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Balancing risks: making decisions for maternal treatment without data on fetal safety



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Introduction

Evaluating and balancing the appropriateness of medical therapy and other treatments during pregnancy continue to be challenging issues in law and ethics. With few exceptions, these truisms hold: what is best for a pregnant person's health is also best for their pregnancy, and what is good for the fetus is also good for the mother. For example, using insulin to optimally control blood is a “win-win” situation because it improves the health outcomes of the pregnant patient and the fetus. However, challenges can arise when treatment to improve maternal health brings some risk to fetal health or, conversely, an intervention with the potential to improve fetal health brings risk to a mother's well-being. For example, chemotherapy is performed to treat rare cases of aggressive cancer arising during pregnancy; however, such treatment may impair fetal growth, and as a result, patients may be reluctant to undergo treatment. Another example is the administration of digoxin in pregnancy to treat fetal cardiac arrhythmia. Digoxin

Challenges arise when treatment to improve maternal health brings the possibility of risk to fetal health. The coronavirus disease 2019 (COVID-19) vaccine is the most recent, but hardly the only, example. Because pregnant patients are often specifically excluded from trials of new therapies, this is often the dilemma that patients and providers face when considering new treatments. In this study, we used the COVID-19 vaccine as an exemplar to question the broader issue of how society, in general, and obstetricians, in particular, should balance obligations to pregnant women's right of access to new therapeutic agents with the physician's desire to protect the fetus from potential risks. We will argue that in almost all circumstances (with few exceptions, as will also be discussed), maternal benefit and respect for autonomy create the uncertainty that absent safety data bring. Consequently, if pregnant women choose to try new interventions and treatments, such as the COVID-19 vaccination, they should be offered those new regimens and their decision supported. In addition, we will argue that the right solution to avoid the dilemma of absent data is to include pregnant individuals in clinical trials studying new treatments, drugs, and other therapies. We will also discuss the basis for our opinion, which are mainstream obstetrical ethics, precedents in law (supreme court ruling that forbids companies to exclude women from jobs that might pose a risk to the fetus), and historic events (thalidomide). The ethical framework includes the supposition that sacrifice to improve fetal outcome is a virtue and not a mandate. Denying a pregnant patient treatment because of threats to their life can create absurd and paradoxical consequences. Either requiring abortion or premature delivery before proceeding with treatments to optimize maternal health, or risking a patient's own life and ability to parent a child by delaying treatment brings clear and significant risks to fetal and/or neonatal outcomes. With rare exceptions, properly and ethically balancing such consequential actions cannot be undertaken without considering the values and goals of the pregnant patient. Therefore, active participation of both the pregnant patient and their physician in shared decision making is needed.

Key words: coronavirus disease 2019 vaccine, coronavirus disease 2019, discrimination, Food and Drug Administration, fetal beneficence, fetal risks, maternal autonomy, maternal choice, medication in pregnancy, pregnancy, thalidomide

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is effective in treating fetal cardiac arrhythmia but may have harmful effects on the mother's health.

When maternal and fetal interests appear misaligned, most obstetrical ethicists believe that the pregnant patient is the one most appropriate to make choices regarding if and how to proceed.¹ The control of pregnant women to make such decisions is supported by both professional organizations² and case law.³ Generally, patients will go to great ends to optimize the outcome of their pregnancy, and, informed of the options and possible risks and benefits,

pregnant patients have the capabilities similar to nonpregnant individuals in determining the risks or limits to their own health, assessing their well-being, and ensuring fetal benefit. Sacrifice—in this case to improve fetal outcome—is a virtue but not a mandate and, at a practical level, we must engage patients to advance diets, and other behaviors as well as 102 treatments that are best for a pregnancy's health. Notably, no treatment to improve fetal well-being can be undertaken without going through the body of the pregnant patient. Forced maternal intervention is both immoral,

limiting maternal autonomy and potentially bringing physical harm (ie, could result to assault), and impractical, requiring detention or forcing compliance despite the unwillingness of the patient to participate in therapy. When force and confinement have been brought to light, the courts, ethicists, and society have generally responded with horror and disapproval.⁴ Conversely, denying a pregnant patient treatment for immediate threats to their life and well-being can create absurd and paradoxical consequences. Either requiring abortion or premature delivery before proceeding with treatments to optimize maternal health, or risking a patient's own life and ability to parent a child by delaying treatment, brings clear and significant risks to fetal and/or neonatal outcomes. Properly and ethically balancing such consequential actions cannot be undertaken without considering the values and goals of the pregnant patient.

Given this established framework for decision making during pregnancy, how should we approach decisions where available data limit what is known what is known about the fetal consequences of therapies that have recognized benefits for a pregnant individual? Because pregnant patients are often specifically excluded from trials of new therapies, this is the dilemma that patients and providers face when considering new and innovative options for treatment in pregnancy; furthermore, this is the current dilemma of those making decisions about coronavirus disease 2019 (COVID-19) vaccination in pregnancy. In this study, we will use the COVID-19 vaccine as an example to question the broader issue of how society, in general, and obstetricians, in particular, should balance obligations to pregnant women's right of access to new therapeutic agents with the physician's desire to protect the fetus from potential risks. We will argue that in almost all circumstances (with few exceptions as discussed below), maternal benefit and respect for the autonomy of pregnant patients trump the uncertainty that absent safety data bring. Consequently, if pregnant women choose to try new interventions and

treatments, such as the COVID-19 vaccination, they should be offered those new regimens and their decision supported. In addition, we will argue that the right solution to avoid the dilemma of absent data is to include pregnant individuals in clinical trials studying new treatments, drugs, and other therapies.

We share the widespread hope that the COVID-19 vaccination will bring an end to the *annus horribilis* that was 2020, and to the pandemic. Frontline workers are the highest priority group for vaccination. More than 300,000 health professionals are pregnant women who are at increased risk of complications and death if they contract the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).⁵ However, although some regulatory bodies and professional organizations support pregnant individuals choosing vaccination, there is hesitancy to recommend and, in some countries, to even allow vaccination for that group. For example, British regulators have "advised against" offering the vaccine to pregnant individuals,⁶ and although the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention did not advise against vaccination of pregnant individuals,⁷ they stopped short of recommending vaccination as they did for nonpregnant individuals. This therapeutic diffidence reflects the absence of reassurance about the fetal safety of the COVID-19 vaccination during pregnancy. As data are limited, COVID-19 vaccines are the most recent, but certainly not the only, therapeutic agents that have been approved for general use before substantial evidence of efficacy or safety has been demonstrated for use during pregnancy. This gap stems in large part from the practice of routinely making known, intended, and, sometimes, recent pregnancy, exclusion criteria for trials conducted to gain approval of therapeutic agents. This exclusion was certainly the case in all recent and ongoing clinical trials of the COVID-19 vaccines. Left without needed data, the FDA, in contrast to their analogous British agency, opted to recommend a

shared decision between a pregnant patient and her doctor. They stated "People who are pregnant and part of a group recommended to receive the COVID-19 vaccine may choose to be vaccinated. If they have questions about getting vaccinated, a discussion with a healthcare provider might help them make an informed decision." We have argued that the FDA did the right thing, whereas the British regulators did not; however, others feel that the FDA should have gone even further. Ruth Faden, a leading bioethicist and founder of the Berman Institute of Bioethics at Johns Hopkins, lamented, "I wish we had an absolutely unambiguous recommendation."⁸

Ethical Considerations

A foundational principle underpinning these arguments is respect for patient autonomy: the right of informed patients to balance benefits against risks, including unknown risks, and decide among treatment options, including an option to decline treatment altogether. That is not to say that a physician does not play a key role in guiding women through the thicket of oft competing considerations. Shared decision making is critical. As we have previously written, physicians "meaningfully shape therapeutic options, and assist patients in making difficult decisions. It is dependent on the physician being aware of the role of both their patients' values, and health values (eg, autonomy, fertility) in decision making. . . . To make a good decision, women need more than accurate information. They also need to be supported and sense empathy and understanding from their physicians and feel cared for. Although the facts (benefits and harms related to any given choice) are a necessary component of counseling, without discussion of values, they do not lead to a truly informed decision."⁹

Respect for maternal autonomy extends to times before during and immediately after pregnancy. The principle recognizes that with few exceptions, the locus of decision making for the fetus lies with the pregnant individual and that they are best able to evaluate

the mix of maternal and fetal risks and benefits, a decision-making capacity that is especially necessary and appropriately assuming what seems best for the fetus brings significant risks to maternal health. The exceptions to respect for maternal autonomy should be the same exceptions for individuals who are not pregnant: inability to learn and understand relevant evidence and choices because of limitations in intellectual capacity, illness, or infirmity.

In considering a patient's decision-making authority, a physician's obligation to acknowledge their pregnant patient's wishes will vary depending on whether the pregnant patient is asserting negative autonomy (they do not want something, such as a cesarean delivery or a therapeutic agent) or is asserting affirmative autonomy (requesting something, such as surgery or a therapeutic agent). In the former case, the mother's autonomy in almost all imaginable circumstances is inviolate. In the latter case, a physician can give more weight to fetal beneficence, and that is the issue with the COVID-19 vaccine.

Legal and Historic Considerations

Importantly, 3 administrative and legal precedents in the 20th century, 1 heroic and prescient act by a young employee at the FDA and 2 pairs of holdings by a renowned Supreme Court Justice, have provided a context and framework to explore the aforementioned abstract principles.

The first event occurred in 1960 when Dr Frances Kelsey was a junior employee at the FDA reviewing new drug applications to assure that there was adequate evidence of a drug's safety.¹⁰ One of the first applications she was assigned was for thalidomide, which was already available in dozens of countries around the world for use as a sedative. Despite pressure from the company, Dr Kelsey withheld the approval of the medication because of inadequate evidence of its effects. Approximately a year later, researchers in Germany and Australia linked thalidomide to clusters of rare, severe congenital anomalies—phocomelia—

that involved thousands of babies. The drug was never marketed in the United States, and Dr Kelsey's reluctance to approve its use because of absent safety data prevented the neonatal outcomes seen elsewhere. The impact of the near disaster led to the passage of a bill that fundamentally changed drug regulation by requiring drug manufacturers to provide evidence of effectiveness and safety as part of new drug applications.

Speaking to the other side of the balance between maternal and fetal health are the decisions from 2 court cases. Before considering those precedents, it is worth acknowledging that ethics and law are related but are not synonymous. The law is tethered to societal mores in ways that are at times almost discernable. It has been said that laws speak to the lowest acceptable standard of human behavior and ethics to the highest. Consequently, the cited cases do hint at ethical concerns and evaluations while speaking directly to legal considerations.

The first case that illustrated the issues at hand is the 1991 Supreme Court decision in *United Autoworkers v. Johnson Controls*.¹¹ Writing for a unanimous court, Justice Harry Blackman ordered that pregnant and fertile employees could not be barred from their jobs to prevent exposing a known or potential pregnancy to lead because of the fear that high levels of lead would adversely affect fetal health. Despite acknowledged fetal risks, such policies prohibiting a woman from continuing her employment in that circumstance were judged discriminatorily and in violation of Title VII and the Pregnancy Discrimination Act of 1978.

It is clear and worth emphasizing that a COVID-19 vaccine, which offers a clear health advantage, is not lead, which has no known health benefits for mother or fetus. Early reports have suggested that approved efficacy of vaccines in preventing clinical illness from SARS-CoV-2 will be greater than 90%. Furthermore, the disease prevented is particularly consequential for pregnant women (higher death rates and admissions in the intensive care unit) and, potentially, their pregnancies (more preterm

births).⁵ These facts, along with the holding in *Johnson Controls*, suggest a consequent ethical question. If a woman cannot be compelled to put her livelihood at risk even if her work creates a known hazard for her fetus, can regulatory agencies demand that she put her life at risk by forgoing vaccination, which has clear benefits and has not yet been identified as hazardous to the fetus?

In consideration of the aforementioned arguments, one might be tempted to dismantle any scaffolding that hinders full and free access by pregnant women to the COVID-19 vaccine and other therapeutic advances. Standing against those uncertain beliefs is the example of Frances Kelsey discussed above. If the plaintiffs in *Johnson Controls* successfully limited infringements on women's autonomy in the name of fetal safety, then Frances Kelsey illustrated the potential danger in going too far in the other direction by allowing unrestricted access of pregnant women to therapeutic agents.

How then are we to balance these seemingly competing precedents alternately focused on prioritizing patient autonomy and minimizing the risk of adverse fetal consequences from treatments in pregnancy? What distinguishes prudence in the absence of evidence, as with thalidomide, from undue prudence, which is what we think will prove the case with COVID-19 vaccines? That is a question with resonance beyond vaccines, speaking as well to other potentially life-saving or life-extending medications, such as chemotherapeutic agents that may bring fetal risk.

Surprisingly, there is a language in the original *Roe v Wade* decision (the last case we offer to frame our arguments and another authored by Justice Blackmun), which may provide some guidance. It might be assumed, per *Roe*, that once the fetus is viable, a woman's freedom to terminate her pregnancy is outweighed by the state's strong interest in protecting viable fetal life, and all focus should be on fetal well-being. However, as stated in the decision, "For the stage subsequent to viability the state, in promoting its interest in the

potentiality of human life, may, if it chooses, regulate, and even proscribe, abortion except where necessary, in appropriate medical judgment, for the preservation of the life or health of the mother.”¹² Therefore, paradoxically, this landmark abortion case is instructive not in support of the restrictions on maternal autonomy after viability but as an argument against those abortion restrictions that fail to include pain and suffering exceptions. Thus, by imposing a life or health exception to state abortion bans, the Supreme Court instructs that a woman’s interest in protecting her life and health overrides the state’s interest in a viable fetus. This override was reaffirmed subsequently in *Carhart*, often referred to as the case banning “partial birth” abortion. Although the case upheld an abortion procedure ban, it stated that the law would be unconstitutional if it “subjected women to significant health risks” under its previous precedents.¹³ What is crucial is that the Supreme Court recognizes that the woman cannot be used simply for the fetus’s survival: if she suffers harm from her pregnancy, she should not be compelled to continue it regardless of fetal age. Surely the same must hold true for COVID-19 vaccination in which it is almost certain that any eventually identified effects on fetal well-being would be less than those of abortion.

Conclusions

What then are physicians’ obligations to optimize fetal well-being and, consequently, future neonatal outcomes, and is it possible to reconcile respect for a woman’s autonomy with protection of fetal well-being? How can they tack between the sharply contrasting lessons and legacies of Johnson Controls and thalidomide?

As we approach the issue of unknown risks, it is worth pausing to consider how society deals with known risks. Although risk is composed of likelihood and weightiness (eg, a large chance of a medication causing a rash has less salience than a smaller chance of it causing a brain tumor), society does allow, or at least does not ban, pregnant women from choosing to smoke or

drink or, if diabetic, to experience diabetic ketoacidosis and fetal death because of poor dietary choices. Certainly, known risks may be minimal despite being present, and unknown risks, by definition, cannot be dismissed as being minimal. To remind us, there is the example of thalidomide. However, one can interpolate from knowns to try to create a context for a shared decision. For example, because of theoretical concern of placental and fetal infection, vaccines that use live (attenuated) viruses are contraindicated in pregnancy, but the COVID-19 vaccine contains no live virus. These sorts of considerations can provide a context while giving due deference to maternal agency.

In light of all of the above we would offer the following concluding recommendations. First, if the risks of an agent are known and are substantial, and the benefits are nonlife sparing, or effective alternatives exist (eg, thalidomide for nausea), then we believe that physicians should counsel strongly against using such agents, and their actions in exercising their own right of refusing to recommend the treatment despite the patient’s persistence in their request would be justified. In contrast, if a hypothetical medication is the only known means of saving a pregnant individual’s life (or prevent severe compromise of her health), even if it poses a risk to the fetus, then access to the medication should be at pregnant patients’ discretion, allowing them to balance risks and benefits in the context of their values, and physicians’ action in assisting the woman in obtaining the medication or treatment in question would be justified. Neither patient nor provider should be forced to resort to more extreme and consequential actions of interrupting a pregnancy by either premature delivery or abortion to access appropriately chosen treatment. If the agent reduces the risk of being infected with a life-threatening virus, as is the case of the COVID-19 vaccination, and the risks to the fetus are unknown, then shared decision making, as recommended by the FDA, should be undertaken, and an informed woman’s choice should be

honored. As we emphasized above, shared decision making requires physicians to actively engage, not to merely inform, step back, and defer.

Finally, we note that these ethical dilemmas are the residue of a different challenge that pregnant women often face: their exclusion from clinical trials. The reticence of investigators to enlist pregnant women is understandable for it requires pregnant subjects to assume an unknown risk before any therapeutic efficacy can be demonstrated.

However, not enrolling pregnant individuals in studies leads to a predictable and not atypical dilemma: the often slow pace of access by pregnant women to the benefits of known effective therapies and preventive treatments. Several medical organizations have advocated the inclusion of pregnant women in vaccination trials, “particularly when the following criteria are met: (1) pregnancy poses increased susceptibility to or severity of a disease; (2) the best approach to protect the infant is through passive placental antibody transfer, which provides the most efficient and direct protection to the newborn before an infant can be vaccinated; and (3) there is an active outbreak.”¹⁴

Until a time when pregnancy is no longer a routine contraindication to participation in most studies, the obstetrician’s north stars should remain prioritizing both maternal well-being and autonomy. They remain set points that should only be challenged when the risks to the fetus are real and substantial, and the benefits to the mother are less significant. ■

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