cases, the judge was called to the hospital on an emergency basis to rule on the order, without any legal briefing on the issues and very often without counsel present to represent the pregnant woman's interests.<sup>82</sup> Of the orders that were granted in the aforementioned 30 year time period, an astonishing 88% were decided within a mere six hours of the physician's request.<sup>83</sup> This rapid turnover suggests little if any time was devoted to inquiry into the relevant law or any measured consideration of the issues. Often there are also more subtle forms of procedural unfairness to the mother, such as the fact that the prospect of imminent compelled surgery will likely make a woman visibly upset and unable to articulate her position as calmly and collectedly as the hospital's in-house counsel.<sup>84</sup>

With so few safeguards for pregnant women's rights, it is no wonder that many judge determine that a procedure is necessary for the health of the fetus only to later find out that they were wrong. For example, in one case a pregnant woman in the advanced stages of cancer was forced by court order to submit to a cesarean operation to give a fetus with dubious viability a "better though slim chance" of survival.<sup>85</sup> The fetus did not survive the premature delivery, and, in her weakened state, the mother died within two days of the operation, which was a contributing cause of her death.<sup>86</sup> In another case a women was ordered to undergo an involuntary cesarean section because her placenta was blocking the birth canal, but before the

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<sup>82</sup> George J. Annas, *Protecting the Liberty of Pregnant Patents*, 316 NEW ENG. J. MED. 1213, 1213 (1987).

<sup>83</sup> Purdy, *supra* note 80, at 67.

<sup>84</sup> See Annas, *supra* note 82, at 1213.

<sup>85</sup> Janet Gallagher, *Collective Bad Faith: "Protecting" the Fetus*, in REPRODUCTION, ETHICS, AND THE LAW: FEMINIST PERSPECTIVES 343, 347 (Joan C. Callahan ed., 1995); Purdy, *supra* note 80, at 66.

<sup>86</sup> Gallagher, *supra* note 85, at 345; Purdy, *supra* note 80, at 66.

operation could be performed her placenta shifted and she was able to give birth to a healthy baby vaginally.<sup>87</sup>

If a doctor were to seek an involuntary treatment for any patient other than a pregnant women, the situation would look quite different. As previously mentioned, there is no recognized duty in the law for one person to undergo invasive medical treatments for the benefit of another, even when that person is one's own child. It does not suffice to distinguish the cases on the basis of necessity by saying that a fetus cannot be treated without breaching the mother's physical integrity, and so his mother's bodily invasion is his only means of securing medical treatment. A parent has no comparable duty to undergo surgery for child who will surely die without an emergency organ transplant, even if the parent is the only compatible organ donor available. Nor can you distinguish this scenario by arguing that a pregnant of women has a unique conflict of interest that interferes with her decisionmaking capabilities, because a parent asked to undergo surgery for an older child has the very same conflict when asked to undergo a risky surgery for their child's benefit. While one can certainly laud the self-sacrificing parent who would give a kidney for their child, just as one may lauds the man who jumps in front of train to a rescue his child who has wandered onto the tracks, or, indeed, just like as one may praise the countless women who voluntarily undergo cesarean sections for their fetus' benefit, the law does not and should not require people to incur so great a detriment to themselves for the benefit of their offspring.

Furthermore, in a case involving any patient other than a pregnant woman, there are greater procedural safeguards in place. A court order can only issue if the patient is deemed

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<sup>87</sup> Terry Keville, *Gender Bias in Clinical Research and Testing*, in Norma Swenson et al., *Women's Health Law Symposium, Rutgers School of Law-Newark, April 6, 1994*, 16 WOMEN'S RTS. L. REP. 17, 21 (Fall 1994).

incompetent to participate in his or her own medical decisions. A determination that a person is legally incompetent is a classification normally reserved for patients who are unconscious or have severe mental disease,<sup>88</sup> not for healthy pregnant women whose sole “abnormality” is that they disagree with their doctor about how they would like to give birth to their baby. Medical ethicists maintain that adults should be presumed competent to make their medical decisions unless evidence proves otherwise.<sup>89</sup> Also, for any other patient, the court order may only issue after a formal adversarial hearing and detailed fact-finding.<sup>90</sup> This process is a far cry from the chaotic, haphazard, uninformed decisions that judges are called upon to make about pregnant women’s competence in the urgent atmosphere of the emergency room.

In addition, in any other involuntary treatment order case the standard used by the court is “substituted judgment,” and the relevant inquiry whether the patient would necessarily consent to the presently unwanted medical treatment if he or she were mentally competent.<sup>91</sup> The inquiry is *not* whether third parties would benefit from performing the unwanted procedure on the patient, such as if doctors were to seek an order for an unwilling patient to submit to a bone marrow transplant to cure a close relative’s leukemia. Yet for pregnant women, the courts appear to rank the fetus’ wellbeing over the mother’s stated preferences without ever inquiring whether a reasonable, sane woman might refuse to subject herself to an invasive cesarean surgery that carried an uncertain prospect of benefit to the fetus.

For a court to decide that a woman is as mentally incompetent solely because she is unwilling to risk life for the benefit of her fetus is grossly insulting. For the court to accord her fewer procedural protections than an unconscious, imprisoned or insane individual is unfair.

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<sup>88</sup> Purdy, *supra* note 80, at 69.

<sup>89</sup> See DERENZO & MOSS, *supra* note 58, at 83.

<sup>90</sup> *Id.*

<sup>91</sup> Gallagher, *supra* note 85, at 360.

This lack of basic legal protection for the mother is uniquely and disturbingly flippant towards a pregnant woman's autonomy and legal rights.

This exceptional treatment does not make sense according to any analogy to existing parental obligations under the law or other legal procedures relating to incompetence in our society. It does make sense if you accept that it is partially attributable to unconscious sex discrimination based on gender stereotypes. The determination of incompetency coincides with longstanding myths that hormones in pregnancy induce a kind of hysteria that makes women literally crazy. It also communicates the view that no rational woman could value her own safety more than of her fetus. This demands a level of self-sacrifice that is unreasonable and likely based on sex stereotypes of a mother's selfless devotion to her children. It also espouses the patriarchal, proprietary notion that a woman's rights are subordinate to a fetus' because a woman has value only as a mere vessel for a man's offspring. This treats her as a means for the survival of a man's progeny rather than as an end in and of herself.

It is also a view that is shared by some elements of the Fetal Rights Movement—the anti-abortion backlash against *Roe v. Wade*. Anti-abortion legislation has similarly presumed that women are incompetent to responsibly make abortion decisions without forced waiting periods to rethink their decision and mandatory abortion counseling to help them more thoughtfully and deliberately appreciate the risks and benefits of abortion.<sup>92</sup> At the same time the statutes require no such cautionary counseling for women who choose to carry their pregnancies to term even though there are similar complex risks and benefits inherent in that decision. This asymmetry

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<sup>92</sup> See Planned Parenthood v. Casey, 505 U.S. 833, 881–87 (1992) (upholding a Pennsylvania regulation that required a mandatory counseling for women seeking abortion); Thornburgh v. Am. College of Obstetricians & Gynecologies, 476 U.S. 747, 762 (1986) (striking down a law that required more specific counseling about fetal development as an excessive invasion of the doctor-patient informed consent process).

carries with it the erroneous assumption that a woman is abnormal and somehow mentally deficient if she determines that her own wellbeing under the particular circumstances at hand should take precedence over the wellbeing of her fetus. As Justice Stevens argued in his dissent from *Casey*, it is condescending to assume that a woman cannot make a reasoned decision to have an abortion without counseling, because “[n]o person undertakes such a decision lightly—and States may not presume that a woman has failed to reflect adequately merely because her conclusion differs from the State’s preference.”<sup>93</sup>

Some feminist scholars have attributed the rise of the fetal rights movement to a male backlash against growing female independence. This perspective suggests men resent the fact that women have abandoned their “traditional nurturing role” as mothers in favor of having a career, and thus men seek to force women to conform to their view of self-sacrificing motherhood.<sup>94</sup> As one author wrote:

“Men experiencing a loss of control over the individual women in their lives attempted to reassert it through the courts, urging judges to assert their power as *parens patriae* (“father[s] of the country”) or to invoke a “state interest” in the fetus.”<sup>95</sup>

Regardless of whether this is indeed the case, the state actions still create the appearance that the state views women at least incompetent and, at worst, deviant and selfish, while at the same time viewing the fetus as a victim in need of state protection from its mother’s bad decisions.<sup>96</sup> These stereotypes are intolerable in a modern society, and yet they appear repeatedly in the context of government regulation of pregnant women and, I argue, in the current regulations governing pregnant women’s participation in clinical trials.

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<sup>93</sup> *Casey*, 505 U.S. at 919 (Stevens J., dissenting).

<sup>94</sup> INSTITUTE OF MEDICINE, *supra* note 15, at 79–80; Gallagher, *supra* note 85, at 352.

<sup>95</sup> Gallagher, *supra* note 85, at 345.

<sup>96</sup> *See id.* at 352.

ii. Pregnancy Exceptionalism in the Treatment of Pregnant Substance Abusers

Since the early 1980s, the government's response to pregnant substance abusers has been drastic and overblown. Courts routinely terminated the parental rights of substance abusers as soon as their babies were born.<sup>97</sup> Prosecutors use distorted interpretations of child endangerment laws to penalize pregnant substance abusers.<sup>98</sup> The judiciary has harshly penalized pregnant substance abusers for crimes wholly unrelated to their illegal drug use as a pretext for incarcerating them. A Washington, D.C. judge sentenced Brenda Vaughn, a first time offender convicted for check fraud, to 180 days in jail even though the prosecutor asked only for probation.<sup>99</sup> The judge was unambiguous about his reasons for doing so; aware that Brenda was pregnant and had tested positive for cocaine, he declared at her sentencing hearing, "I am going to keep her locked up until the baby is born."<sup>100</sup>

However, scientific data is inconclusive as to whether alcohol, tobacco, opioids, amphetamines and even cocaine actually cause any lasting harm to fetuses.<sup>101</sup> In fact, the drug that appears from scientific data to cause the most harm, more than heroin or cocaine, is alcohol,

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<sup>97</sup> SUSAN C. BOYD & LENORA MARCELLUS, *WITH CHILD: SUBSTANCE USE DURING PREGNANCY: A WOMAN-CENTERED APPROACH* 11 (2007); SHEIGLA MURPHY & MARSHA ROSENBAUM, *PREGNANT WOMEN ON DRUGS: COMBATING STEREOTYPES AND STIGMA* 143–45 (1999).

<sup>98</sup> Gallagher, *supra* note 85, at 355.

<sup>99</sup> *Id.*, at 343–44.

<sup>100</sup> *Id.* (citing Victoria Churchville, *D.C. Judge Jails Woman as Protection for Fetus*, WASH. POST, July 23, 1988 at A1).

<sup>101</sup> See BOYD & MARCELLUS, *supra* note 97, 45–53 ("some researchers believe there are no long-term effects [of tobacco];" "there is no consensus about these more subjective effects [of opiates] and, in fact, they are somewhat controversial;" "recent research points to the importance of the environment and parenting . . . [as causes of] many findings once thought to be specific effects of prenatal cocaine exposure;" "in addition to there being only a limited number of available studies [on marijuana use in pregnancy], results have been inconsistent").

if it causes harm at all.<sup>102</sup> The side effects attributed collectively to the aforementioned substances are increased likelihood of miscarriage, premature birth, low birth weight, irritability and difficulty sleeping in the first few days or weeks after birth, delayed speech, and poor educational performance later in life. Alcohol uniquely carries the added risk of fetal alcohol syndrome, which is associated with flattened facial features in addition to the previously-discussed symptoms.

Many studies have concluded that higher incidences of these side effects among substance abusing mothers may actually be attributable to environment causes commonly shared by maternal substance abusers other than the drugs themselves.

One such factor is poverty, which carries with it numerous aspects like malnutrition, stress, overwork, lack of prenatal care, and domestic violence that can all independently cause low birth weight and stunted fetal development. An especially compelling study compared middle class alcoholic women with impoverished alcoholic women.<sup>103</sup> Both groups frequently consumed excessive quantities of alcohol during pregnancy. Yet 70.9% of children born to impoverished mothers suffered from fetal alcohol syndrome, compared to only 4.5% of children born to middle-class mothers.<sup>104</sup>

Other scientists point out that due to substance abusers lifestyles, fetuses are more likely to be born with a range of medical conditions unrelated to the drug use itself, such as HIV and Hepatitis C, which can explain many of the symptoms associated with the substance abuse.<sup>105</sup>

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<sup>102</sup> *Id.* at 46.

<sup>103</sup> Nesrin Bingol et al., *The Influence of Socioeconomic Factors on the Occurrence of Fetal Alcohol Syndrome*, 6 ADVANCES IN ALCOHOL AND SUBSTANCE ABUSE 105, 105–18 (1987)

<sup>104</sup> *Id.*

<sup>105</sup> BOYD & MARCELLUS, *supra* note 97, at 48.



Issues related to the infant's parenting environment are also likely contributors to post-birth "side-effects" of prenatal drug exposure. For example, early researchers believed that infants born to opiate-addicted mothers exhibited withdrawal symptoms, but almost all of the infants used in those early studies had been removed from their mothers and observed in a clinical, rather than a natural home setting.<sup>106</sup> Later research showed that when mother and baby are allowed to remain together during clinical observations, the "symptoms" of the supposed withdrawal (irritability, crying, tensed muscles, difficulty sleeping and reluctance to feed) largely disappeared.<sup>107</sup> For cocaine, scientists have now reached a consensus that despite early alarm about "crack babies" in the media, cocaine use during pregnancy does not cause babies to experience withdrawal.<sup>108</sup>

Scientists also now believe that parenting and environment cause many of the long-term development, educational and behavioral problems once attributed to prenatal substance abuse. For instance, although children whose mothers used opiates during pregnancy are statistically more likely to have low attention span, delayed speech and other learning disabilities, these effects all but disappeared in cases where children were raised in what researchers deemed "a supportive environment," and the mothers did not use alcohol or a combination of other drugs during pregnancy.<sup>109</sup> The same holds true for cocaine and marijuana, and methamphetamines.<sup>110</sup> A recent study even found that the majority of methamphetamine exposed children do not show *any* statistical increase in developmental delays over the normal population, even when the

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<sup>106</sup> *Id.*

<sup>107</sup> *Id.* at 47–48

<sup>108</sup> *Id.* at 49.

<sup>109</sup> *Id.* at 48.

<sup>110</sup> *Id.* at 49–51.

parental environment is less than optimal.<sup>111</sup> Although it is still unclear whether the drugs combine with the other environmental factors to produce some cumulative negative effect on children born to substance abusers, or whether the environment causes are solely to blame, the one conclusion that is inescapable is that “the effects of prenatal substance use are not as profound as once believed.”<sup>112</sup>

At the same time that the courts vilify pregnant substance abusers, they also overlook comparable, if not worse, parental malfeasance by men. In one case, a pregnant woman was admitted to the hospital after having been severely beaten by her husband.<sup>113</sup> The authorities did not charge the husband with any crime, but instead prosecuted the woman for child endangerment because hospital tests revealed she had been drinking.<sup>114</sup> Indeed, some researchers observe that female substance abuse is often a byproduct of male violence, explaining that women who are abused “self-medicate with alcohol, illicit drugs, and prescription medication in order to cope with the violence.”<sup>115</sup> 70% of female substance abusers are physically abused.<sup>116</sup> Additionally, any harmful effect on the fetus from maternal drug use can be exacerbated by preconception *paternal* drug use. Fathers’ preconception use of drugs and alcohol has been correlated with lower birth weight and other fetal injuries commonly associated with maternal substance abuse.<sup>117</sup>

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<sup>111</sup> *Id.*

<sup>112</sup> *Id.* (summarizing the conclusions of a 2006 evidence review conducted by researchers at the University of California–Berkeley).

<sup>113</sup> Gallagher, *supra* note 85, at 358.

<sup>114</sup> *Id.*

<sup>115</sup> Hortensia Amaro et al., *Violence During Pregnancy and Substance Use*, 80 AM. J. PUB. HEALTH 575, 578 (1990).

<sup>116</sup> Joan E. Bertin, *Regulating Reproduction*, in REPRODUCTION, ETHICS, AND THE LAW: FEMINIST PERSPECTIVES 391 (Joan C. Callahan ed., 1995).

<sup>117</sup> *Id.* at 392

Feminist voices argue that this gender asymmetry in the treatment of substance abusers is due to the perception that substance abusing women deviate from longstanding social norms of what it means to be a good mother. Diana Meyers explained that “[m]others are culturally represented as self-sacrificial, unconditionally loving, and totally identified with their children.”<sup>118</sup> Janet Gallagher observed that as a consequence of those one-sided gender stereotypes “men’s deviations from parenting ideals are largely ignored by officials and by the media” even though men are more likely to physically and sexually abuse their children and can also harm their offspring through preconception drug and alcohol use, whereas widely-publicized media and political campaigns fiercely admonish women not to drink or smoke during pregnancy.<sup>119</sup>

I do not wish to suggest that I condone pregnant women’s use of recreational drugs. I merely wish to illustrate how the government and the public has, in the case of pregnant substance abusers, rushed to condemn those women as bad mothers and imposed serious sanctions on them without first determining that actual harm to the fetus occurred, and if it did occur, that recreational drugs were the cause rather than the innumerable other reasons approximately 4% of babies are born with severe birth defects.<sup>120</sup> In fact, for recreational drugs that actually do cause significant harm to the fetus, like methamphetamine, the government could very well be justified in prohibiting use of those drugs by pregnant women. This does not, however, justify a ban in the clinical trial context, where any risk to the fetus is unknown and unproven because the drug has not yet been tested in pregnant women. There is a real difference

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<sup>118</sup> Diana Meyers, *The Rush to Motherhood – Pronatalist Discourse and Women’s Autonomy*, 26 *SIGNS* 735, 764 (2003) (cited in AMY MULLIN, *RECONCEIVING PREGNANCY AND CHILDCARE* 77 (2005)).

<sup>119</sup> Gallagher, *supra* note 85, at 358–59.

<sup>120</sup> MARCUS & BAIN, *supra* note 2, at 32 (further noting that less than 1% of these birth defects are attributable to any kind of drug exposure, legal or illegal).

between preventing pregnant women from taking action that is certain to cause specific, identifiable harm and preventing women from exposing their fetus to the mere possibility of vague, unknowable harms. In addition, while recreational drugs have no benefit for women other than entertainment, medicinal drugs can have significant, even life-saving benefit for a mother. Thus while it may make sense to restrict a woman's freedom with regard to recreational drugs, there are added concerns that make it less appropriate to intrude on pregnant women's freedom to participate in clinical trials of therapeutic drugs.

iii. Pregnancy Exceptionalism the Current Government Regulation of Pregnant Women's Participation in Clinical Trials

Although the government's exceptional treatment of pregnant women in the context of clinical drug trials is not viscerally distasteful on its face as involuntary cesareans, it too perpetuates unconscious sex stereotypes that portray women as mentally inferior to and socially less valuable than their unborn fetuses. Although the FDA has yet to promulgate any specific rules for pregnant women in clinical research, the Department of Health and Human Services (DHHS) places additional restrictions on pregnant women's participation in any clinical research trials that is financially supported by the Department.<sup>121</sup> This includes any research that is funded by DHHS grants, which constitutes a large proportion of academic research, research that is conducted by any DHHS employees, and research that is conducted by persons unaffiliated with DHHS who conduct research at DHHS facilities.<sup>122</sup> Although the regulations do not bind private researchers conducting their research on private property, they do capture a large swath of clinical drug trials across the country.

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<sup>121</sup> 45 C.F.R. § 46.201(a).

<sup>122</sup> *Id.*

a. The DHHS Regulations Inappropriately Classify Pregnant Women as a “Vulnerable” Population

Under the current regulatory scheme, pregnant women are classified as “vulnerable” research subjects.<sup>123</sup> The Department uses this classification as the basis for its “additional safeguards” which restrict researchers’ ability to obtain IRB approval for studies involving pregnant women.

According to the International Ethical Guidelines for Biomedical Research, vulnerable persons are individuals who are “incapable of protecting their own interests” due to “insufficient power, intelligence, education, resources, [or] strength.”<sup>124</sup> The international guidelines, unlike DHHS, do not include pregnant women under this category.<sup>125</sup> The rationale that justifies placing special restrictions on the freedom of vulnerable persons to consent to research is that those individuals lack the “capacity or freedom” to meaningfully consent.<sup>126</sup> A person lacks *capacity* to consent when their mental state prevents them from appreciating the risks and benefits of the clinical trial. A person lacks *freedom* to consent when external coercive forces pressure them into consenting when they would otherwise consent. The latter typically is found to occur when the vulnerable person is in a position of powerlessness relative to the researchers or the third party exerting the coercive pressure.

The DHHS regulations specify that vulnerable populations include children, prisoners, pregnant women, mentally disabled persons, the handicapped, educationally disadvantages

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<sup>123</sup> 45 C.F.R. §§ 46.107(a), 46.111(a)(3), (b).

<sup>124</sup> COUNCIL FOR INT’L ORGS. OF MED. SCIS. (CIOMS), INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS 64 (Geneva, 2002)

<sup>125</sup> *Id.* at 64–66.

<sup>126</sup> INTERNATIONAL GUIDELINES, *supra* note 124, at 64.

persons or economically disadvantaged persons.<sup>127</sup> The regulations go on to explain that such groups are innately vulnerable to “coercion or undue influence,” thereby adopting the “lack of freedom” rationale of the international guidelines test.<sup>128</sup> Feminist scholars have criticized the government’s assumption that pregnant women are inherently susceptible to coercion or undue influence, claiming that such an assumption is inappropriately paternalistic.<sup>129</sup> All of the vulnerable groups in the regulation aside from pregnant women do, for the most part, fit the rationales articulated in the regulation and in the international guidelines. All lack freedom because they are dependent on others in ways that make them vulnerable to coercion: children are wholly dependent on their parents for survival; prisoners are dependent on their wardens and can be punished by them for noncompliance; mentally-disabled are dependent on their caregivers, psychiatrists, and legal guardians; the economically disadvantaged are dependent on researchers for money in payment for their participation; and the educationally disadvantaged are dependent on researchers for information about the risks and benefits of their participation. Some of these groups may also lack capacity to appreciate the risks of the study: children lack capacity by virtue of their developing cognitive abilities and their inexperience; the mentally disabled lack capacity by virtue of their mental illness; and the educationally disadvantaged lack capacity by virtue of their lesser experience with complex decisionmaking and limited understanding of medical science.

All of this makes one wonder what it is that made DHHS presume all pregnant women meet their definition of vulnerability. It is possible that under some circumstances a pregnant woman could have attributes that would make her unable to meaningfully consent to

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<sup>127</sup> 45 C.F.R. §§ 46.107(a), 46.111(a)(3), (b).

<sup>128</sup> 45 C.F.R. § 46.111(a)(3), (b).

<sup>129</sup> Keville, *supra* note 87, at 26.

participation in research. For example, a pregnant woman might become vulnerable research subject if she faces spousal or other familial pressures to undergo risky experimentation for the benefit of her fetus. Yet if this is what DHHS had in mind, it makes little sense that the regulation goes on to permit pregnant women's participation any time the purpose of the research is for the health needs of the fetus. Also, unlike a child who faces pressure from a parent, a pregnant woman is an autonomous adult who is better able to resist pressures from others. She is no different from a man who faces pressure from his adult children to participate in research for a treatment for Huntington's disease or a kind of cancer that is genetically transmissible and so likely to benefit his children. Yet we do not prohibit people with genetic disorders from participating in research because of the likelihood their family will pressure them, because people with genetic disorders are not necessarily dependent or powerless in a way that prevents them from withstanding that pressure.

It is arguable that pregnant women are more vulnerable to familial pressures than most because they may be financially dependent on a husband or other family members at a time when they face the imminent prospect of significant expenses from giving birth and raising a child. However, if that were the case, she would fall into the existing "economically disadvantaged" category in the regulation's list of vulnerable groups, which would render the separate category for pregnant women redundant. Also, it is demeaning to imply that a pregnant woman is necessarily incapable of financially supporting herself and her child. Single mothers do so all the time. While the state might plausibly argue that pregnancy discrimination in employment is a pervasive problem in this country that prevents many pregnant women from supporting themselves, such discrimination is illegal and it is unfair to restrict a pregnant woman's freedom to participate in clinical research because other people might break the law. To do so would give

discriminatory employers veto power over a pregnant woman's free choice. Such a rationale would also likely run afoul of the Constitution, which prohibits state action that is premised on the existence of discrimination by private actors.<sup>130</sup>

A pregnant woman might also be vulnerable if she experiences mental illness as a side effect of pregnancy, as a substantial minority of pregnant women do. But again, the regulations already recognize mental deficiency as a vulnerable class, so a separate category for pregnant women cannot be justified on the ground of mental illness.

It also is wrong to deem pregnant women as a class to be vulnerable the way the DHHS regulations do on the grounds that *some* but not *all* pregnant women will be vulnerable in the above-listed ways. The aforementioned international ethical guidelines stress that the proper inquiry for classifying a group as vulnerable is not whether individual persons within a group are vulnerable, but whether all the persons receiving special treatment have individual attributes that make him or her vulnerable.<sup>131</sup> For example, some elderly people are vulnerable because they may have dementia that makes them incapable of understanding the risks of research, or they may be institutionalized in a nursing home or hospital whose staff could coerce them into giving consent.<sup>132</sup> However, the vulnerability of a subset of elderly persons is not sufficient to establish vulnerability for the entire class of elderly persons. Elderly research subjects are only vulnerable

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<sup>130</sup> See, e.g., Palmore v. Sidoti, 466 U.S. 429 (1984) (holding that the state cannot grant custody of a child to her white father on the grounds that her white mother was cohabitating with black man and the child would consequently face racially-motivated scorn from the intolerant local community. The court reasoned that such action by the family courts would ratify private discrimination in violation of the Constitution.); Shelley v. Kraemer, 344 U.S. 1 (1948) (holding that judicial enforcement of private real estate covenants which exclude African American homebuyers is unconstitutional state action).

<sup>131</sup> See INTERNATIONAL GUIDELINES, *supra* note 124, at 64–66.

<sup>132</sup> *Id.* at 65.



“if and when they acquire vulnerability-defining attributes.”<sup>133</sup> The groups in the DHHS regulation are different from the elderly in this regard because coercion or incapacity are necessary characteristics of those groups. Since children cannot be legally emancipated from their parents or guardians, they will always be dependent to parents and therefore always subject to coercion. Prisoners by virtue of their imprisonment are subject to coercion by the state. Economic disadvantage is the very reason economically-disadvantaged persons are subject to coercion from offers of payment by researchers. Mental illness and lack of education are the reasons that mentally-disabled and educationally-disadvantaged persons, respectively, lack capacity. In other words, for the other vulnerable populations enumerated in the DHHS regulation, the group is defined by the trait that makes that group vulnerable. Pregnancy by itself is not a trait that causes coercion or lack of capacity. A pregnant woman who is mentally sound and economically independent has absolutely no inherent restrictions on her autonomy or her mental capacity that would necessarily render her any more unfit than the average adult to give informed consent.

In the end, it is hard to imagine what nondiscriminatory reason the DHHS had in mind when it deemed pregnant women vulnerable, because nothing inherent to pregnancy itself makes a pregnant woman less capable than any other adult of appreciating the risks and benefits of participation in medical research. The only reason to categorically view all pregnant women as vulnerable in the context of medical research is if you argue all pregnant women are either lack freedom to consent because they are subject to special coercive pressures, or that all pregnant women lack capacity to consent because of their mental state. Both arguments are unjustified by reality and demeaning to women. To argue that all women are dependent on others in the same

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<sup>133</sup> *Id.*

way that children, prisoners, and the indigent are suggests that women are equally as incapable of financially supporting themselves. Any cursory glance at employment statistics reveals this simply is not true. To argue that some pregnant women are subject to coercion from emotional pressures placed on them by their family views ignores the numerous contexts in which men and nonpregnant women can be subject to familial pressures that are equally coercive.<sup>134</sup> In order to plausibly distinguish pregnant women and justify their exceptional treatment under the law, you have to view them as somehow less mentally resilient or less capable of independent decisionmaking than ordinary adults. This unfounded stereotype that women, and especially pregnant women, have a weak mental constitution relative to men is reprehensible.

Similarly unacceptable is the suggested that a woman, merely by being impregnated, somehow loses the mental faculties that allowed her to make informed decisions about clinical research participation before she became pregnant. Any argument that a pregnant woman lacks mental capacity to fully appreciate the risks and benefits of clinical trials echoes the invidious stereotype of pregnant women as “hysterical”—the archaic belief that a the state of pregnancy so governs a woman’s mental processes that she cannot make rational, autonomous decisions the

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<sup>134</sup> In addition to the previously-discussed example of genetically transmissible conditions, family pressure is likely to occur in many research settings. One such scenario is a man with testicular cancer who has a choice between a conventional, proven surgical treatment that would render him infertile and enrolling in a clinical trial for an experimental new drug or gene therapy that has unknown safety risks. That man may have a wife or other relationship with a woman who wishes to have children and vehemently pressures him to enroll in the study to preserve his reproductive potential. Another situation could involve a woman who has undergone an abortion and has a family member with Parkinson’s disease—a condition for which stem-cell research has been promising. That family member might pressure her to contribute the fetus to research that might provide a cure for his or her condition.

way men can, so men should make the decisions for her.<sup>135</sup> Such rationales were once used to promote the exclusion of women from the workforce and from voting.<sup>136</sup>

Some suggest that the vulnerability classification exists not because pregnant women are vulnerable, but because the fetuses. This argument does make sense to a certain degree given that children are also vulnerable subjects, and both children and fetuses are incapable of meaningfully participating in informed consent. However, if this is the case, the regulation should unambiguously state that fetuses are the vulnerable population, not pregnant women. This would avoid the demeaning connotations of labeling pregnant women vulnerable. Whether or not DHHS' decision to designate all pregnant women vulnerable actually is based in part by unconscious sex discrimination, it certainly is an odd presumption that sends an unseemly message about pregnant women's autonomy.

b. The DHHS Regulations Inappropriately Restrict Pregnant Women's Ability to Participate in Clinical Research

Even if fetuses can be justifiably classified as a vulnerable population, like children, the DHHS regulation is exceptional because it goes much further than the restrictions placed on research involving child subjects in ways that yet again invoke invalid stereotypes. I argue that as a matter of sound public policy, the existing regulations should be changed to provide women with meaningful access to clinical trials for themselves and their fetuses. I contend that for the reasons discussed below the regulations as they currently stand are unduly prohibitive of research.

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<sup>135</sup> See Joan W. Scott, *How did the Male Become the Normative Standard for Clinical Drug Trials?*, 48 FOOD & DRUG L. J. 187, 188 (1993).

<sup>136</sup> See *id.* at 189–92.

To begin with, the regulation has internal contradictions that could confuse and deter research. The regulation requires informed consent for pregnant subjects to comply with the general rules for informed consent for all other subjects in DHHS supported research.<sup>137</sup> However, for research on pregnant women, the regulation also prohibits outright certain communications between the researcher and pregnant subjects. Specifically, the regulation obligates researchers to have “no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.”<sup>138</sup> These prohibitions likely prohibit a researcher from meeting the ethical standard for informed consent. According to the International Ethical Guidelines for Biomedical Research Involving Human Subjects, a researcher must inform a pregnant subject about the option of terminating the pregnancy as part of the informed consent process, provided abortion is legal under those circumstances.<sup>139</sup> DHHS informed consent rules further require “a description of any foreseeable risks or discomforts to the subject,” and elective abortion can be a foreseeable risk in many clinical trial contexts. If a pregnant woman has a serious medical condition which the clinical trial is designed to treat, it may be the case that she is not cured by the trial therapy and her medical condition necessitates terminating the pregnancy for the sake of her health or even her life. Similarly, an experimental drug could have the potential for rare side effects that are so devastating to the mother’s health that abortion would be necessary to preserve the health or life of the mother. Under the current regulation, a researcher would be helpless to warn a pregnant woman of the exact nature of the risk she faces. If he tells her any details of the relative risks and discomforts of various available abortion procedures at different stages of

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<sup>137</sup> 45 C.F.R. § 46.204(d).

<sup>138</sup> 45 C.F.R. § 46.204(i).

<sup>139</sup> INTERNATIONAL GUIDELINES, *supra* note 124, at 73.

pregnancy, he could be deemed to have had a part in determining the timing or method of pregnancy termination.

Also, since terminating the pregnancy can mean birth in addition to elective abortion, the regulations interfere with their own requirement that all risks be minimized. For a study of the effects of drugs in late pregnancy, it may be best for a researcher to encourage a subject to induce labor if she goes significantly past her due date to avoid harm to the baby and the mother from excessively delayed birth. Moreover, if it appears the drugs are harmful to the fetus, simply withholding future medication may not be enough to minimize harm to the fetus. Many drugs can remain in the pregnant woman's system long after she ceases to take them, causing additional harm to the fetus. In such cases, it may be best to induce labor to prevent further damage to the viable fetus' development. The DHHS regulations prevent this not only by excluding the researcher from the decision to end a pregnancy, but also through a separate provision that prevents a researcher from having any part in determining the viability of a fetus.<sup>140</sup>

The regulation bars researchers from offering any "inducement, monetary or otherwise" to end a pregnancy.<sup>141</sup> Although it is understandable that the department would wish to avoid pressuring a woman to have an abortion, it is unwise to set up a system in which researchers cannot compensate a woman who understandably wants an abortion because of her participation in the study. A woman could, for example, find out via ultrasound that her fetus will be born with severe birth defects that would cause the child to suffer, or a woman may need to abort a fetus for health reasons related to the clinical trial. Since research subjects may be unable to pay for an abortion themselves, which runs an average price tag of \$400 in the first trimester but

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<sup>140</sup> 45 C.F.R. § 46.204(j).

<sup>141</sup> 45 C.F.R. § 46.204(h).

costs thousands if performed later in the pregnancy,<sup>142</sup> a researcher may not be able to recruit participants unless he can compensate them for the expense of a necessary abortion. Ironically, the rules prohibit compensation for the kind of loss that a pregnant woman might most want compensation for.

In addition to the internal contradictions in the regulation, the regulation has other substantive limits on pregnant women's participation that are unreasonably restrictive. For any study with greater than minimal risk to the fetus, a woman cannot participate in a study unless she can show that the study will directly benefit either herself or the fetus.<sup>143</sup> This puts the burden on researchers to prove the drug's therapeutic value before it has even been tested in a relevant clinical population.

Even if the research is designed to directly benefit the woman or the fetus, the regulations require that the "risk is the least possible for achieving the objectives of the research."<sup>144</sup> This too puts researchers in an awkward and perhaps impossible position because it forces them to prove the risks of a particular therapy before they have human data to support their risk estimates. Moreover, it unreasonably interferes with a researcher's assessment of drug effectiveness, because the most effective dose in a pregnant woman may present more risk to the fetus than a less effective but safer dose. A researcher may also feel constrained by the "least possible" risk requirement to test only at the lowest dose that could be effective, even if a higher dose would be more medically beneficial to women suffering from a particular disease or ailment.

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<sup>142</sup> See, e.g., Monica Davey, *Battle on Late-Term Abortions Shifts to a Clinic in Nebraska*, N.Y. TIMES, Dec. 4, 2009, at A1; Katherine Q. Seelye, *Another Standoff May be Looming on the Abortion Issue*, N.Y. TIMES, Nov. 15, 2009, at A26.

<sup>143</sup> 45 C.F.R. § 46.204(b).

<sup>144</sup> 45 C.F.R. § 46.204(c).

The statute also allows a study to proceed if it presents only “minimal risk” and “the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.”<sup>145</sup> Again, it is unrealistic to expect a researcher to declare that a drug has minimal risk before clinical research has been conducted, because without research it is difficult to determine a risk is no greater than minimal.<sup>146</sup> A cautious researcher would very likely be reluctant to vouch that a drug has a minimal risk of harm only to be proved wrong later when clinical testing shows otherwise. Also, the researchers may have a difficult time reconciling this provision with their informed consent obligations, because it may appear misleading for them to declare on the one hand to the IRB that the drug presents only minimal risk to the fetus, and then inform their research subjects that their fetuses may experience unforeseen serious side effects from the drug.

Also inexplicable is the requirement that in addition to only minimal risk, the study must be necessary to uncover important biomedical knowledge that cannot be obtained through any other means. This is a surprisingly high threshold for a researcher to meet given that the minimal risk is defined as such a low risk under the statute. Minimal risk is risk of harm or discomfort that is no more likely to occur or more severe than harm or discomfort which occurs in ordinary life or in routine physical examinations.<sup>147</sup> In other words, a study with minimal risk leaves a fetus as well off after the experiment as it would have been had the experiment not occurred. Such a risk is virtually inconsequential. Yet even for studies with so low a risk, the statute

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<sup>145</sup> 45 C.F.R. § 46.204(b).

<sup>146</sup> See R. Alta Charo, *Protecting Us to Death: Women, Pregnancy and Clinical Research Trials*, 38 ST. LOUIS U. L. J. 135, 160 (1993) (“animal studies may be insufficient to demonstrate a “minimal” risk to the fetus”); William F. Rayburn & Kevin C. Farmer, *Off-Label Prescribing During Pregnancy*, 24 OBSTETRICS & GYNECOLOGY CLINICS OF NORTH AM. 471, 472 (1997) (minimal risk “is frequently difficult to determine with accuracy”).

<sup>147</sup> 45 C.F.R. § 46.204(b).

requires that a researcher show he will gain “important” knowledge that he could not have any other way. This opens the door for an IRB to reject out of hand any study with minimal risk simply because it does not view the research sufficiently important, or because it believes post-market studies or registries or studies in nonpregnant women or men could provide adequate information instead. It also represents a much more stringent standard than studies on children and even newborn infants, which DHHS allows any time there is no greater than minimal risk and at least one parent consents.<sup>148</sup> To treat a fetus as deserving of greater protections than a living child is so unprecedented that it is almost absurd. While it may be justifiable to have a system that gives the *same* protections for children and a viable fetus, or a fetus with sentience or the ability to feel pain, there can be no explanation for why a fetus should be protected more than a living child.

Furthermore, minimal risk is itself simply too constraining a limit on nontherapeutic studies on pregnant women. When a woman recreationally uses alcohol or tobacco she exposes her fetus to greater than normal (i.e. not minimal) levels of risk.<sup>149</sup> Although such actions are socially frowned-upon, they are still legal. In the context of recreational drug use, at least the law permits pregnant woman to do what a nonpregnant woman or a man could do, despite risk to the fetus. However, if a pregnant chooses to enroll in a clinical drug trial that presents more than minimal risk with the altruistic goal of promoting medical knowledge and improving public health, the law prohibits her from doing while at the same time allowing any other adult to take on those risks.<sup>150</sup> It can scarcely be contested that a pregnant woman’s altruistic reasons for

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<sup>148</sup> 45 C.F.R. § 46.404, 408(a).

<sup>149</sup> See BOYD & MARCELLUS, *supra* note 97, at 45–46.

<sup>150</sup> Even prisoner subjects, another vulnerable adult class under the regulations, is permitted to participate in research with greater than minimal risk that is nontherapeutic so long as the risks



imbibing drugs in the context of a clinical trial are more socially beneficent than purely the recreational motives of women who smoke or drink during pregnancy. Also, a clinical trial minimizes harm to the fetus through ongoing monitoring and, if necessary, medical treatment. Such supervision is lacking in recreational uses of alcohol and tobacco, meaning the rationale for government intervention is even stronger there than in clinical trials. Yet in spite of this the law inexplicably accords greater respect to a woman's freedom in the context of recreational legal drug use than in the context of medically-supervised clinical trials.

The fact of the matter is that women engage in an enormous range of activities that pose a greater than minimal risk to the fetus. Driving a car, participating in sports, living in a town near a chemical factory, working with chemicals, gaining excessive weight and overindulging in caffeine all expose a gestating fetus to risks that are out of the ordinary.<sup>151</sup> Yet we do not revoke pregnant women's driver licenses, force them to relocate and quit their hazardous jobs, give them specially restricted menus at restaurants, or ban them from Starbucks. The government's decision to single out clinical trials as the one area of a woman's life that they will not tolerate minimal risk to a fetus is an unjustified exception to practice of tolerating risk from women's choices in other aspects of her life. If the government were to prohibit risk to the fetus in all situations, a pregnant woman's activities would be so constrained she could not function with any semblance of normality. We routinely permit women to do things that could increase risk to her fetus because we trust a mother to weigh the risks and make an informed decision. Indeed, it is even more likely she will be able to make a fully informed decision in the context of a clinical

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are no greater than risks that would be accepted by nonprisoner volunteers. 45 C.F.R. § 46.305(a)(3).

<sup>151</sup> See e.g., SAMUELS & SAMUELS, *supra* note 5, at 26–27, 133; Dawn Johnsen, *From Driving to Drugs: Governmental Regulation of Pregnant Women's Lives after Webster*, 138 U. PENN. L. REV. 179, 192 (1989); Schonfeld et al., *supra* note 10, at 112–113.

trial than in her everyday life, because researchers must fully inform subjects of the risks and benefits before obtaining their consent.

The Department of Health and Human Services' decided to take the risk-benefit decision out of a pregnant woman's hands and decide for itself what level of risk is acceptable. The International Ethical Guidelines for Biomedical Research Involving Human Subjects express the opinion that the decision whether to accept the fetal risks posed by a clinical trial should be made by the pregnant subject as part of the informed consent process.<sup>152</sup> The Department's decision is only logical if you accept the premise that a pregnant women cannot be trusted to properly weigh the risks to herself and her fetus against the benefits of the research. This assumption plays into the stereotype that women are inherently selfish and therefore cannot make "good" decisions during pregnancy. The statute's presumption of excluding women unreasonably concludes that pregnant women will make bad choices if they are presented with a choice, and so no choice should be left up to them.

The Department's policy also penalizes all pregnant women for the mistakes of an errant minority who make decisions without giving due weight to the fetus' wellbeing. As a report from the Committee on Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies explains:

"Virtually all women desire healthy infants, even when their pregnancies are unplanned.

While occasionally there may be pregnant women who are incapable of acting in the interest

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<sup>152</sup> INTERNATIONAL GUIDELINES, *supra* note 124, at 74. The guidelines go on to stress that women should be allowed to make this choice even when the risks are unknown or ambiguous. *Id.*

of their future children, it would be inappropriate to base a public policy on an atypical case, rather than a normative case.”<sup>153</sup>

By defining minimal risk as no greater than the ordinary level of risk a fetus would experience from everyday life, the statute also presumes that it is unacceptable for a woman to expose her fetus to any risk that is greater than normal, even if it is only a marginal increase over everyday risk, unless her use of the drug is therapeutic. This ignores the indirect benefits of drug testing to a pregnant woman such as increased knowledge about drug safety that can be for used by other pregnant women or, indeed, by her in subsequent pregnancies if a medical need for the drug later arises. A normal risk-benefit calculus usually factors in societal benefits. The DHHS circumvents this for pregnant women by concluding that no societal benefit can ever outweigh a slightly elevated risk to a particular fetus. Overall, DHHS’s willingness to decide these risk-benefit decisions on behalf of pregnant women is troubling as a matter of policy, because risks and benefits have very subjective value,<sup>154</sup> and because it suggests that women’s ability to make an informed decision is less trustworthy than a man’s.

## B. Constitutional Challenges to the Current Governmental Restrictions on Pregnant Women’s Participation in Clinical Research

### i. Due Process

One avenue for challenging the existing DHHS regulations is by analogy to the Fourteenth Amendment due process right to abortion first articulated in *Roe v. Wade*. *Roe* set out a structure for balancing the maternal privacy interest in abortion against the state’s compelling interest in the protection of fetal rights. For the first trimester, the maternal right

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<sup>153</sup> INSTITUTE OF MEDICINE, *supra* note 15, at 195.

<sup>154</sup> See Stacey E. Pauker, *From Protectionism to Access: Women’s Participation in Clinical Trials – Conflict, Controversy and Change* (2002), in Peter Barton Hutt, ed., *Food and Drug Law: An Electronic Book of Student Papers* at 33–34.

always prevails, for the period between the start of the second trimester and viability, the state's interest justifies restrictions that do not constitute an undue burden on the women, and after viability the state's interest justifies an outright ban on abortion.<sup>155</sup> The court subsequently reaffirmed *Roe's* essential holding in Planned Parenthood v. Casey,<sup>156</sup> and clarified that any state-imposed restrictions before viability may not constitute an undue burden on a woman's right to an abortion.<sup>157</sup>

There are two chief difficulties with forming an analogy to abortion. First, while an aborted fetus only ever has a potential for life outside the womb before viability, a fetus in a clinical trial may go on to be born and attain full personhood. Because of this distinction, it could be argued the state has a greater interest in protecting a fetus from clinical trial harms that can affect the fetus after birth, than from abortion, which by definition only affects the fetus before birth.

Another reason it is difficult to analogize a right to an abortion to a right to a clinical trial is because of the nature of interests at stake. One of the interests articulated by the *Roe* court is the interest in preventing "direct harm medically diagnosable in early pregnancy."<sup>158</sup> However, the DHHS regulations do accommodate this interest by allowing participation by pregnant women in research when the research presents a direct health benefit to the mother. Other maternal interests articulated by the *Roe* court include imminent psychological distress, mental and physical, the distress of an unwanted child or a child that the woman is unable to care for, or the stigma of unwed motherhood.<sup>159</sup> For the kind of research that the DHHS restricts, i.e.

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<sup>155</sup> Roe v. Wade, 410 U.S. 113, 164–65 (1973).

<sup>156</sup> Planned Parenthood v. Casey, 505 U.S. 833, 846 (1992).

<sup>157</sup> *Id.* at 874.

<sup>158</sup> 410 U.S. at 153.

<sup>159</sup> *See id.*

participation in research that does not have a direct medical benefit for the mother, it is harder to articulate the kinds precise personal harms that ensue from a woman's lack of access. The harms from the DHHS regulation are more indirect than the harms of being denied an abortion. As previously discussed, the DHHS regulations overly deter drug testing in women, meaning that all women suffer collective harm from being denied information they need when they become pregnant and have taken or will take untested medication. While this harm can have serious effects on pregnant women's stress levels, hazardous consequences for their health and their fetuses wellbeing, and can result in an unwanted abortion due to fears of the uncertain risks, it is hard to directly attribute these harms to the DHHS regulations themselves because the harms are somewhat attenuated from the government action and because the women who suffer the harms may not necessarily be the same women who are denied access to a particular drug trial.

The decision by a woman to participate in clinical trials while pregnant could also be likened to the right to terminate artificial life support, i.e. the "right to die" that was upheld by the Supreme Court in *Cruzan v. Missouri Dep't of Health*.<sup>160</sup> One could argue that if a woman has a privacy right to make a medical decision that would end her life, she should certainly have the right to participate in the decision to undergo medical risk to save the lives of others by providing needed information about pregnancy remedies for their illnesses.<sup>161</sup> Although the state will likely argue its interest in protecting fetal life should outweigh the individual's right to medical self-determination, the state of Missouri attempted to make the same argument in *Cruzan* by asserting "an interest in the preservation of human life" generally, and the state's argument failed then.<sup>162</sup> However, the court emphasized that the decision to end one's life was a

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<sup>160</sup> See generally *Cruzan v. Mo. Dep't Health*, 497 U.S. 261 (1990).

<sup>161</sup> See INSTITUTE OF MEDICINE, *supra* note 15, at 144.

<sup>162</sup> 497 U.S. at 282.

“deeply personal decision of obvious and overwhelming finality,” which tilted the balancing of interests in favor of the individual’s privacy right over the state’s interest in life.<sup>163</sup> It may be harder to argue that a woman’s decision to participate in a clinical trial is as deeply personal an interest when she would not directly benefit from the trial. Since the DHHS regulations do allow participation with direct benefit to the pregnant woman, the argument that the regulations violate Due Process under *Cruzan* is harder to make.

ii. Equal Protection

There is no question that the DHHS regulations treat men and women differently. The most blatant unequal treatment of men and women under the law governing clinical research is the fact that the DHHS regulations place restrictions only placed on pregnant and pregnable women, and not men that are capable of conceiving children. Yet men are also capable of causing birth defects in their offspring through preconception and postconception exposure to teratogens.<sup>164</sup> Such inequality is wrong because shifts all responsibility, and therefore all blame, for fetal injury to mothers while at the same time completely relieving men of that responsibility.<sup>165</sup>

There is one FDA guidance document that suggests a need for increased protections for research subjects in studies involving male teratogens. That guidance document indicates that where animal studies or other data shows a propensity for causing sperm, testicular, or

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<sup>163</sup> *Id.* at 281.

<sup>164</sup> INSTITUTE OF MEDICINE, *supra* note 15, at 179–81; Epstein, *supra* note 23, at 364–65. Male teratogens can cause fetal abnormalities in three ways: (1) gene mutations in the sperm, (2) epigenic damage to the sperm that affects the processes that control the expression of phenotypes in the offspring, and (3) transport of the teratogen into the uterus via ejaculate during sexual intercourse, which exposes the fetus to the teratogen postconception in utero.

<sup>165</sup> Joan C. Callahan, *Prenatal and Preconceptive Harm: Introduction*, in REPRODUCTION, ETHICS, AND THE LAW: FEMINIST PERSPECTIVES (Joan C. Callahan ed., 1995); *see* Bertin, *supra* note 116, at 385.

chromosomal anomalies, the decision to include men in clinical trials should take into account “the nature of the abnormalities, the dosage at which they occurred, the disease being treated, the importance of the drug, and the duration of drug administration.”<sup>166</sup> In other words, the guidance recommends that the researcher perform the ordinary risk/benefit analysis for male teratogens. The guidance further states that “in some cases special written consent forms, even in Phase III may be required.”<sup>167</sup> Significantly, this ‘requirement’ is not even enforceable by the FDA since the beginning of the guidance document specifically states that the guidelines are recommendations only, and “are not to be interpreted as mandatory requirements by the FDA.”<sup>168</sup> This written consent provision also leaves the decision of whether to participate in the drug trial up to the male research subject, thereby allowing a father to unilaterally consent to a process that may harm a fetus conceived during the experiment. In contrast, the DHHS regulations require a father’s consent in addition to the mother’s before she is permitted to participate in a trial that would not directly benefit her.<sup>169</sup> This inconsistency implies that a man can be trusted to unilaterally make decisions that could result in birth defects to his offspring, but a woman cannot be allowed to make the same decision unless the father agrees with her choice. Not only is this inconsistency unequal, it is also an unreasonable burden on pregnant women’s ability to make decisions about her own body, because it gives a veto power to any biological father aside from a rapist whose consent can be obtained.<sup>170</sup> This veto power applies even if that biological father is estranged from the mother, a domestic abuser, an extortionist who attempts to

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<sup>166</sup> U.S. DEPT. HEALTH AND HUM. SERVS., FOOD AND DRUG ADMIN., CTR. DRUG EVAL. RES. (CDER), GUIDANCE FOR INDUSTRY: GENERAL CONSIDERATIONS FOR THE CLINICAL EVALUATION OF DRUGS 14 (1997).

<sup>167</sup> *Id.*

<sup>168</sup> *Id.* at 3.

<sup>169</sup> 45 C.F.R. § 46.204(e).

<sup>170</sup> *Id.*

secure a bribe in return for his consent, or a man who has no intention of assuming any parental responsibilities towards or having any relationship with his biological child.

A further example of the government's unequal treatment of the sexes can be seen through the precautions the government requires from researchers who test drugs in women who could become pregnant over the course of the study. One industry survey shows that the FDA asks 79% of pharmaceutical companies to exclude fertile women from early stage drug trials.<sup>171</sup> In one example, the drug Proscar was known to cause teratogenic effects when used by men prior to conception. Yet in a study involving Proscar, the IRB approved research that simply accepted man's promise that he would use contraception during the trial, without any follow up to ensure compliance.<sup>172</sup> Pregnable women on the other hand must undergo far greater protectionist measures before they can be exposed to known teratogens. Accutane, a popular acne-fighting prescription drugs that is used by approximately 200,000 people each month,<sup>173</sup> is another known teratogen that causes severe heart and brain damage in children born to parents who use the drug.<sup>174</sup> Although the FDA requires that both men and women who take Accutane enroll in a registry to study to the effects in their offspring, only women have to comply with additional stringent FDA restrictions on their use of the drug.<sup>175</sup> Before a woman can obtain a prescription for Accutane from her doctor, she must enroll by phone in an FDA-mandated program, called "iPledge" in a registration process that many doctors and pharmacists complain

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<sup>171</sup> Bonnie J. Goldmann, *A Drug Company Report: What is the Same and What is Changing with Respect to the Inclusion/Exclusion of Women in Clinical Trials*, 48 FOOD & DRUG L. J. 169, 173 (1993)

<sup>172</sup> Nancy L. Buc, *Women in Clinical Trials: Concluding Remarks*, 48 FOOD & DRUG L. J. 223, 224 (1993).

<sup>173</sup> Jonathan D. Rockoff, *Complaints Won't Delay FDA Acne Drug Program*, BALT. SUN, Feb. 24, 2006, at A5.

<sup>174</sup> Editorial, *When Warnings Fail*, TIMES-PICAYUNE (New Orleans), Aug. 15, 2005, at M4.

<sup>175</sup> *Id.*



is lengthy and confusing.<sup>176</sup> Once enrolled in the program, the woman must immediately take two pregnancy tests to confirm she is not pregnant before obtaining her prescription.<sup>177</sup> Prior to each monthly refill, she must take and pass another pregnancy test.<sup>178</sup> While using the drug, the woman must successfully pass an examination composed of questions designed to test her understanding of her birth control obligations and the pregnancy risks of the drug.<sup>179</sup>

Thus the FDA imposes a double standard. When a man could impregnate a woman and father a child with birth defects caused by his exposure to a teratogenic drug, his word that he will use contraception is enough. Yet when a woman could become pregnant with a child who may have birth defects because of her drug exposure, the government requires her to undergo numerous onerous procedures designed to ensure she uses contraceptives. Whether intentional or not, this practice sends a message that men can be trusted to safeguard the welfare of their potential future children, but women are too unreliable to trust their word alone on under the exact same circumstances.

It may be the case that measures like iPledge are necessary for people to comply with their doctor's or researcher's instructions for taking a known severe teratogen. Yet even if this is the case there is still no articulable scientific basis for requiring those measures only for women and not from men. Though it is true that a woman might lie about her contraception plans, forget to use contraception, or use contraception that fails, the same is true for a man.<sup>180</sup> Even if male teratogens might cause less frequent or less severe injury on average than female teratogens, which we have no way of knowing because of the shortage of clinical research on teratogenic

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<sup>176</sup> Rockoff, *supra* note 173, at A5.

<sup>177</sup> *When Warnings Fail*, *supra* note 174, at M4.

<sup>178</sup> *Id.*

<sup>179</sup> Schonfeld et al., *supra* note 10, at 107 (2009).

<sup>180</sup> Buc, *supra* note 172, at 226.

effects, it is still unacceptable that the law singles out pregnant women for restrictions while adopting a laissez-faire attitude towards fertile men.<sup>181</sup>

The evidence that women and men are treated differently under the current regulatory system is clear. However, the mere fact of unequal treatment may not be enough to constitute sex discrimination under the Constitution. Although the constitutional language on its face says that no state can “deny any person . . . the equal protection of the laws,”<sup>182</sup> the Supreme Court has interpreted this narrowly as applied to sex discrimination. In Geduldig v. Aiello, the Supreme Court announced that not all discrimination on the basis of pregnancy is discrimination on the basis of sex.<sup>183</sup> The court held that California statute which required disability insurance for all medical conditions except pregnancy did not invidiously discriminate against women, because (1) the statute discriminates between pregnant women and nonpregnant persons (including nonpregnant women), not between similarly situated men and women, and because (2) the benefits of the coverage for non-pregnancy related conditions “accrue to members of both sexes.”<sup>184</sup> It is worth noting at the outset that *Geduldig* has been heavily criticized by scholars and subsequent Supreme Court cases limit its holding to insurance claims.<sup>185</sup> Thus it is an open question whether a current or future Court might reverse *Geduldig* and hold pregnancy discrimination is sex discrimination.

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<sup>181</sup> See Charo, *supra* note 146, at 154.

<sup>182</sup> U.S. CONST. amend. XIV § 1.

<sup>183</sup> Geduldig v. Aiello, 417 U.S. 484, 497 n.20 (1974).

<sup>184</sup> *Id.* But see Geduldig v. Aiello, 417 U.S. 484, 501 (1974) (Brennan, J. dissenting) (observing that the California statute actually confers additional benefits on men that women do not enjoy by providing disability coverage for male-specific medical conditions like circumcision and prostate cancer).

<sup>185</sup> L. Elizabeth Bowles, *The Disenfranchisement of Fertile Women in Clinical Trials: The Legal Ramifications of and Solutions for Rectifying the Knowledge Gap*, 45 VAND. L. REV. 877, 899 (1992)

However, even if *Geduldig* is good law it is still distinguishable from the DHHS regulations in ways that could render the regulations unconstitutional. First, the men at issue in *Geduldig* were not similarly situated to the women women because the men could never personally obtain any benefit from pregnancy disability coverage. Thus the court could arguably maintain that the California statute did not give women anything less than it gave men, because it gave them the same coverage, that is, coverage for all conditions except pregnancy. The clinical trial regulations are different because men are similarly situated to women since both men and women alike can risk birth defects in their offspring through exposure to experimental drugs. Thus the statute gives men unhindered access to clinical trials, while giving women access to the same trials, with the same risks, under only limited and prohibitive circumstances. This treats women different than similarly situated men in a way that the California disability statute did not.

Additionally, the regulatory regime does not provide men and women with the same underlying benefits of clinical trial research, because men are guaranteed clinical data on drug safety and effectiveness that allows them to make informed decisions about medication use throughout their entire lives, and women are not assured access to the same clinical data during any period in their lives when they are pregnant. This disparity puts women at a disadvantage relative to men that could be enough to constitute sex discrimination.<sup>186</sup> Men and women also do not receive the same access to clinical trials, which can be a benefit in and of itself to the extent that the trials provide compensation, enable subjects to feel they are contributing to a good cause, or medically benefit the subjects.<sup>187</sup>

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<sup>186</sup> See Charo, *supra* note 146, at 162.

<sup>187</sup> See Karen H. Rothenberg, *Gender Matters: Implications for Clinical Research and Women's Health Care*, 32 HOUS. L. REV. 1201, 1254 (1996).

Another case that provides a basis for a legal challenge to the DHHS regulations is *Johnson Controls*.<sup>188</sup> There the court invalidated an employer's policy which excluded pregnant or pregnable female employees from jobs that would expose them to lead, an environmental teratogen.<sup>189</sup> The court based its decision on the fact that despite the employer's claim that the policy had a nondiscriminatory purpose of fetal protection, the policy did not equally protect the offspring of male and female employees:

“Despite evidence in the record about the debilitating effect of lead exposure on the male reproductive system, Johnson Controls is concerned only with the harms that may befall the unborn offspring of its female employees.”<sup>190</sup>

The Court went on in dicta to express its opinion that choices involving risks to the fetus should rest with the parents who will experience the costs of those risks, not with the employer or the courts. It stated, “Decisions about the welfare of future children must be left to the parents who conceive, bear, support, and raise them.”<sup>191</sup> Such broad language implies that the decision to participate in trials of potentially teratogenic drugs should be left up to the parents through the informed consent process rather than imposed on them by a regulatory mandate.

Although *Johnson Controls* specifically addressed Title VII of the Civil Rights Act rather than the Constitution, it still governs paid research subjects if they can be considered “employees” of the drug company conducting the research. If research subjects are not found to be employees under Title VII, *Johnson Controls* nonetheless indicates that the Supreme Court may be more inclined in the future to accept pregnancy discrimination as a form of sex

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<sup>188</sup> *Int'l Union v. Johnson Controls*, 499 U.S. 187 (1991).

<sup>189</sup> *Id.* at 190–92.

<sup>190</sup> *Id.* at 198.

<sup>191</sup> *Id.* at 206.

discrimination under the Constitution where men and women are similarly able to cause birth defects, and a fetal protection policy excludes only women from activities involving teratogens.

Johnson Controls also illuminates the way in which invidious stereotypes can underlie a policy that appears on its face to be based on a neutral rationale of fetal protection. A defense expert was asked during deposition why he did not prohibit male employees' exposure to lead when all scientific evidence indicated that such exposure caused birth defects in children conceived by those men. His response was not that he doubted the studies' veracity, but that he simply "can't control that situation."<sup>192</sup> Implicit in his response was his belief that female reproduction can be legitimately controlled by her employer, but men's freedom to reproduce is inviolate.<sup>193</sup>

#### IV. The Unjustified Nature of Manufacturer's Fears of Liability in Light of Prevailing Tort Doctrine

Many pharmaceutical companies allege that even if the regulatory restrictions on research were lifted, they could not possibly conduct clinical research in pregnant subjects because of the enormous litigation costs that would inevitably ensue. These allegations are heavily exaggerated at best, and are directly contradicted by the relevant tort law at worst.

Ever since Thalidomide and DES caused serious birth defects among children born to pregnant users of the drugs, the pharmaceutical industry has taken a hands-off approach to pregnancy testing and cited fears of litigation as its reason.<sup>194</sup> However, neither drug was ever

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<sup>192</sup> Charles W. Fishburn, Transcript of Deposition, *Int'l Union v. Johnson Controls*, E.D. Wis. No 84-C-0472, June 13, 1985, at 85.

<sup>193</sup> See *Bertin*, supra note 116, at 385.

<sup>194</sup> Keville, supra note 87, at 25–26.

tested in pregnant women prior to its release onto the market.<sup>195</sup> DES did not undergo any animal teratogenicity testing either.<sup>196</sup> Thalidomide underwent some animal testing which suggested reproductive safety in animals, but as the FDA employee reviewing the manufacturer's application for approval observed, thalidomide is metabolized very differently in animals than in humans and so animal tests could not serve as a valid indicator of teratogenicity.<sup>197</sup> Had the tests been conducted in humans the dangers would have been immediately apparent, since 100% of women exposed during the timeframe when limb malformations in pregnancy occur gave birth to babies with noticeable birth defects.<sup>198</sup>

Another case study often cited by the pharmaceutical industry is that of Bendectin, an anti-nausea drug that its manufacturer, Merrell Dow, withdrew voluntarily from the market in the face of growing litigation costs.<sup>199</sup> The Bendectin lawsuits were since proven frivolous—premised on “junk science” conducted by plaintiffs' experts-for-hire.<sup>200</sup> As a result, Merrell Dow lost a profitable U.S. market, although the drug is still sold abroad,<sup>201</sup> and American

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<sup>195</sup> *Id.* At least one postmarket study aimed at measuring DES efficacy at preventing miscarriages included pregnant women and was a subject of a lawsuit. The lawsuit, however, was based not a negligence or strict liability claim derived from the drug's harmful side effects, but instead was based on a battery theory because that the physicians conducting the study on behalf of the drug company secretly administered the drug to their patients during prenatal care without informing the women the drug they were taking was DES and without even telling the women that they were part of an experiment. *Mink v. U. Chicago*, 460 F. Supp. 713, 715–720 (N.D. Ill. 1978). The suit was allowed to proceed the sole ground that the subjects had not consented at all to the research performed on them, and as such is irrelevant to determining the viability of lawsuits brought by pregnant research subjects who knowingly participated in clinical trials or lawsuits brought by their children.

<sup>196</sup> Keville, *supra* note 87, at 25.

<sup>197</sup> See Howard B. Yeon, *Thalidomide Revisited* (1998), in Peter Barton Hutt, ed., *Food and Drug Law: An Electronic Book of Student Papers* at 7.

<sup>198</sup> See *id.* at 8.

<sup>199</sup> Marlene Cimos, *Long Shunned, Morning Sickness Drug May Be Staging a Comeback*, L.A. TIMES, Dec. 7, 2000, at A30.

<sup>200</sup> *Id.* at A30.

<sup>201</sup> *Id.*

consumers lost a valuable remedy for morning sickness which, in severe cases, can cause extreme dehydration, weight loss, and even death in pregnant women.<sup>202</sup>

While the Bendectin case is unfortunate, upon closer examination it does not in any way support the industry's proposition that drug testing in pregnant women would result in increased liability. Merrell Dow was never actually held liable for its Bendectin sales in any court of law. All of the lawsuits against it were either dismissed, overturned on appeal, or settled for small amounts of money.<sup>203</sup> Even though it underwent costs of defending the suits, none of those lawsuits were brought by participants in a clinical drug trial, because Merrell Dow did not conduct clinical trials in pregnant women.

Moreover, the Bendectin litigation gave rise to an important Supreme Court decision concerning the drug. The case, *Daubert v. Merrell Dow Pharmaceuticals*, raised the standard for admissibility of expert testimony<sup>204</sup> and has since significantly cut back on the kind of speculative science that allowed the Bendectin suits to be brought in the first place. After *Daubert*, the likelihood of widespread frivolous litigation against pharmaceutical companies has diminished.<sup>205</sup> Plaintiffs' lawyers can no longer proceed with claims unless the pharmaceutical company sold the drug without adequate warnings in spite of reliable scientific evidence obtained with proven methods showing the existence of birth defects. In the end, the Bendectin litigation provided the solution to its own problem of frivolous litigation.

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<sup>202</sup> *Id.* ("Morning sickness afflicts up to 90% of all pregnant women. . . about 1% suffer an extreme form, hyperemesis gravidarum, which can be dangerous to the fetus. It can produce weight loss, dehydration and electrolyte imbalances, sometimes requiring hospitalization.")

<sup>203</sup> *Id.*

<sup>204</sup> See *Daubert v. Merrell Dow Pharmaceuticals*, 509 U.S. 579, 593–95 (1993) (*holding* that expert evidence is only admissible under Rule 702 of the Federal Rules of Evidence if it is sufficiently reliable, which courts can determine using such factors as scientific methodologies, publication, peer review, known rates of errors, general acceptance in the scientific community and similar indicia of reliability).

<sup>205</sup> Cimons, *supra* note 199, at A30.

As the law currently stands, pharmaceutical companies may run a greater risk of litigation now than if they were to conduct clinical studies. There is no automatic strict liability for harmful drugs under common law because pharmaceutical drugs meet the “unavoidably unsafe” exception to strict liability. The comments to the Restatement 2<sup>nd</sup> of Torts identify drugs as “an especially common” form of “unavoidably unsafe” products, because drug side effects are a “known, but apparently reasonable risk.”<sup>206</sup> However, in order to qualify for this exception the drugs must be accompanied by “proper directions and warning.”<sup>207</sup> Strict liability applies only to “unreasonably” dangerous products,<sup>208</sup> and a product is not unreasonably dangerous if it has known risk that renders it unavoidably unsafe, provided the manufacturer warns the buyer of the risks. The warning must include notice of all dangers that the manufacturer knows of, or should know, based on “the application of reasonable, developed human skill and foresight.”<sup>209</sup>

If drug companies were to conduct reliable premarket clinical research in pregnant women, they would know of the drug’s risks and include them in the drugs’ warning, which would insulate the manufacturers from liability.<sup>210</sup> Without conducting research of their own, drug companies run a significant risk being held strictly liable for any injury that ensues because a court could find that the manufacturer should have known of the risk in light of the present state of “reasonable developed human skill and foresight.” This standard is essentially the same

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<sup>206</sup> Restatement 2d of Torts, §402A comment k.

<sup>207</sup> *Id.*; Needham v. White Labs, 639 F.2d 394, 402 (7th Cir. 1981); Filler v. Rayex, 435 F.2d 336, 338 (9th Cir. 1970).

<sup>208</sup> Restatement 2d of Torts, §402A.

<sup>209</sup> *Id.* at comment j.

<sup>210</sup> Reyes v. Wyeth Labs, 498 F.2d 1264, 1282 (5th Cir. 1997) (holding that there been a warning issued with a vaccine that it carried a slight risk of polio, “[i]t unquestionably would have avoided Wyeth’s liability”).



as a negligence standard; thus failure-to-warn lawsuits can be brought under either a strict liability theory, negligence doctrine, or both.<sup>211</sup>

A minority of jurisdictions have no scienter requirement and hold the manufacturer simply liable for failure to warn of the specific risks to pregnant women, even if there is no proof the manufacturer should have known of the risks.<sup>212</sup> For those jurisdictions, the only way a manufacturer can warn of a pregnancy risk and avoid liability is to discover it through testing.

For the jurisdictions that only impose liability for failure to warn where a defendant should have known of a risk, clinical testing still may be necessary to avoid liability. In one case, a court allowed the question of liability to go to the jury where a manufacturer failed to conduct animal studies on a possible correlation between their drug and a retinal disorder after receiving anecdotal accounts from doctors that patients who had used the medicine subsequently developed the disorder.<sup>213</sup> The court held that a reasonable juror could conclude the manufacturer should have known of the risk and should have conducted studies that would enable them to adequately warn consumers of the risk.<sup>214</sup> The court reasoned:

“Purchasers cannot try out drugs to determine whether they kill or cure . . . Where experiment or research is necessary to determine the presence or the degree of danger, the product must not be tried out on the public. . . . The claim that a hazard was not foreseen is not available to one who did not use foresight appropriate to his enterprise.”<sup>215</sup>

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<sup>211</sup> See Denemark, *supra* note 22, at 421.

<sup>212</sup> See Woodill v. Parke-Davis, 402 N.E.2d 194, 197 (Ill. 1980), *citing* Little v. PPG Industries, 579 P.2d 940 (Wash. App. 1978), Berkebile v. Brantly Helicopter Corp., 337 A.2d 893 (Pa. 1975).

<sup>213</sup> See Hoffman v. Sterling Drug, 485 F.2d 132 (3d Cir. 1973).

<sup>214</sup> See *id.*

<sup>215</sup> *Id.* at 141, *quoting* Dalehite v. U.S., 346 U.S. 15, 51–52 (1953) (Jackson, J., *dissenting*).

Following *Hoffman*, courts can hold manufacturers liable for failure to conduct studies to apprise themselves of the information necessary to adequately warn consumers about a drug's risk of a specific harm. Given that so many companies now have registries, they are likely to receive reports of adverse pregnancy outcomes from doctors or patients like those in *Hoffman* that would similarly give them notice to conduct a study and subject them to liability if they do not. Even if a company does not receive such reports, the broad language in *Hoffman* suggests that they could be liable under the theory that "experiment or research" is always necessary to determine "the presence or the degree of danger" of teratogenic effects, and that a drug company's failure to test for those risks displayed a lack of foresight. As one commentator put it, "manufacturers will have a difficult time arguing that a drug is "unavoidably unsafe if they fail to test the drug in a population that might foreseeably use it."<sup>216</sup>

A company cannot escape liability by issuing a vague warning that their drug poses risks to a fetus and/or should not be used in pregnant women. The adequacy of any warning is almost always a question of fact for a jury.<sup>217</sup> In order for a pharmaceutical company to obtain summary judgment and thereby avoid the significant expense of a trial the drug company must show that the warning was "clear and unambiguous" and the plaintiff's injuries "are identical to those the warning described."<sup>218</sup> A drug manufacturer cannot possibly achieve so specific a warning unless they are fully aware of the exact nature of a drug's risks. Nor can a company rely on FDA approval of its warning language to prove that its warning was adequate.<sup>219</sup>

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<sup>216</sup> INSTITUTE OF MEDICINE, *supra* note 15, at 166.

<sup>217</sup> *See, e.g., Felix v. Hoffman-LaRoche*, 513 So.2d 1319, 1321 (Fl. Ct. App. 1997)

<sup>218</sup> *Id.*

<sup>219</sup> *Brochu v. Ortho Pharmaceutical Corp.*, 642 F.2d 652, 658 (1st Cir. 1981).

There is even some precedent that failure to conduct additional drug testing needed to adequately warn consumers can be the basis for punitive damages.<sup>220</sup> In that case, *Wooderson v. Ortho Pharmaceutical Corp.*, independent post-market studies by third-party researchers suggested that that Ortho's oral contraceptive carried risks of kidney damage and hypertension.<sup>221</sup> The court held that these independent studies should have conducted further research to "prove or disprove" the allegations in the studies.<sup>222</sup> This means that if third party researchers, pregnancy registries, or government-run studies indicate teratogenic effects in a drug after it has already been on the market, the drug company may be obligated to perform follow-up studies of its own.

This duty to test can be triggered by any scientific data of the type that is used by experts in the field: it need not be limited to proven clinical studies.<sup>223</sup> If such data exists and the manufacturer continues to sell the drug, the burden is on the manufacturer to prove that the information was unavailable to them.<sup>224</sup> It could also be argued by analogy that if a company's own preliminary toxicology testing reveals teratogenic potential, a manufacturer may have a duty to test the drug further to ascertain the existence and nature of the risk.<sup>225</sup>

*Hoffman* dealt with the duty to conduct experimental tests as a subpart of the duty to warn. The duty to warn itself requires even less of a trigger than the duty to test. In *Wells v. Ortho Pharmaceutical Corp.* the court held that a drug manufacturer must issue a specific warning of a harmful birth defect "as soon as there was a *hint* of a possibility that the Product

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<sup>220</sup> *Wooderson v. Ortho Pharmaceutical Corp.*, 681 P.2d 1038, 1064 (Kan. 1984).

<sup>221</sup> *Id.* at 1063.

<sup>222</sup> *Id.*

<sup>223</sup> *Feldman v. Lederle Labs*, 479 A.2d 374, 454–55 (N.J. 1984)

<sup>224</sup> *Id.* at 455.

<sup>225</sup> *See* Denmark, *supra* note 22, at 445.

causes birth defects.”<sup>226</sup> The duty to warn in that case was held to be triggered at even though no published studies had indicated birth defects.<sup>227</sup> Two unpublished studies had suggested the *possibility* of a link between spermicides generally and birth defects.<sup>228</sup> The court concluded these studies were a sufficient basis for a jury to conclude that the manufacturer should have known of a risk of birth defects, and consequently should warned the public of those defects.<sup>229</sup>

It is possible a drug company responding to this tort regime will still wish to wait to conduct the studies until third party warnings trigger the need to conduct further testing in pregnant women. They may view the delay as favorable because it allows them to profit from selling the drug without specified warnings to pregnant women in the interim. However, it is more likely that the delay would work against them. Women who took the drug in the interim and had children with birth defects will be all the more tempted to sue if it appears the manufacturer intentionally turned a blind eye to the possibility of harm and waited to conduct the test until tort law explicitly required it of them. Also, since a manufacturer is held to have the same constructive knowledge of the likelihood of risks as “an expert in the field,”<sup>230</sup> a plaintiff could argue that since the third party researcher later thought to study a particular suspected teratogenic effect in the drug, the manufacturer too should have known to suspect and test for that risk. With the prospect of punitive damages, a sympathetic plaintiff, and the appearance of

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<sup>226</sup> Wells v. Ortho Pharmaceutical Corp., 615 F.Supp. 262, 294 (N.D. Ga. 1985) (emphasis added). In *Wells*, parents sued a manufacturer of spermicidal cream on behalf of their child born with birth defects they attributed to the product. *Id.* at 266–69. A jury awarded her over \$5 million in damages. *Id.* at 266.

<sup>227</sup> *Id.* at 269.

<sup>228</sup> *Id.* at 275–77.

<sup>229</sup> *Id.* at 294.

<sup>230</sup> Feldman, *supra* note 223, at 452–53; Vassalo v. Baxter Healthcare, 629 N.E.2d 909, 923 (Mass. 1998).

intentional delay, it would be unwise for manufacturers to wait for a ‘red flag’ before they begin testing for teratogenicity.

Manufacturers may be concerned that the children of their test subjects will prevail in a tort suit based on injuries that occurred as a result of the clinical trial. While there is very little case precedent on the subject, at least one court has held that a mother has an absolute right to consent on behalf of her fetus to experimental *therapeutic* medicine,<sup>231</sup> but there is no caselaw on the effect of maternal consent on liability for nontherapeutic fetal experimentation.<sup>232</sup> In the absence of direct precedent, commentators have speculated that informed consent by the mother would very likely preclude a tort suit against the drug manufacturer by the child, because the mother’s voluntary participation after informed consent would constitute an intervening cause that would make it impossible for the child to prove the manufacturer, rather than the mother, caused the child’s injuries.<sup>233</sup> Also, the manufacturer could liken maternal consent for fetal participation in a study to parental consent for children who are too young to meaningfully consent to participation in a study. It is highly unlikely a child whose parents gave fully informed consent to enrollment in a study could successfully sue his or her researchers,<sup>234</sup> and it makes little sense for the industry to fear litigation from a fetus but not from a newborn. Other scholars have pointed out that any claim by the offspring of research subjects would have to proceed on the assumption that an adult woman is not capable of properly weighing the benefits of the trial against the risks to the fetus despite being fully informed of this risks: the same

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<sup>231</sup> *Roberts v. Patel*, 620 F. Supp. 323, 324–25 (N.D. Ill. 1985).

<sup>232</sup> INSTITUTE OF MEDICINE, *supra* note 15, at 162.

<sup>233</sup> *Id.* at 164.

<sup>234</sup> Anna C. Mastroianni, *HIV, Women, and Access to Clinical Trials: Tort Liability and Lessons from DES*, 5 DUKE J. GENDER L. & POL’Y 167, 179–80 (1998)

stereotypes that are condemned in the context of government regulation.<sup>235</sup> Finally, even if manufacturers could be held responsible for injuries to the offspring of their research subjects, it would still be less costly for manufacturers to conduct premarket clinical trials on a limited number of women than to market the drug to the general public and expose themselves to enormous potential liability from every pregnant women in the country who takes the drug.<sup>236</sup>

In sum, I contend that despite manufacturers' vague assertions that that the prospect of tort liability precludes clinical testing in pregnant woman, the existing tort case law actually indicates that clinical tests will reduce manufacturers' potential liability in tort. By apprising themselves of the risks of drug use in pregnant women, drug manufacturers can provide warnings of this risk and immunize themselves against the threat of liability. I am further incredulous about drug companies claims about litigation fears, because they already face the risk of litigation from expose fertile men to male teratogens that can cause birth defects in children conceived while men were exposed to the drug.<sup>237</sup> Notably, in the context of birth defects caused by workplace exposure to teratogens, more men than women have filed lawsuits against their employers.<sup>238</sup>

One could ask why manufacturers protest so strongly if conducting clinical research would not increase their tort liability. One possible answer is that they may lack a detailed understanding of tort law. Another answer is that it is economically beneficial for drug manufacturers to exclude pregnant women from clinical trials. If manufacturers had to begin

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<sup>235</sup> Bowles, *supra* note 185, at 908.

<sup>236</sup> See Mastroianni, *supra* note 234, at 187.

<sup>237</sup> See Epstein, *supra* note 23, at 365.

<sup>238</sup> Purdy, *supra* note 80, at 71; see also Uma Narayan, *The Discriminatory Nature of Industrial Health-Hazard Policies and Some Implications for Third World Women Workers*, in *REPRODUCTION, ETHICS, AND THE LAW: FEMINIST PERSPECTIVES* 398, 402 (Joan C. Callahan ed., 1995).

conducting research with pregnant subjects to obtain FDA approval, they would need to go through the added expense of tracking down and recruiting pregnant volunteers, producing extra quantities of the drug for those volunteers, compensating them for their participation and for any medical procedures that become necessary as a result of the drug trial, and maintaining operating costs for the nine or more months they must wait before they can obtain results from the trial. Also, since pregnant women respond differently to medication in terms of dosage, data from their participation in the trial cannot be compared with data from nonpregnant study populations, and the drug manufacturer will essentially have to conduct two separate full clinical trials to accommodate for the differences inherent in the pregnant group. Indeed, it is a basic precept among the scientific community that increasing homogeneity among test subjects allows you to decrease the size, and therefore cost of a clinical trial by reducing the number of variables that could affect trial outcomes.<sup>239</sup> Pregnancy increases variables among the clinical trial population that can influence a drug's effects and necessitates a larger pool of subjects. These extensive, inevitable costs of pregnancy testing are likely a far stronger deterrent drug companies than the vague, uncertain costs of potential litigation. Litigation threat is a convenient scapegoat for drug companies to give as the reason for why they do not test drugs in pregnant women; it is far easier for drug companies to blame unscrupulous plaintiffs' lawyers than to blame their own unwillingness to undertake the costs necessary to ensure that drugs commonly used by pregnant women are safe and effective.

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<sup>239</sup> See, e.g. INSTITUTE OF MEDICINE, *supra* note 15, at 97–98; Jonathon A. Roskes, *The Inclusion of Women in Clinical Trials: Yesterday and Today* (1994), in Peter Barton Hutt, ed., *Food and Drug Law: An Electronic Book of Student Papers* at 6.

One author has observed that if the goal of achieving homogeneity were truly a major concern for drug companies, they could just as easily achieve the same homogeneity by employing only female test subjects and extrapolating the results to males. See Bowles, *supra* note 185, at 880–81.

V. Regulatory Solutions to the Lack of Pregnant Women’s Participation in Clinical Research

A. Gov’t funded studies and patent extension

One potential solution to pregnant women’s inadequate access to clinical drug trials could be for the government to financially subsidize those trials, either through direct funding or through extensions of patent terms that give increased revenue to researchers to offset the increased cost of testing on the pregnant female subpopulation.

This approach was implemented by Congress to improve clinical trial research for another underrepresented subpopulation: children. Legislators implemented this approach through three successive statutes: the Food and Drug Administration Modernization Act of 1997 (FDAMA), the Best Pharmaceuticals for Children Act (BPCA) and the Food and Drug Administration Amendments Act of 2007(FDAAA). These statutes and the FDA rules made pursuant to them created financial incentives by offering six month patent extension as a reward for pediatric testing,<sup>240</sup> and government financing of third party research.<sup>241</sup> Another form of government subsidy of clinical trials occurs through direct research conducted by government employees. The FDA has already begun to implement this strategy. In 2002, the FDA made research grants to two universities to determine the appropriate dosage level for two hypertension drugs, labetalol and atenolol in pregnant women.<sup>242</sup>

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<sup>240</sup> See Lauren Hammer Breslow, *The Best Pharmaceuticals for Children Act of 2002: The Rise of the Voluntary Incentive Structure and Congressional Refusal to Require Pediatric Testing*, 40 HARV. J. LEGIS. 133, 155 (2003)

<sup>241</sup> BPCA § 3(3)(b) (codified at 42 U.S.C. § 284 (2003)). Government funding of third party pregnancy studies has also occurred under the Orphan Drug Act. Marlene E. Haffner, *Studies Involving Orphan Products for Treating/Diagnosing Women’s Diseases*, 48 FOOD & DRUG L. J. 205, 210 (1993) (describing such studies as research on acyclovir use for genital herpes during pregnancy and ritodrine to prevent preterm labor).

<sup>242</sup> Kritz, *supra* note 7, at F1.



Much has been said of the success of these financial incentives. One FDA spokesperson declared that the “pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date.”<sup>243</sup>

Much has also been said of their shortcomings. Patent extensions have been criticized for failing to provide any incentive for research on drugs whose patents have expired by are still routinely used by groups for which there is no adequate clinical data.<sup>244</sup> They similarly present little or no advantage to drug companies whose products have an active patent, but who nonetheless lack market exclusivity because of fierce competition from rival drugs.

The government subsidy provisions in the BPCA attempted to remedy some of these problems by allowing the government to pay for pediatric research manufacturers refuse to conduct, but government funding of research is also problematic. An average clinical trial costs an average of \$3.87 million to conduct, and for the year 2002 alone Congress appropriated \$200 million to carry out the subsidy option in the BOCA.<sup>245</sup> When the research is conducted by NIH or other government researchers, the trials also costs the government personnel, building space, and other limited resources that could be spent on innumerable other research opportunities. While a private pharmaceutical company at least has the possibility of recouping its investment in research by gaining better access to the submarket of pregnant women, the government has no such opportunity to cover its losses. The result is that the government may prioritize only those medications that it deems the most necessary for women or the fetus’ health. Ironically these

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<sup>243</sup> FDA, DEP’T OF HEALTH AND HUM. SERVS., THE PEDIATRIC EXCLUSIVITY PROVISION: JANUARY 2001 STATUS REPORT TO CONGRESS ii (2001) (*cited in* Breslow, *supra* note 240, at 163).

<sup>244</sup> *See* Breslow, *supra* note 240, at 166–67.

<sup>245</sup> *Id.* at 134.

may be the medicines for which scientific information is the least valuable to pregnant women, because a woman who truly needs medicine is more likely to take it even if the data shows it produces birth defects, and so teratogenicity is less likely to be a determinate factor in her decisionmaking as it would be for a medicine that is highly beneficial but not lifesaving.

A financial-incentives approach works best if the reasons for the industry's lack of testing are exclusively financial. Pediatric studies can increase costs to drug manufacturers because it may be difficult, and therefore expensive, to recruit children because of a general reluctance by concerned parents to subject their children to risks. Another financial obstacle to pediatric research is a fear of lawsuits. The industry could believe that lawsuits are likely to be more frequent because parents might be overly reactionary when their children have an adverse side effect, and because children might disagree with their parents' choice to enroll them in the study and sue on their own behalf when they reach the age of maturity. Jury verdicts are also likely to be enhanced by the sympathetic nature of a child victim who could not meaningfully consent to the procedure, and by the fact that a child with lifelong industries needs more years of compensation than an adult. Where such financial impediments restrict children's access to drug trials, providing a financial subsidy seems an appropriate solution.

Many of these rationales apply to pregnant women. However, there are also nonfinancial reasons that pregnant women are excluded from trials that would not be resolved by a financial incentive. One such barrier could be the increased time it takes to conduct pregnancy studies, because a great deal of follow-up is needed to spot teratogenic effects that are not immediately apparent in the womb or even at birth. Financial incentives also do not address the regulatory barriers in place that prohibit some kinds of research on pregnant women and deter others. Nor do they address biases or concerns held by individual researchers, such as the desire for

homogeneity in the subject class, beliefs that pregnancy is an atypical state compared to the male-normative ideal, and therefore an unimportant field to research. Another bias could come from researchers' subjective disapproval of pregnant women who fail to conform to expected roles by putting their fetuses at risk. Given the strong historical backdrop of fetal protectionism and fears of maternal-fetal conflicts, money may not be enough to incentivize research.

#### B. FDA Labeling Requirements

In 2008, the FDA proposed a significant change to its requirements for pregnancy-related drug labeling.<sup>246</sup> This proposed rule would have required drug companies to include a “Pregnancy” subsection on their label, which would include: (1) information about any existing pregnancy registries for the drug, (2) a “fetal risk summary” that includes a conclusion about the drug’s likelihood of risk (such as “high likelihood of increased risk”) or a statement that there is insufficient data, (3) a narrative statement describing in detail any particular risks that are known, and (4) a “clinical considerations” sections that includes additional information on dosing.<sup>247</sup> Notice of the proposed rule was published in the Federal Register, and comments were received until August 27, 2008,<sup>248</sup> but no final rule has issued since the comment period terminated.

While the FDA’s rulemaking is admirable in that it attempts to increase pregnant women’s access to information, the comments to the rule illustrate its fundamental flaw; drug manufacturers cannot provide women with detailed information on the drug label if that detailed information is not known to drug manufacturers. Several comments observed that given the present inadequate state of knowledge about the pregnancy safety of most medications, drug

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<sup>246</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling*, 73 Fed. Reg. 30831 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201).

<sup>247</sup> *Id.* at 30863–64.

<sup>248</sup> *Id.* at 30831.

companies would have no legitimate basis for asserting that a drug has a high, low or moderate likelihood of increased risk to the fetus.<sup>249</sup> One comment explained that under the regulation, data from pregnancy registries could be used by drug companies as a basis for making a conclusion about risk, and that those conclusions could be misleading because registries conflate data from women exposed to different doses at different times in their pregnancies, often have too few numbers of participants, and have too little follow-up to account for external factors that could affect the fetus.<sup>250</sup> In other words, the new labeling requirements would not incentivize drug companies to do more and better premarket research, it would only make them report the existing, poor quality research that may even more be unhelpful and even misleading to pregnant women than no information at all.<sup>251</sup> The information presented may be all the more confusing to prescribers and patients because of the fact that there is no standardized type of data that drug companies will use to base their conclusions on. Some may use animal studies, while others might use postmarket registries, and within those subgroups the methods, size of the research population, species of animal, and many other variables may further reduce standardization.<sup>252</sup> Thus one company's idea of "low risk" may differ considerably from another company's idea of "low risk" and so on.

Although labeling is a valuable tool in most circumstances, it is only as valuable as the information used by drug companies to write their labels. Labeling alone is incapable of

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<sup>249</sup> See generally Elizabeth Barbehenn, Peter Lurie & Sidney M. Wolfe, Public Citizen, Comment: Docket No. FDA-2006-N-0515, Aug. 27, 2008; Biotech. Indus. Org. (BiO), Comment: Docket No. FDA-2006-N-0515, Aug. 27, 2008; Pharmaceutical Research and Manufacturers of America (PhRMA), Comment: Docket No. FDA-2006-N-0515, Aug. 27, 2008.

<sup>250</sup> Barbehenn, Lurie & Wolfe, *supra* note 249, at 1–2.

<sup>251</sup> See BiO, *supra* note 249, at 2.

<sup>252</sup> See PhRMA, *supra* note 249, at 18. The comment went on to recommend that the narrative state instead be accompanied by a detailed description of the nature of the studies used to form the drug company's assessment of safety to help obstetricians evaluate the studies' reliability and relevance. See *id.*

resolving the problem pregnant woman’s lack of access to drug safety information, because there is not enough reliable scientific clinical data for drug manufacturers to base their labels on.

### C. Regulatory Requirement

One final method of achieving greater participation by pregnant women in research is for the government to require it. To that end, the National Institutes of Health’s policies regarding the inclusion of women in clinical research serve as a useful comparison. The NIH Revitalization Act of 1993 set certain criteria for the NIH to implement through guidelines with the aim of increasing the proportion of women and minorities in clinical research.<sup>253</sup> The statute requires that the NIH “ensure that . . . women are included as subjects” in clinical research<sup>254</sup> in a manner that is adequate to reveal any differences in how the drug or other medical treatment affects men and women.<sup>255</sup> The statute allows for exceptions to this blanket rule if there is “substantial scientific data” demonstrating that there is no difference between men and women with respect to the variable being studied,<sup>256</sup> or if women’s inclusion is “inappropriate” because of the women’s health, the purpose of the research, or other circumstances that the director of NIH can designate.<sup>257</sup> Notably, the statute forbids the financial cost of including women from being considered as part of the determination of whether it is appropriate to include women in any given clinical trial.<sup>258</sup> The latest NIH guidelines implementing this statute make clear that the burden for excluding women is a high one; women must be included in all NIH-funded

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<sup>253</sup> NIH Revitalization Act of 1993, Pub. L. No. 103-43 (codified at 42 U.S.C. § 289a-2 (2006)).

<sup>254</sup> 42 U.S.C. § 289a-2(a)(1)(A), (d).

<sup>255</sup> 42 U.S.C. § 289a-2(c).

<sup>256</sup> 42 U.S.C. § 289a-2(d)(B).

<sup>257</sup> 42 U.S.C. § 289a-2(b).

<sup>258</sup> 42 U.S.C. § 289a-2(d)(A)(i).

research unless there is a “clear and compelling” rationale for why their inclusion is inappropriate.<sup>259</sup>

This statute can serve as a valuable model for mandatory pregnancy testing. It would shift the burden under the regulatory regime from a presumption that research is forbidden unless the researcher can prove the study meets an exception, to a system in which research is required unless a drug company can prove they are exempt. Instead of facing the hurdle under the DHHS rules of proving that a has minimal risk to the fetus or direct benefit to the mother before any data is available to corroborate such claims, a researcher would be able to proceed with pregnancy studies without fear of running afoul of government regulations.

Some could argue that a pregnant woman is different from other women for whom inclusion in research is required, because the pregnant woman is composed of two research subjects: herself and the fetus. However, this alone cannot justify excluding a pregnant woman from research, since the government has seen fit to give both women (aka the mother) and children (aka the fetus) access to clinical trials. If both adult women and children must be allowed access to research when they are in two separate bodies, it makes little sense to prohibit their participation in research when they are in one body.

### CONCLUSION

When I begin conversations with others about the topic of this paper, their initial reaction is usually one of surprise and incredulity. Many have asked, “But how could you ever get pregnant women to take experimental drugs?” I believe that the FDA, DHHS, and pharmaceutical industry also wonder the same thing, given the historical fears that stemmed from

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<sup>259</sup> NAT’L INSTITUTES OF HEALTH, AMENDED NIH POLICY AND GUIDELINES ON THE INCLUSION OF WOMEN AND MINORITIES AS SUBJECTS IN CLINICAL RESEARCH (October, 2001), *available at* [http://grants.nih.gov/grants/funding/women\\_min/guidelines\\_amended\\_10\\_2001.htm](http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm).

the Thalidomide and DES disasters, and the widespread overestimation of the risk of fetal drug use. Yet this history is not longer a reality. It has now become commonplace for large numbers of pregnant women to take medications during pregnancy for chronic conditions, mental health problems, pregnancy-induced or exacerbated diseases, and even for preventative care like the H1N1 vaccine. If women had the information they need to properly assess the risks and benefits of their medications, this increased use would only be a good thing. Forgoing drug treatment for medical conditions during pregnancy can cause a mother unnecessary stress, suffering, damage to her health, and effects on the fetus that can be far more severe than those from the medication. But without the information to make an informed decision about medication use during pregnancy, women are left adrift, forced to experiment on their own instead of in a controlled, monitored research setting. For these reasons I contend that the existing DHHS regulations are unduly prohibitive, and as a result pregnant women should be given the same access to clinical research participation as their nonpregnant counterparts.