Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Should women undergoing in vitro fertilization treatment or who are in the first trimester of pregnancy be vaccinated immediately against COVID-19

Meredith L. Snook, M.D.,[a] Richard H. Beigi, M.D., M.Sc.,[b] Richard S. Legro, M.D.,[c] and Catharine I. Paules, M.D.[d]

[a] Division of Reproductive Endocrinology and Infertility, [b] Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh Medical Center Magee-Womens Hospital, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; and [c] Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, and [d] Division of Infectious Diseases, Department of Medicine, Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania

Disclaimer: Authors for "fertile battles" are chosen to represent the full breadth of opinions. Individual authors, even within one side of the debate, do not necessarily agree with all viewpoints expressed.

PRO: Women undergoing in vitro fertilization treatment or who are in the first trimester of pregnancy should be vaccinated immediately against COVID-19

Meredith L. Snook, M.D.

Richard H. Beigi, M.D., M.Sc.

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is far from over and, despite the rapid emergence of effective vaccines, shows no indication of coming to a quick conclusion. As of May 26, 2021, documented COVID-19 cases exceed 33×10^6 in the United States (US) and over 168×10^6 globally. Additionally, deaths attributed to COVID-19 have surpassed 590,000 in the US and approach 3.5×10^6 worldwide (1). In the US, pregnant women are estimated to account

CON: A universal recommendation for COVID-19 vaccination in women undergoing in vitro fertilization treatment or who are pregnant is not supported by clinical trial data.

Richard S. Legro, M.D.

Catharine I. Paules, M.D.

In this past year, we have seen an unprecedented accomplishment of science—the rapid development, testing, and emergency use authorization (EUA) of highly effective COVID-19 vaccines, including those using novel mRNA and viral vector technologies. Concurrently, we have seen systemic social upheaval and heightened consciousness to provide equal rights and opportunities to all Americans regardless of race, gender, sexual orientation, socioeconomic status, etc. In this regard, we have

You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/33044
M.L.S. has nothing to disclose. R.H.B. has nothing to disclose. R.S.L. has nothing to disclose. C.I.P. has nothing to disclose.
Reprint requests: Richard S. Legro, M.D., Penn State College of Medicine, Hershey, Pennsylvania Department of Obstetrics and Gynecology, PO Box 850, 500 University Drive, Hershey, PA 17033-0850, United States (E-mail: rsl1@psu.edu).
https://doi.org/10.1016/j.fertnstert.2021.05.083

PRO: Women undergoing in vitro fertilization treatment or who are in the first trimester of pregnancy should be vaccinated immediately against COVID-19 *(continued)*

for approximately 1% of the general population (2), whereas almost 8% of women of reproductive age are believed to be pregnant, seeking pregnancy, or up to 6 weeks postpartum at any given time (3). Although the overall risk of severe COVID-19 among pregnant women is relatively low for an individual patient, those who get infected and develop symptoms are at increased risk of more severe illness compared with their nonpregnant counterparts. Specifically, pregnant women with symptomatic COVID-19 demonstrate an increased risk of admission to an intensive care unit, need for mechanical ventilation, and death compared with that in symptomatic nonpregnant individuals (4–7). Infection earlier in pregnancy may increase the risk of adverse fetal outcome (8). Furthermore, a recent systematic review and meta-analysis of 42 studies involving 438,548 pregnancies concluded that SARS-CoV-2 infection may be associated with increased risk of preeclampsia, preterm birth, and stillbirth (9). As such, the US Centers for Disease Control & Prevention (CDC) considers pregnancy a risk factor for an increased risk of severe illness related to COVID-19 (10). Therefore, preventing disease in pregnancy, in major part through active vaccination against SARS-CoV-2, and specifically early vaccination either in the periconceptional period or first trimester, is of paramount importance to potentially reduce both maternal and fetal COVID-19–related morbidity and mortality.

In general, non-live-attenuated vaccines are widely utilized and recommended in pregnancy. Maternal immunization through prenatal vaccination has improved maternal and neonatal health with regard to numerous infectious conditions (11). Although the advantage of vaccination during pregnancy sometimes focuses on the potential fetal and infant benefit through passive immunization, the impact of severe maternal infectious disease prevention in pregnancy should not be minimized (12). This is especially important for respiratory disease prevention, including influenza and COVID-19, from which pregnant women are at heightened risk of adverse outcomes. Other than live-attenuated vaccines, which are relatively contraindicated in pregnancy, almost all vaccines are permissible in pregnancy (if not actively recommended, like influenza and Tdap) when the benefits are believed to outweigh the risks. The current vaccines developed and demonstrated to have significant potential for prevention of severe infection related to SARS-CoV-2 among the general population undoubtedly will in addition provide substantial benefit to pregnant individuals. This is the primary reason that the leading professional societies in women's and reproductive health recommend that the vaccine should not be withheld from this population (13–15).

As of May 2021, there are currently three vaccines developed for the prevention of COVID-19 that have received Emergency Use Authorizations (EUA) by the US Food and Drug Administration (FDA). These include the messenger ri-

CON: A universal recommendation for COVID-19 vaccination in women undergoing in vitro fertilization treatment or who are pregnant is not supported by clinical trial data. *(continued)*

not seen one woman who is pregnant enrolled in the initial clinical trials used to obtain EUA of COVID-19 vaccines by the US Food and Drug Administration (FDA), despite the propensity for more serious manifestations of COVID-19 in this population. This exclusion represents systemic discrimination against women unfairly stigmatized by the natural and physiologic condition of pregnancy and has led to an inability to gather key safety and efficacy data for COVID-19 vaccines in an at-risk population.

Medical recommendations for vaccination of women who are pregnant ideally should be subject to the same rigid scrutiny and evidence as recommendations for vaccination in other adults. Thus far, this has not been the case for COVID-19 vaccines. A universal recommendation for COVID-19 vaccination in pregnancy cannot be made without acknowledging crucial gaps in scientific knowledge. The chief argument here is not for the *systemic exclusion* of women who are pregnant from COVID-19 vaccination but rather the *systemic inclusion* of women who are pregnant in the studies of pandemic vaccines, so that data-driven vaccine recommendations can be made in the future.

Historical Context: "Pregnant Women" as "Vulnerable" Subjects

The ethical conduct of human medical research in the US is guided by the Federal Policy for the Protection of Human Subjects or the "Common Rule". The Common Rule, which was first issued in 1981, is part of the Code of Federal Regulations (CFR). The CFR is published by the executive branch of the government, specifically the Department of Health and Human Services, and then codified in separate regulations by 15 Federal departments and agencies that accept the Common Rule. The FDA, against assumption, is not considered one of these agencies, because its regulations differ from the Common Rule. However, as mandated by the 21st Century Cures Act, the FDA is required to harmonize with the Common Rule whenever permitted by law.

Up until the revision of the Common Rule in 2018, "pregnant women" were described as "vulnerable" subjects who required special protection in research studies. Although the 2018 revision removed the vulnerable designation, it still listed 10 conditions that must be met before research can be initiated in women who are pregnant (36). It is the first condition that has been the largest hurdle:

> *Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.*

This first condition thus sets up two preliminary steps that must be completed before a study can be conducted in women

PRO: Women undergoing in vitro fertilization treatment or who are in the first trimester of pregnancy should be vaccinated immediately against COVID-19 *(continued)*

bonucleic acid (mRNA) vaccines from Pfizer-BioNTech and Moderna that each requires two doses 21 and 28 days apart, respectively, along with the single-dose adenovirus-vector vaccine from Janssen BioTech Inc. (Johnson & Johnson). All have demonstrated high efficacy with regard to their clinical trial end points. In individuals with no prior evidence of SARS-CoV-2 infection, the mRNA vaccines appear to be 94%–95% effective at prevention of laboratory-confirmed COVID-19 illness (16, 17), meaning those who received two doses of these vaccines had a 94%–95% lower risk of contracting COVID-19 compared with a non-vaccinated control group. Similarly, the adenovirus-vector vaccine has demonstrated 66% efficacy for the prevention of all levels of disease and 85% efficacy against severe disease globally (18). These vaccines do not contain live virus; therefore, there is no real nor theoretical risk of infection related to the vaccine itself. Along these lines, the American Society of Reproductive Medicine (ASRM, formerly The American Fertility Society) Coronavirus/COVID Task Force states that "since the vaccine is not a live virus, there is no reason to delay pregnancy attempts because of vaccination administration or to defer [fertility] treatment until the second dose has been administered" (15).

Data from the Development and Reproductive Toxicity (DART) studies regarding use of the approved vaccines are very encouraging. Animal studies demonstrated no increased adverse reproductive effects such as on female fertility or embryonic/fetal/postnatal development when these vaccines were delivered pre-mating or during early or late gestation (19–21). The theoretical concept that has grown from unclear sources about vaccines against COVID-19 being linked to infertility is wholly unfounded and has thus been discredited by leading societies in reproductive health (14).

It is acknowledged that there are relatively limited safety data regarding the use of COVID-19 vaccines in human pregnancy, because the vaccines currently available under the EUA have not yet been tested directly in pregnant women. However, vaccine trials have now commenced in this population. In addition, ongoing safety data that are being collected and reported from the CDC and FDA (i.e., through the Vaccine Adverse Event Reporting system [VAERS]) fail to demonstrate any adverse safety signals in regards to pregnancy outcomes or side effect profiles (22, 23). Specifically, the CDC has established v-safe, an active safety monitoring and surveillance smartphone-based tool for after vaccine follow-up. Participants can indicate pregnancy status and enroll in the v-safe COVID-19 vaccine registry, which provides ongoing information regarding the use of the vaccine in the periconceptional period and people who are pregnant. Pregnancy and neonatal outcomes of interest include miscarriage, stillbirth, and pregnancy complications such as preeclampsia, growth restric-

CON: A universal recommendation for COVID-19 vaccination in women undergoing in vitro fertilization treatment or who are pregnant is not supported by clinical trial data. *(continued)*

who are pregnant: studies in other adult populations and preclinical studies in pregnant animals.

Studies in other adult populations. Although the term "vulnerable" as a principle to protect women who are pregnant from harmful research has been expunged from the ethical guidance, medical vulnerability has not been incorporated as a scientific justification to escalate the study of these women. As discussed by our colleagues during their "pro" argument, women who are pregnant and develop COVID-19 are at an increased risk for intensive care admission, invasive ventilation, extracorporeal membrane oxygenation, and death compared with women who are not pregnant (6). In addition, there are nonrespiratory complications of COVID-19 in pregnant women that must be considered, including an increased risk of venous thromboembolism, hypertensive disorders of pregnancy, preterm delivery, and cesarean section (37). One might argue that the increased risk to women who are pregnant, though suspected at the time when COVID-19 vaccination trials were being designed, was not strong enough to bypass the Common Rule conditions. However, we know from our experiences with other infectious diseases, such as influenza and Ebola that women who are pregnant are disproportionately impacted by pandemics, and that pregnancy is often a risk factor for infectious disease-related morbidity and mortality (38, 39). Thus, despite a lack of COVID-19 vaccine studies in other adult populations early in the pandemic, it was not only scientifically inappropriate to exclude these women from clinical trial enrollment, it was ethically inequitable. Pregnant women should have been among the first groups studied, rather than relegated to the end of the line.

Developmental and reproductive toxicity studies. The second Common Rule hurdle in the first condition remains; the necessity to conduct preclinical studies in pregnant animals to look for embryonic/fetal lethality and anomalies. This requirement for DART studies derives its underlying ethical principles from the Belmont Report of 1979. It is linked to the thalidomide tragedy that occurred from 1957–1961 (40). Thalidomide first appeared as an over-the-counter antiemetic agent in Germany and was widely used until reports of limb abnormalities emerged. These abnormalities included phocomelia, which was characterized by severe reduction or loss of the proximal long bones with retention of the distal hand/foot plate (41).

DART studies are routinely performed in animals such as rats and rabbits and may not be entirely generalizable to human populations. It should be noted that thalidomide did not display teratogenic effects in rats and only showed limb abnormalities in rabbits at doses well above those given to people (42). In addition, DART studies require significant time to complete. In fact, only preliminary

PRO: Women undergoing in vitro fertilization treatment or who are in the first trimester of pregnancy should be vaccinated immediately against COVID-19 *(continued)*

tion, preterm birth, congenital anomalies, and neonatal death. As of May 24, 2021, almost 120,000 v-safe participants have indicated that they were pregnant at the time they received COVID-19 vaccination and over 5,000 are enrolled in the v-safe COVID-19 vaccine registry. To date, there have not been any observed safety concerns for those pregnant people enrolled in v-safe. Moreover, early data collected from over 1200 completed pregnancies in the v-safe pregnancy registry do not indicate any safety concerns with regard to pregnancy and neonatal outcomes following COVID-19 vaccination with mRNA vaccines (23) (CDC personal communication).

For additional vaccine safety monitoring, the CDC and FDA comanage the VAERS, an early warning system for identifying possible safety concerns after vaccination including detection of rare adverse effects. Limited by reporting bias, VAERS is not designed to assess for causality nor is there an unvaccinated control group. Of those adverse events in pregnant women after receiving an mRNA COVID-19 vaccine that were reported to VAERS through February 28, 2021, most (70%) involved non-pregnancy-specific adverse events (local and systemic reactions) (23). Although miscarriage was the most frequently reported pregnancy-specific adverse event, the observed rate among women receiving one of the mRNA COVID-19 vaccines was 12.6% (104/827 completed pregnancies), falling well within published and expected background rates of miscarriage (23, 24).

Despite the relatively limited data of COVID-19 vaccines in pregnant women, there are no data suggesting that the vaccines should be contraindicated in this population or in those individuals planning pregnancy.

It is noted, however, that the Janssen adenovirus-vector COVID-19 vaccine has recently been associated with thrombosis with thrombocytopenia syndrome (TTS), a rare but serious condition of which most cases have occurred in nonpregnant women of reproductive age (25). A thorough review of these cases by the Advisory Committee on Immunization Practices was performed, after which recommendations for the use of the Janssen COVID-19 vaccine were reaffirmed (49). Women of reproductive age and those who are pregnant can receive any available FDA-authorized COVID-19 vaccine with appropriate counseling regarding the rarity and risk of TTS following receipt of the Janssen COVID-19 vaccine (approximately seven out of every one million doses to females 18-49 years) (25), and should be aware of other COVID-19 vaccines available (13).

In general, the available vaccines against COVID-19 appear to be relatively safe and highly effective in preventing severe illness, and there is no evidence to date that COVID-19 vaccination in the periconception or prenatal period is associated with increased reproductive, pregnancy, or neonatal adverse outcomes compared with background rates. In this vein, it is recommended that patients undergoing fertility

CON: A universal recommendation for COVID-19 vaccination in women undergoing in vitro fertilization treatment or who are pregnant is not supported by clinical trial data. *(continued)*

DART data were available at the time of the EUA by the FDA of the Pfizer-Biotech and Moderna COVID-19 vaccines (20, 43). For the Janssen adenovector virus, reproductive toxicity study in female rabbits concluded that the vaccine given before mating and during gestation periods at doses up to two times the human dose did not have any effects on female reproduction, fetal/embryonal development, or postnatal development. (44)

The absence of complete DART data was not seen as a compelling reason to limit access of women who are pregnant to the COVID-19 vaccines under EUA. This leads to the question of why the completion of these DART studies remain a Common Rule and FDA Vaccine Guidance hurdle to clinical trial participation at all, particularly in the setting of a pandemic.

Because of the exclusion of pregnant women from the initial COVID-19 vaccine studies, guidance for COVID-19 vaccination in women who are pregnant is based largely on expert opinion rather than on science. This defaults to a risk-benefit discussion with the individual's physician, and one must weigh what is known vs. what is not known to balance decision-making. The dilemma for the heirs of Archie Cochrane and practitioners of evidence-based medicine is how to discuss the risk-benefit ratio of COVID-19 vaccination during pregnancy when there are no Level 1 data from randomized trials (45). However, as the pandemic rages on, is it even possible to take a true "con" side to delaying COVID-19 vaccination of individuals in this high-risk group? In some cases, advising a woman who is pregnant to defer COVID-19 vaccination could be seen as outside their best interests, given the "abundance of data" in other adult populations and the overwhelming support for "not withholding" it from pregnant women by US professional medical societies (13) (although our own ASRM used intentional language to recommend vaccination) (15).

Yet, despite strong support for recommending COVID-19 vaccines in women who are pregnant, there remain unanswered questions regarding the safety of these vaccines in this group. Already, we have seen that side effect profiles differ on the basis of the population to which they are administered. Younger individuals report more local and systemic adverse events after the Pfizer-BioNTech and Moderna mRNA vaccines than older individuals do (46), whereas anaphylaxis after these vaccines has been largely seen in individuals with a history of allergies or allergic reactions (47, 48). A rare but serious side effect, thrombosis with thrombocytopenia syndrome, has been reported after the Janssen adenovirus-vector vaccine and is most common in women <50 years of age. (49). It is critical that vaccine safety data in one population not be directly extrapolated to another population.

Caution must be taken when administering COVID-19 vaccines to pregnant women in the absence of these safety data. As more vaccines are given under EUA to women who

PRO: Women undergoing in vitro fertilization treatment or who are in the first trimester of pregnancy should be vaccinated immediately against COVID-19 *(continued)*

treatment receive vaccination when eligible (15), either in the periconceptional period or early pregnancy, while adhering to guidance set forth by the ASRM Coronavirus/COVID-19 Task Force to avoid vaccination within three days before or after an elective surgical or fertility-related procedure such as oocyte retrieval, embryo transfer, or intrauterine insemination (26). This guideline regarding timing considerations is important because known common side effects of vaccines (fever, chills, myalgia, fatigue, etc.) could confuse possible perioperative evaluation for complications, and many facilities may not allow patients to enter or proceed with procedures if they have COVID-like symptoms, which can be similar to the side effects of vaccines.

The decision to receive the vaccine while undergoing in vitro fertilization (IVF) treatment or early in pregnancy should not be weighed solely against the theoretical and "unknown" risk of the vaccine itself, but more so within the context of the real increased risk of adverse outcomes associated with severe COVID-19 illness while pregnant and the known ability of the vaccines to prevent disease. Any delay in taking the vaccine would facilitate pregnant women to incur the risks of contracting and experiencing severe illness and adverse outcomes related to COVID-19 infection, including maternal and fetal death.

Delaying vaccination while undergoing fertility treatment could lead to an unknown period of delay as fertility and IVF treatments are often not successful on the first attempt and may require numerous attempts to achieve an ongoing pregnancy. Treatment success relies on numerous variables, and despite the clinical team's best attempts, cannot always be predicted. Of those patients who conceive a successful pregnancy, time to pregnancy after initiation of fertility treatment could be 8–12 months (27, 28) or longer. Some patients will not ever conceive. Therefore, given the uncertainty surrounding treatment success, it is reasonable to recommend vaccination once eligibility criteria are met and "at the soonest possible time, whether pre-conception or during pregnancy", as supported by ASRM (26). In addition, there is likely some flexibility with regard to scheduling the vaccine if a patient is in an active treatment cycle, to avoid the 6-day window surrounding a possible procedure, or, there may be the luxury of scheduling the start of a fertility treatment cycle around first and, if needed, second vaccine doses. Additionally, as opposed to other vaccines, the vaccines against SARS-CoV-2 are still serving as a relatively scarce resource and may not always be readily available to specific populations at any given time. Electing to delay vaccination may mean it is not readily available in the future.

Fever, a common side effect of any vaccine, is reported in up to 9% and 16% of individuals after the single dose of the Janssen vaccine (29) or final dose of both mRNA vaccines, respectively (20, 30). Fever may be of concern in early pregnancy because of an observed association with congenital

CON: A universal recommendation for COVID-19 vaccination in women undergoing in vitro fertilization treatment or who are pregnant is not supported by clinical trial data. *(continued)*

are pregnant, there will be less incentive to collect data in randomized, double-blind, placebo-controlled clinical trials. Many clinicians will be recommending vaccination to all of the women who qualify for a vaccine study but do not participate, yet allowing a placebo (and withholding the vaccine) to those who do participate. It will, in our opinion, take a particularly enlightened and altruistic person to choose to participate in these trials and accept the possibility of a placebo when the overwhelming professional position is moving toward a general recommendation for vaccination. In addition, companies may decide not to pursue these studies altogether as enrollment becomes increasingly difficult. In this regard, Pfizer-BioNTech has recently suspended enrollment in their COVID-19 vaccine pregnancy study within the United States where COVID-19 vaccines are readily available.

As observational data for safety of COVID-19 vaccines in pregnant women accumulates, there may even be an argument of loss of research equipoise to continue clinical trials that include a placebo arm. Recently, the CDC published COVID-19 vaccine safety data, collected by their surveillance systems, in 35,691 pregnant women. Reported local and systemic adverse events were similar to those seen in nonpregnant adults and among 3,958 participants who were contacted for further assessment, adverse pregnancy and neonatal outcomes were in line with those reported in other vaccine studies before the COVID-19 pandemic. Although these data are reassuring, there are important limitations that must be recognized. One such limitation is the utilization of a historical comparator for pregnancy and neonatal outcomes rather than a placebo control group. The individuals assessed in this observational cohort were largely health care workers and likely differ with the historical comparator in terms of age, ethnic group, access to medical care, and other characteristics that are known to impact pregnancy and neonatal outcomes. In addition, vaccine safety data in the peri-conception and early pregnancy periods are lacking, as there are relatively few of these individuals included in the registry and many of these pregnancies are still ongoing. Although useful, observational studies lack the high-quality, granular data obtained in placebo-controlled trials, and by basing recommendations solely on these data, we accept a lower standard for pregnant vs. nonpregnant adults.

Planning for the Next Pandemic: Modification of the Common Rule

In terms of clinical trial participation, we live in a world where personalized medicine is becoming the gold standard. The decision to include women who are pregnant in initial studies of new vaccines must be individually adjudicated on the basis of the severity and threat of the illness. There must be a way to bypass the current infrastructure that is scientifically determined and allows the ethically sound design and implementation of clinical trials in women who are pregnant.

PRO: Women undergoing in vitro fertilization treatment or who are in the first trimester of pregnancy should be vaccinated immediately against COVID-19 *(continued)*

anomalies (31), especially neural tube defects, but this association was not observed in a recent, large cohort study (32). In addition, a causal relationship is challenging to construct because of retrospective study designs, reporting bias, inconsistency of reported degree/duration of fever, and the fact that fever is typically caused by a response to an underlying infection, and therefore any association with congenital anomalies would need to distinguish the effects of fever itself from those related to an underlying infection. Furthermore, any association between hyperthermia and congenital anomalies appears to be mitigated in the setting of adequate folic acid intake (31, 33) and single-agent acetaminophen use (34). The observed fevers after vaccination to COVID-19 are short-lived, and taking acetaminophen for alleviation is recommended (13) without any perceived risk, advice with which most pregnant women will comply.

In conclusion, contraction of SARS-CoV-2 during pregnancy may have devastating maternal and fetal outcomes. Further, emerging data suggest vaccination may lead to maternal antibody transmission to the fetus providing potential protection against infant infection (35). Current safety data surrounding the vaccines against COVID-19 are reassuring and do not indicate safety concerns for individuals who are planning pregnancy or are in the first trimester, while at the same time demonstrate high efficacy in the general population. For those patients undergoing IVF treatment or in early pregnancy, it is in their best interests to strongly consider vaccination once eligible, and sooner rather than later, as they may incur the risk of severe COVID-related illness and associated morbidity and mortality the longer they wait.

CON: A universal recommendation for COVID-19 vaccination in women undergoing in vitro fertilization treatment or who are pregnant is not supported by clinical trial data. *(continued)*

The executive branch of the federal government has the power to modify the CFR and guidances to industry. One key priority is a modification of the Common Rule to remove existing roadblocks to studying women who are pregnant in certain circumstances, such as a pandemic. This could be achieved by adding an 11th item to Subpart B of the Common Rule:

> *The above requirements can be waived or modified in the face of an illness that is severe and life threatening to women who are pregnant.*

Other groups, including the Task Force on Research Specific to Pregnant Women and Lactating Women established by the 21st Century Cures Act, have similarly advocated for modifications to Subpart B of the Common Rule to facilitate the participation of women who are pregnant in clinical trials (50).

Even with modifications to the Common Rule, the potential liability to industry and other stakeholders from any reproductive toxicity that resulted from accelerated, modified, or omitted DART testing or early enrollment in clinical trials before completion of trials in other adults will remain a hurdle. Expansion of programs or legislative initiatives that mitigate liability when vaccine development is a public health priority will speed vaccine development for women who are pregnant in future pandemics (51). One current example is the Countermeasures Injury Compensation Program, which provides compensation for women who are pregnant and other individuals not pregnant who are harmed by products designed to prevent or treat public health threats such as COVID-19 (52).

Systemic Discrimination in the Segregation of Women who are Pregnant into Separate and Unequal Vaccine Trials Must End with COVID-19:

> No State shall … deny to any person within its jurisdiction the equal protection of the laws.
>
> [el6][rlEqual Protection Clause of the 14th Amendment to the U.S. Constitution.

Ultimately COVID-19 vaccination in pregnancy illustrates a human rights issue in which a category of adults has been systematically deprived of the opportunity to participate in research or make medical decisions on the basis of evidence because of a natural condition.

We have seen the concept of "separate but equal" for school segregation rejected by the Supreme Court of the United State in Brown vs. the Board of Education in 1954 as violating the Equal Protection Clause of the 14th Amendment to the U.S. Constitution. Subsequent Supreme Court decisions have cited this clause to strike down laws that discriminated against women. Discriminatory laws and policies must be supported by an "exceedingly persuasive justification" that is substantially related to an important government objective and cannot

PRO: Women undergoing in vitro fertilization treatment or who are in the first trimester of pregnancy should be vaccinated immediately against COVID-19 *(continued)*

CON: A universal recommendation for COVID-19 vaccination in women undergoing in vitro fertilization treatment or who are pregnant is not supported by clinical trial data. *(continued)*

be on the basis of stereotypes about gender roles (53). Applying the Equal Protection Clause may be the key to increasing access of woman who are pregnant (or capable of pregnancy) to research participation.

The systematic exclusion of women who are pregnant (or may become pregnant) from vaccine trials has resulted in unequal and inferior treatment. Calls for greater inclusion of women, including women who are pregnant, in clinical trials is overwhelming and has been advocated exhaustively by experts (54), task forces (50), working groups (55, 56) (including one authored by our opponent in this debate, Dr. Beigi) (57), professional organizations (58), and the National Academy of Medicine (59). Women who are pregnant do not need protection against participating in vaccine trials. They can make informed decisions. In 2021, the only "exceedingly persuasive justification" is for the inclusion of women who are pregnant in COVID-19 vaccine trials at the same time as other adults.

If not us, then who? If not now, then when?
John L. Lewis

Providers of care to women who are pregnant are obligated to advocate for fair and equitable treatments for their patients. How can we as clinicians and researchers make recommendations to our patients who are pregnant without scientific proof of safety and efficacy and how can we, if we are proponents of equal rights, allow the systemic exclusion of women who are pregnant from the pivotal vaccination trials? The two concepts of medical research that require evidence for all and access to all are inextricably linked. Are we going to accept that COVID-19 vaccines are safe and effective during pregnancy on the basis of observational data or do we insist on adequately powered prospective placebo-controlled randomized trials such as the ones that led to the FDA EUAs of vaccines in other adult populations?

Are we as providers upholding equal rights or perpetuating a "separate but equal" arrangement whereby vaccines and medications will be tested in women who are pregnant at some indeterminate point in the future according to some lesser clinical study standard or maybe not at all because of an inability to complete trials when clinical practice has moved beyond the question? If women who are pregnant are being asked to make an informed decision about whether to receive a COVID-19 vaccine under EUA with insufficient pregnancy data, why is it believed that they cannot make an informed decision to participate in a research study of these vaccines in the same absence of data? In a public health emergency in which women who are pregnant are at increased risk for severe illness and mortality, the doctrine of delayed and "separate but equal" clinical trials for women who are pregnant is inherently unequal. The COVID-19 pandemic has given us the opportunity and the imperative to advocate for change, so that during the next pandemic there is only a "pro" argument for vaccination of pregnant women!

REFERENCES

1. Johns Hopkins University and Medicine Coronavirus Resource Center website. Available at: https://coronavirus.jhu.edu/. Accessed May 26, 2021.
2. Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 2009;374:451–8.
3. Daniels K, Abma JC. Current contraceptive status among women aged 15-49: United States, 2017-2019, NCHS Data Brief, No. 388. Hyattsville, MD: National Center for Health Statistics 2020.
4. Delahoy MJ, Whitaker M, O'Halloran A, Chai SJ, Kirley PD, Alden N. Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed COVID-19 — COVID-NET, 13 States, March 1–August 22, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1347–54.
5. Panagiotakopoulous L, Myers TR, Gee J, Lipkind H, Kharbanda EO, Ryan DS, et al. SARS-CoV-2 infection among hospitalized pregnant women: reasons for admission and pregnancy characteristics—eight US health care centers, March 1–May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1355–9.
6. Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status—United States, January 22–October 3, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1641–7.
7. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. Br Med J 2020;370:m3320.
8. Di Mascio D, Sen C, Saccone G, Galindo A, Grunebaum A, Yoshimatsu J, et al. Risk factors associated with adverse fetal outcomes in pregnancies affected by coronavirus disease 2019 (COVID-19): a secondary analysis of the WAPM study on COVID-19. J Perinat Med 2020;48:950–8.
9. Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. CMAJ 2021;193:E540–8.
10. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): people with certain medical conditions. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed March 27, 2021.
11. Moniz MH, Beigi RH. Vaccination during pregnancy. Obstet Gynecol Surv 2016;71:178–86.
12. Swamy GK, Beigi RH. Maternal benefits of immunization during pregnancy. Vaccine 2015;33:6436–40.
13. American College of Obstetricians and Gynecologists' Immunization, Infectious Disease, and Public Health Preparedness Expert Work Group. ACOG practice advisory: vaccinating pregnant and lactating patients against COVID-19. Available at: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/vaccinating-pregnant-and-lactating-patients-against-covid-19. Accessed May 23, 2021.
14. American Society for Reproductive Medicine. ASRM, ACOG and SMFM issue joint statement: medical experts continue to assert that COVID vaccines do not impact fertility. Available at: https://www.asrm.org/news-and-publications/news-and-research/press-releases-and-bulletins/asrm-smfm-acog-issue-joint-statement-medical-experts-continue-to-assert-that-covid-vaccines-do-not-impact-fertility/. Accessed March 28, 2021.
15. Coronavirus/COVID-19 Task Force of the American Society for Reproductive Medicine. ASRM patient management and clinical recommendations during the coronavirus (COVID-19) pandemic: update no. 11—COVID-19 vaccination December 16. Available at: https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covid-19/covidtaskforceupdate11.pdf. Accessed March 28, 2021.
16. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockart S. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020;383:2603–15.
17. Baden LR, Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403–16.
18. Centers for Disease Control and Prevention. Overview of Janssen's single-dose COVID-19 Vaccine, Ad26.COV2.S. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/28-03-01/02-COVID-Douoguih.pdf. Accessed March 28, 2021.
19. United States Food and Drug Administration. Fact sheet for healthcare providers administering vaccine (vaccination providers). Emergency use authorization (EUA) of the Pfizer-BioNTech COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19). Available at: https://www.fda.gov/media/144413/download. Accessed March 28, 2021.
20. United States Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee meeting December 17, 2020—FDA briefing document: Moderna COVID-19 vaccine. Available at: https://www.fda.gov/media/144434/download. Accessed March 28, 2021.
21. United States Food and Drug Administration. Fact sheet for healthcare providers administering vaccine (vaccination providers). Emergency use authorization (EUA) of the Janssen COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19). Available at: https://www.fda.gov/media/146304/download. Accessed March 29, 2021.
22. Centers for Disease Control and Prevention. V-safe COVID-19 vaccine pregnancy registry. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafepregnancyregistry.html. Accessed May 26, 2021.
23. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulous L, et al. Preliminary findings of mRNA COVID-19 vaccine safety in pregnant persons. N Engl J Med. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2104983. Accessed May 23, 2021.
24. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG practice bulletin no. 200: early pregnancy loss. Obstet Gynecol 2018;132:e197–207.
25. Shimabukuro T. Thrombosis with thrombocytopenia syndrome (TTS) following Janssen COVID-19 vaccine. Advisory Committee on Immunization Practices (ACIP). Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-04-23/03-COVID-Shimabukuro-508.pdf. Accessed May 23, 2021.
26. Coronavirus/COVID-19 Task Force of the American Society for Reproductive Medicine. ASRM patient management and clinical recommendations during the coronavirus (COVID-19) pandemic: upate no. 13—variants, vaccines, and vaccination February 22, 2021. Available at: https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covid-19/covidtaskforceupdate13.pdf. Accessed March 28, 2021.
27. Reindollar RH, Regan MM, Neumann PJ, Levine BS, Thornton KL, Alper MM, et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil Steril 2010;94:888–99.
28. Goldman MB, Thornton KL, Ryley D, Alper MM, Fung JL, Hornstein MD, et al. A randomized clinical trial to determine optimal infertility treatment in older couples: the Forty and Over Treatment Trial (FORT-T). Fertil Steril 2014;101:1574–81.e1.
29. United States Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee meeting 26 February 2021: COVID-19 vaccine Ad26.COV2.S VAC31518 (JNJ-78436735) sponsor briefing document. Available at: https://www.fda.gov/media/146219/download. Accessed March 28, 2021.
30. United States Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee meeting December 10, 2020—FDA briefing document: Pfizer-BioNTech COVID-19 vaccine. Available at: https://www.fda.gov/media/144245/download. Accessed March 28, 2021.
31. Dreier JW, Andersen AM, Berg-Beckhoff G. Systematic review and meta-analyses: fever in pregnancy and health impacts in the offspring. Pediatrics 2014;133:e674–88.
32. Sass L, Urhoj SK, Kjaergaard J, Dreier JW, Strandberg-Larsen K, Nybo Andersen AM. Fever in pregnancy and risk of congenital malformations: a cohort study. BMC Pregnancy Childbirth 2017;17:413.
33. Kerr SM, Parker SE, Mitchell AA, Tinker SC, Werler MM. Periconceptional maternal fever, folic acid intake, and the risk for neural tube defects. Ann Epidemiol 2017;27:777–82.e1.
34. Feldkamp ML, Meyer RE, Krikov S, Botto LD. Acetaminophen use in pregnancy and risk of birth defects: findings from the National Birth Defects Prevention Study. Obstet Gynecol 2010;115:109–15.

35. Gray KJ, Bordt EA, Atyeo C, Deriso E, Akinwunmi B, Young N, et al. COVID-19 vaccine response in pregnant and lactating women: a cohort study. Am J Obstet Gynecol 2021, 2021.03.07.21253094.
36. Anonymous. Subpart B — additional protections for pregnant women, human fetuses and neonates involved in research. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/common-rule-subpart-b/index.html. Accessed April 5, 2021.
37. Metz TD, Clifton RG, Hughes BL, Sandoval G, Saade GR, Grobman WA, et al. Disease severity and perinatal outcomes of pregnant patients with coronavirus disease 2019 (COVID-19). Obstet Gynecol 2021;137:571–80.
38. Haddad LB, Jamieson DJ, Rasmussen SA. Pregnant women and the Ebola crisis. N Engl J Med 2018;379:2492–3.
39. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol 2012;207(Suppl 3):S3–8.
40. Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. Birth Defects Res C Embryo Today 2015;105:140–56.
41. Vargesson N. The teratogenic effects of thalidomide on limbs. J Hand Surg Eur 2019;44:88–95.
42. Fratta ID, Sigg EB, Maiorana K. Teratogenic effects of thalidomide in rabbits, rats, hamsters, and mice. Toxicol Appl Pharmacol 1965;7:268–86.
43. United States Food and Drug Adminstration. Pfizer-BioNTech COVID-19 vaccine (BNT162, PF-07302048) Vaccines and Related Biological Products Advisory Committee briefing document: meeting date 10 December 2020. Available at: https://www.fda.gov/media/144246/download. Accessed April 6, 2021.
44. United States Food and Drug Adminstration. Vaccines and Related Biological Products Advisory Committee briefing document: February 26, 2021—FDA briefing document Janssen Ad26.COV2.S Vaccine for the prevention of COVID-19. Available at: https://www.fda.gov/media/146217/download. Accessed May 1, 2021.
45. King JF. A short history of evidence-based obstetric care. Best Pract Res Clin Obstet Gynaecol 2005;19:3–14.
46. Chapin-Bardales J, Gee J, Myers T. Reactogenicity following receipt of mRNA-based COVID-19 vaccines. J Am Med Assoc 2021. https://doi.org/10.1001/jama.2021.5374.
47. Centers for Disease Control and Prevention (US), Food and Drug Administration. COVID-19 Response Team; Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine — United States, December 14–23, 2020. MMWR Morb Mortal Wkly Rep 2021;70:46–51.
48. Centers for Disease Control and Prevention (US), Food and Drug Administration. COVID-19 Response Team; Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Moderna COVID-19 vaccine — United States, December 21, 2020–January 10, 2021. MMWR Morb Mortal Wkly Rep 2021;70:125–9.
49. Centers for Disease Control and Prevention. Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States. Available at: https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html. Accessed April 30, 2021.
50. Byrne JJ, Saucedo AM, Spong CY. Task force on research specific to pregnant and lactating women. Semin Perinatol 2020;44:151226.
51. Heyrana K, Byers HM, Stratton P. Increasing the participation of pregnant women in clinical trials. J Am Med Assoc 2018;320:2077–8.
52. Bianchi DW, Kaeser L, Cernich AN. Involving pregnant individuals in clinical research on COVID-19 vaccines. J Am Med Assoc 2021;325:1041–2.
53. Martin E. Reed v. Reed at 40: a landmark decision. Available at: https://nwlc.org/blog/reed-v-reed-40-landmark-decision/. Accessed April 7, 2021.
54. Riley LE, Jamieson DJ. Inclusion of pregnant and lactating persons in COVID-19 vaccination efforts. Ann Intern Med 2021, M21-0173.
55. Krubiner CB, Faden RR, Karron RA, Little MO, Lyerly AD, Abramson JS, et al. Pregnant women & vaccines against emerging epidemic threats: ethics guidance for preparedness, research, and response. Vaccine 2021;39:85–120.
56. Modi N, Ayres-de-Campos D, Bancalari E, Benders M, Briana D, Di Renzo GC, et al. Equity in coronavirus disease 2019 vaccine development and deployment. Am J Obstet Gynecol 2021;224:423–7.
57. Beigi RH, Krubiner C, Jamieson DJ, Lyerly AD, Hughes B, Riley L, et al. The need for inclusion of pregnant women in COVID-19 vaccine trials. Vaccine 2021;39:868–70.
58. Committee on Ethics. ACOG committee opinion no. 646: ethical considerations for including women as research participants. Obstet Gynecol 2016;127:e100–7.
59. Mastroianni AC, Faden R, Federman D, editors. Women and health research: ethical and legal issues of including women in clinical studies. Washington (DC): National Academies Press; 1994.