

Sources of Vaccine Hesitancy: Pregnancy, Infertility, Minority Concerns, and General Skepticism

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The coronavirus disease 2019 (COVID-19) epidemic continues to evolve, with variants of concern and new surges of COVID-19 noted over the past months. The limited data and evolving recommendations regarding COVID-19 vaccination in pregnancy have led to some understandable hesitancy among pregnant individuals. On social media, misinformation and unfounded claims linking COVID-19 vaccines to infertility are widespread, leading to vaccine skepticism among many men and women of reproductive age. The disproportionate impact of COVID-19 on communities of color, coupled with the unfortunate and troubled history of abuses of African Americans by the biomedical research community in the US, has also led to hesitancy and skepticism about the COVID-19 vaccines among some of our most vulnerable. The complex nature of vaccine hesitancy is evidenced by further divides between different demographic, political, age, geographical, and socioeconomic groups. Better understanding of these concerns is important in the individualized approaches to each patient.

Keywords. COVID-19 pandemic; COVID-19 vaccines; vaccine hesitancy; vaccine skepticism.

There are many sources of vaccine hesitancy surrounding the coronavirus disease 2019 (COVID-19) vaccines. This is not a new phenomenon. We have seen misinformation [1] and debate surrounding influenza and other thimerosal-containing vaccinations for decades, regardless of an abundance of evidence showing their safety and lack of connection to autism or infertility, or other detrimental effects. Early on, there was some public concern [2] about the rapidity with which the COVID-19 vaccines were studied and manufactured under “Operation Warp Speed.” As we have transitioned from a time of severe COVID-19 vaccine scarcity, to a time of more-abundant vaccines and public health concerns about vaccine skepticism, we wish to outline some specific sources of vaccine hesitancy, including evolving recommendations on COVID-19 vaccination in pregnancy, misinformation about infertility and the COVID-19 vaccines, concerns about American medicine in general (and COVID-19 vaccine specifically) among communities of color, and general vaccine skepticism and hesitancy.

EVOLVING AND “SPLIT RECOMMENDATIONS” REGARDING COVID-19 VACCINES IN PREGNANCY

The United States (US) Centers for Disease Control and Prevention (CDC) has noted that there are minimal data on the safety of COVID-19 vaccines in pregnant women, that animal developmental and reproductive toxicity studies are ongoing, and that studies in humans are ongoing [3]. There was also concern about the novel messenger RNA (mRNA) technology [4] used to create the Pfizer BNT162b2 and Moderna mRNA 1273 vaccines. While mRNA vaccines have been studied for many years in both oncology and infectious disease, they have been implemented on a large scale for the first time to address this pandemic. The mRNA vaccines are not live vaccines, they do not enter the nucleus of the cell, and they are degraded quickly by normal cellular processes [4, 5].

Therefore, as with other inactivated vaccines, there is no credible, biologically plausible mechanism for interference with pregnancy or fertility.

Data supporting the safety of COVID-19 vaccines in pregnancy continue to emerge. As of June 2021, >128 000 pregnant individuals had received COVID-19 vaccines, as reported in the CDC's “V-safe after vaccination health checker” [6]. Based on available information, no specific safety signals have been observed in pregnant people who have received a COVID-19 vaccine and enrolled in V-safe; however, longitudinal follow-up is still needed. Worldwide experience on COVID-19 vaccination in pregnancy have also yet to identify any signals for concern, although data remain preliminary. Globally, many pregnant individuals report being receptive to COVID-19 vaccination;

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however, hesitancy is higher among pregnant persons in the US as compared to many other countries [7].

Given the concerns about severe COVID-19 disease in pregnancy [8–11] and early reports of an increased risk of preterm birth in pregnant women who have COVID-19 [8], the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) have stated that COVID-19 vaccines “should not be withheld from pregnant individuals” and that “routine testing for pregnancy prior to receipt of a COVID-19 vaccine is not recommended” [12]. While the World Health Organization (WHO) had also initially recommended against one of the COVID-19 vaccines during pregnancy, the WHO revised its statement in late January: “While pregnancy puts women at higher risk of severe COVID-19, very little data are available to assess vaccine safety in pregnancy. Nevertheless, based on what we know about this kind of vaccine, we do not have any specific reason to believe there will be specific risks that would outweigh the benefits of vaccination for pregnant women. For this reason, those pregnant women at high risk of exposure to SARS-CoV-2 [severe acute respiratory syndrome coronavirus 2] (eg, health workers) or who have comorbidities which add to their risk of severe disease, may be vaccinated in consultation with their healthcare provider” [13].

In the absence of clear safety data or firm recommendations for vaccination, and with widespread misinformation on social media, many pregnant women have been understandably concerned about the unknown long-term effects of the COVID-19 vaccines in pregnancy. ACOG further stated that “pregnant women who decline the COVID-19 vaccine should be supported in their decision,” that in the interest of patient autonomy, ACOG recommends that “pregnant individuals be free to make their own decision regarding COVID-19 vaccination,” and that “regardless of their decision to receive or not receive the vaccine, these conversations provide an opportunity to remind patients about the importance of other prevention measures such as hand-washing, physical distancing, and wearing a mask” [12]. ACOG and SMFM recommend individual discussions and shared decision-making, with considerations for COVID-19 vaccination during pregnancy to include the level of COVID-19 transmission in the community, an individual’s personal risk of contracting COVID-19, comorbidities associated with disease severity, the risks of COVID-19 to the pregnant person and the potential risks to the fetus, the efficacy and known side effects of the vaccine, and the lack of data about the vaccine during pregnancy.

What to make of such conflicting and confusing recommendations? With each patient, we review misconceptions as well as new evidence regarding the vaccine and pregnancy, and we evaluate each patient’s individual risk. In populations that have been heavily impacted by the pandemic (eg, Native Americans), it is quite likely that the benefit of the COVID-19

vaccine outweighs the risk. Since many patients develop fevers after one or both doses of the mRNA vaccines, it had previously been considered reasonable to wait until after the first trimester to avoid prolonged fever during early fetal development. If fevers occur, acetaminophen is recommended and safe in pregnancy [12].

In summary, if a pregnant patient is very concerned about acquiring COVID-19 disease (or getting a reinfection), especially given the increased circulation of COVID-19 “variants of concern,” it would be reasonable to get the COVID-19 vaccine. However, if a patient is nervous about the COVID-19 vaccine during pregnancy (given the lack of long-term safety data in pregnancy on the fetus or child), it was considered reasonable to defer the COVID-19 vaccine until after pregnancy. Regardless, both groups should be encouraged to remain vigilant about other mitigation strategies to prevent infection, especially while variant strains circulate widely.

The Delta (B.1.617.2) variant of SARS-CoV-2 carries several new mutations [14], appearing first [15] in India last December, and now continuing to evolve and move throughout the US. Amid the skyrocketing number [16] of COVID-19 cases in the country, mostly due to the Delta variant, the ACOG revised and updated [17, 18] its guidance on 30 July 2021 to state the following:

- ACOG strongly recommends that all eligible persons receive a COVID-19 vaccine or vaccine series. Obstetrician-gynecologists and other women’s health care practitioners should lead by example by being vaccinated and encouraging eligible patients to be vaccinated as well.
- ACOG recommends that pregnant individuals be vaccinated against COVID-19.
- ACOG recommends that lactating individuals be vaccinated against COVID-19.

MISINFORMATION ABOUT INFERTILITY AND COVID-19 VACCINES

ACOG and SMFM state that “unfounded claims linking COVID-19 vaccines to infertility have been scientifically disproven. ACOG recommends vaccination for all eligible people who may consider future pregnancy.” The American Society for Reproductive Medicine (ASRM) also specifically states that the mRNA vaccines “are not thought to cause an increased risk of infertility, first or second trimester loss, stillbirth, or congenital anomalies” [19]. But where did these unfounded claims linking COVID-19 vaccines to infertility emerge?

In a recent manuscript [20], 2 of us (A. L. H. and T. B. N.) outlined some of the misinformation and disinformation that has resulted in significant vaccine hesitancy among women with infertility or presenting with preconception concerns. Misinformation is defined as “false or inaccurate information, especially that which is deliberately intended to deceive.” In

contrast, disinformation is defined as “false information which is intended to mislead, especially propaganda issued by a government organization to a rival power or the media.”

Upon a review of the relevant social media, a former Pfizer scientist was noted to have raised the concern that the COVID-19 vaccine may somehow result in female infertility by inducing an autoimmune reaction against the syncytin-1 protein, which is involved in placenta formation. This concern was raised because of the “apparent homology between this viral spike glycoprotein and syncytin-1, a cell-cell fusion protein which is critical for placental development; they further allege that antibodies against the COVID-19 spike glycoprotein could potentially cross-react with syncytin-1, potentially leading to anti-placental antibodies and female infertility” [20].

However, there is no significant sequence homology between the SARS-CoV-2 spike protein and syncytin-1 protein, and the initial “claim was based on a tiny sequence of 5 amino acids, 4 of which are reportedly shared between syncytin-1 and the SARS-CoV-2 spike protein,” a sequence too short to result in autoimmunity due to placental antibodies [20, 21].

Unfounded claims about the COVID-19 vaccines and both female and male infertility have been dismissed by multiple expert organizations, including CDC [22], ASRM [19, 21], and ACOG/SMFM [12]. Currently, there is no credible, biologically plausible mechanism by which either COVID-19 disease or the COVID-19 vaccines may negatively impact female fertility [19–21].

From the male perspective, there may be some potential concern about COVID-19 disease and male reproductive function; specifically, there may be a negative impact of COVID-19 disease on testicular function, sperm production, male sex hormone function, and male fertility [20]. Indeed, orchitis and testicular pain are among the many side effects of the COVID-19 disease—and so for any male individual who is concerned about his fertility relative to COVID-19, the preponderance of evidence suggests that getting the COVID-19 vaccine would be better than getting COVID-19 itself [20].

Given that the COVID-19 pandemic in the US is now being called “a pandemic of the unvaccinated” [21], mostly due to the Delta variant, the ASRM also issued an update on 23 July 2021 to state the following [21]:

- COVID-19 vaccination does not impact male or female fertility or fertility treatment outcomes.
- Existing data suggest COVID-19 vaccination during pregnancy does not increase risk of miscarriage.
- COVID-19 vaccination does not induce antibodies against the placenta.
- None of the currently available COVID-19 vaccines reach or cross the placenta. The intramuscularly administered vaccine mRNA remains in the deltoid muscle cell cytoplasm for just a few days before it is destroyed. However, protective

antibodies to COVID-19 have been shown to cross the placenta and confer protection to the baby after delivery.

- Reproductive endocrinologists should discuss COVID-19 vaccination with all patients and encourage vaccination for all patients during evaluation and treatment for infertility. Vaccination either pre-conception or early during pregnancy is the best way to reduce maternal/fetal complications. Physician counseling has been shown to have significant positive impact on patient willingness to consider vaccination.

CONCERNS IN COMMUNITIES OF COLOR ABOUT COVID-19 VACCINES (AND ABOUT AMERICAN MEDICINE IN GENERAL)

COVID-19 has had a disproportionate impact on underrepresented minority communities [23], especially on African Americans, Hispanic Americans, Native Americans, and certain subgroups of Asians and Pacific Islanders. This impact is partly due to preexisting health disparities (including chronic conditions and medical comorbidities that are more prevalent in particular ethnic groups) and worsened by social inequities including housing, transportation, employment, and access to healthcare. In the US, people of color are more likely to contract COVID-19 due to a host of cultural and socioeconomic reasons. They are more likely to live in multigenerational homes, and communities with higher ethnic populations generally have higher housing density; in addition, these communities are more likely to use public or shared transportation. Immigrant and migrant workers are more likely to have poor working conditions that enable further spread of the virus. According to Census data, approximately 43% of Black and Latino workers are employed in service or production jobs or are front-line workers, compared with 25% of White Americans [24]. While some Americans were able to adhere to stay-at-home orders or work from home by choice to decrease the risk, many diverse populations are not able to work from home. Not only is this population of Americans diagnosed with COVID-19 more often, but morbidity and mortality have also been worse, including rates of hospitalizations, admission to critical care, mechanical ventilation, and long-term sequelae such as stroke and death [9].

There are a variety of factors behind the underlying disparities in underrepresented communities of color. Independent of the pandemic, and compared with non-Hispanic Whites, we know that Black individuals aged 18–49 years are twice as likely to die from heart disease [25], Blacks aged 35–64 years are 50% more likely to have high blood pressure [25], and Native Americans have a life expectancy that is 5.5 years less than all other races (with mortality often linked to diabetes, cirrhosis, and liver disease) [26]. We know that there are also significant disparities in women’s health. Black women have a 3-fold higher risk of maternal mortality than White women in Missouri [27]. Black women with ovarian, endometrial, and cervical cancer

also had worse 5-year survival compared to other groups. To help understand the full impact of the pandemic on minority communities, the American Medical Association has encouraged the US Department of Health and Human Services to make available all COVID-19 race and ethnicity data [28]. As a medical community, our emphasis has been on acknowledging inequities, ensuring access to care and testing, providing community resources, and collecting data.

However, preexisting medical conditions are just one piece of the puzzle. The question that often arises is, “What could explain these disproportionate outcomes?” Quite plainly, “Why do Black Americans seem to do so much worse?” Researchers in social sciences have attempted to answer this question for decades and many theories have been debunked, namely genotypic variance such as the “slavery hypertension hypothesis” [29]. Meanwhile, shameful episodes in American biomedical research include the abusive Tuskegee syphilis study, the atrocities of J. Marion Sims’ effort to advance his surgical techniques via medical experiments on enslaved Black women without anesthesia [30], and research on Henrietta Lacks and her children without their consent.

In addition, research by Dr Arline Geronimus and many others document that Black individuals experience higher levels of allostatic stress over their lifetimes, leading to dysregulated stress responses, chronic inflammation, and accelerated aging [31]. “Allostatic load” is a term coined by Dr Bruce McEwen, referring to the wear and tear on the body that accumulates as an individual is exposed to repeated or chronic stress (such as microaggressions) [32]. In the literature, a direct link has been made from allostatic load to morbidity and mortality for Blacks, and especially Black women; this is the principal theory for why this population fares poorly with a diversity of clinical syndromes including cardiovascular disease, malignancy, autoimmune disease, and sepsis [32, 33]. The health of Black women begins to deteriorate in early adulthood as a physical consequence of socioeconomic disadvantage. This “impact of dealing with disadvantage throughout the life course wears down the body’s organs and tissues, particularly the cardiovascular system, causing advanced health deterioration and early death” [33], and this issue of “weathering” is independent of socioeconomic status, as illustrated by the publicly available stories of Dr Chaniece Wallace, Shalon Irving, and Serena Williams [34].

These past and present health disparities among African Americans, coupled with the toll of allostatic load and weathering, has led to widespread mistrust of institutions such as law enforcement and medicine in many Black communities. Some of our patients also have vaccine skepticism and hesitancy (for both flu shots and the COVID-19 vaccines) because of the historic abuses of African Americans by the biomedical research community in the US. For those individuals, we recommend fully acknowledging the historic abuses perpetrated by American medicine [30] and the biomedical research

community on African Americans and other ethnic minorities. We need to acknowledge and recognize that, while we cannot change the past, we must move forward with communities of color, to assist in decisions affecting diverse patient populations, to pledge to never repeat the abuses of the past, and to confront systemic racism [30, 35] that persists in our medical system. The medical community aims to remain transparent, encourage informed consent, and gain back trust that has been lost.

GENERAL SKEPTICISM

In 1899, Missouri congressman Willard D. Vandiver said, “Frothy eloquence neither convinces nor satisfies me. I’m from Missouri. You’ve got to show me” [36]. This sentiment is echoed by many Missourians today.

Amid Missouri’s “show me” and personal freedom culture, we sympathize with the valiant efforts of our state governments and state health departments to try to assuage public concerns and promote vaccine uptake, even during the time of COVID-19 vaccine scarcity this past winter. We applaud the efforts of our state and federal governments in implementing a multipronged effort including mass vaccination events, hospital distribution, a big push for state vaccinators, and federal distribution through pharmacies and federally qualified health centers. There has also been widespread concern about the ability and capacity of getting vaccine into underrepresented rural [37] and urban communities. In our state, the University of Missouri’s Extension Service Center for Applied Research and Engagement Systems (CARES) has been publishing “story maps” to help elucidate where the greatest need for COVID-19 vaccines exist; this dashboard provides a snapshot of COVID-19 cases in Missouri, as well as “vulnerability indicators” for counties within Missouri [38]. In recent weeks, we have unfortunately seen a substantial rise in case numbers in several of our rural communities, which has been echoed in areas with low vaccination rates across the US.

Vaccine hesitancy is complex and multifactorial [39], and we have seen a divide in attitudes toward the pandemic in general as well as vaccination efforts in many different groups. In a recent survey by the Missouri Hospital Association (MHA), “African Americans and white Evangelicals are less likely to be vaccinated, but the bigger problem here is that very conservative residents and younger Republicans are very resistant to getting the vaccine. Geographically, this vaccine hesitancy is greatest in the Springfield market” [40]. At the time of this writing, the counties around Springfield in southwest Missouri have been experiencing some of the highest rates of COVID-19 in the US. MHA [40] concludes that “the vaccine has become a politicized issue. The fact that concern is higher about getting COVID-19 among those who have been vaccinated than among those who haven’t indicates how difficult it will be to get many of these remaining

Missourians vaccinated.” While hesitancy rates have decreased over time, some who have been staunchly against COVID vaccination have not changed their opinions [39, 40].

CONCLUSIONS

Hopefully, many of those who have opted not to get the vaccine are a “slow yes” rather than a “hard no.” We are aware of many individuals who contracted COVID-19 over the past year and who had opted to delay receiving the vaccine during a time of limited vaccine supply; indeed, the CDC also previously indicated that it would be reasonable to defer the COVID-19 vaccine within the first 90 days after being infected with SARS-CoV-2. With vaccines now widely available to willing recipients in the US, we encourage those with prior SARS-CoV-2 infection to receive the COVID-19 vaccine as recommended by the CDC.

As more data emerge about COVID-19 vaccination during pregnancy, we will gain more insight into the efficacy of vaccines in this population. There remains significant hesitancy among pregnant individuals in the US, compared to other countries. Misinformation and disinformation about COVID-19 vaccines and both male and female infertility are proving difficult to overcome. Given the deplorable history and ongoing racism experienced by African Americans and other communities, vaccine hesitancy and skepticism in these vulnerable communities is not unexpected. Continued efforts to provide honest and straightforward conversations about vaccination are imperative.

To address vaccine hesitancy in their patients, CDC recommends that health care providers “1. Start from a place of empathy and understanding; 2. Assume patients will want to be vaccinated but may not know when to expect it; 3. Give your strong recommendation; and 4. Listen to and respond to patient questions” [41]. The MHA states that “[u]ltimately, the more information residents have regarding the vaccine, the more likely they are to be vaccinated. This information is best communicated by providers, especially their primary care physicians.” As case numbers due to emerging COVID-19 variants continue to rise globally, predominantly in unvaccinated populations here in the US, it will be incumbent upon all of us to address continued vaccine hesitancy and skepticism in the coming months and years.

Notes

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