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REVIEW

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Causes and Effects of COVID-19 Vaccine Hesitancy Among Pregnant Women and its Association with Adverse Maternal, Placental, and Perinatal Outcomes

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Populations identified to be severely affected by COVID-19, such as pregnant patients, require special consideration in vaccine counseling, access, and provider education. Maternal infection with COVID-19 poses a significant risk to the maternal-fetal dyad with known adverse placenta destruction [1-5]. Despite the widespread access and availability of vaccinations, vaccine hesitancy continues to persist and is highly prevalent in pregnant populations [6-9]. Addressing the multitude of social ecological factors surrounding vaccine hesitancy can aid in providing holistic counseling [10]. However, such factors are foremost shaped by maternal concern over possible fetal effects from vaccination. While changes in policy can help foster vaccine access and acceptance, increasing global provider education and incorporation of motivational interviewing skills are the first steps towards increasing maternal acceptance.

INTRODUCTION

Human vaccination continues to be a vital and life-saving achievement throughout modern history. According to the United States Centers for Disease Control and Prevention (CDC), 4 million deaths are prevented yearly from childhood vaccination [11]. However, despite the widespread access and availability of vaccinations, vaccine hesitancy continues to persist. Furthermore, a significant spike in vaccination hesitancy has occurred during the COVID-19 pandemic with the newly created COVID-19 vaccines. This hesitancy has expanded to disapproval of other commonly accepted vaccines, such as the measles-mumps-rubella (MMR) vaccine, causing an increase in the incidence of childhood measles [12]. In particular, minority groups and populations at high

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Abbreviations: MMR, measles-mumps-rubella; ICU, intensive care unit; ACE2, angiotensin converting enzyme 2 receptor; CDC, Centers for Disease Control and Prevention; SGA, small for gestational age; VLBW, very low birthweight babies; CHIV, chronic histiocytic intervillositis; MPFD, massive perivillous fibrin deposition; MVM, maternal vascular malperfusion; RSV, Respiratory Syncytial Virus.

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risk for poor outcomes and those identified to be severely affected by COVID-19 need special consideration in vaccination counseling, access, and provider education. Maternal infection with COVID-19 poses a severe risk to the maternal-fetal dyad and requires closer attention as prior research has shown higher levels of vaccine hesitancy in pregnant populations [1-3,13-16]. We aim to discuss maternal and neonatal outcomes of COVID-19 infection, the consequences to the mother, fetus, and placenta of being unvaccinated for COVID-19, development of the COVID-19 vaccine, vaccine approval in pregnancy, vaccine hesitancy in pregnant populations, and motivational interviewing in vaccine acceptance.

METHODS

This review article was conducted using the following databases: Medline, PubMed, and Scopus. The initial search revealed over 5082 results. After careful selection, the authors chose articles with the following criteria: favoring articles published in the last 5 years, article type limited to systematic reviews, peer-reviewed journal articles, randomized controlled trials, and/or book chapters. Additionally, guidelines and articles from national organizations, such as the CDC, were also sourced. A detailed review of all articles was performed, and 78 articles were selected for use with careful attention made by the authors for avoidance of bias.

OUTCOMES FROM COVID-19 VACCINE REFUSAL IN PREGNANCY

Maternal Effects of COVID-19 Vaccine Refusal

Pregnancy exacerbates the clinical course of SARS-CoV-2 causing more severe disease [17]. Whether a patient was asymptomatic or symptomatic, those who are infected have a higher risk of rapid deterioration, severe disease, and death. COVID-19 in pregnant individuals has shown higher rates of preeclampsia, gestational diabetes, thrombotic disease, preterm birth, low birth weight, severe obstetrical hemorrhage, intra-amniotic infection, pulmonary morbidity, oxygen therapy, cesarean delivery, admission to intensive care unit (ICU), and need for ventilatory support [18-21]. Some of these adverse outcomes in pregnant women may be due to the effects of SARS-CoV-2 on the placenta. SARS-CoV-2 enters the body and infects pulmonary cells by binding to the angiotensin-converting enzyme 2 receptor (ACE2). ACE2 is expressed on various organs in the body, including the placenta [21]. This could provide an explanation for the higher rates of preeclampsia, fetal growth restriction, and preterm birth occurring in pregnant women having COVID-19. Advanced maternal age, gestational age, and existing hypertension are significantly associated with worse maternal outcomes [21]. These adverse effects of COVID-19 jointly effect the maternal-fetal dyad.

Maternal vaccination to COVID-19 has shown significant reduction in overall maternal mortality during pregnancy. In a systematic review by Rahmati et al., they found that vaccinated patients had reduced risks of SARS-CoV-2 infection by 60% (41%-73%), COVID-19 hospitalization during pregnancy by 53% (31%-69%), and intensive care unit admission by 82% (12%-99%). They saw no increase in maternal adverse outcomes during pregnancy including gestational diabetes, gestational hypertension, unassisted vaginal delivery, cesarean section, postpartum hemorrhage, and placental abruption [22].

Fetal Effects of COVID-19 Vaccine Refusal

Maternal COVID-19 vaccine refusal can potentially affect the fetus in three ways. Firstly, unvaccinated pregnant women are at high risk for developing severe morbidity from SARS-CoV-2 infection, especially in women with co-morbidities. These morbidities include but are not limited to pneumonia and respiratory distress syndrome, need for mechanical ventilation, acute myocardial infarction, sepsis syndrome, coagulopathy and thrombosis, hemorrhage and shock, and hypertensive disease [14,23-25]. All of these conditions are potentially harmful, and even life-threatening to the fetus because they affect the mother's cardiovascular system and can inhibit the adequate maternal perfusion and oxygenation of the placenta, causing fetal hypoxia.

As the COVID-19 pandemic developed, studies of pregnant women infected with SARS-CoV-2 revealed increased risk for adverse neonatal outcomes [26]. However, the relationship between maternal SARS-CoV-2 infection and stillbirth initially remained uncertain during the early phases of the pandemic [3,27-29]. It has now been unequivocally demonstrated that COVID-19 during pregnancy is associated with an increased risk for stillbirth [30]. The CDC in Atlanta, GA, analyzed 1 249 634 hospitalizations from March 2020 to September 2021, and found pregnant women having COVID-19 were at increased risk for stillbirth compared with uninfected women (adjusted relative risk (aRR) = 1.90; 95% CI = 1.69–2.15) [15]. This association was highest during the period when the SARS-CoV-2 B.1.617.2 (Delta) variant circulated in the community. In Scotland, Stock et al. analyzed the clinical outcomes of 2364 infants delivered to vaccinated and unvaccinated mothers from December 1, 2020 to October 31, 2021 [31]. There were 11 stillbirths and eight live-born infants who died in the neonatal period, all occurring in unvaccinated mothers. At the close of study enrollment, COVID-19 vaccine coverage

remained significantly lower among pregnant women when compared to non-pregnant childbearing-age women – just 32.3% of women giving birth in October 2021 had received two vaccine doses in contrast to 77.4% of all women. Prasad et al. performed a systematic review and meta-analysis examining perinatal outcomes between 66 067 COVID-19 vaccinated and 424 624 unvaccinated pregnant patients and found vaccination was associated with a 15% reduction in stillbirths [32].

A multicenter cohort study at Providence St. Joseph Health system examined 86 833 pregnant patients and found significantly lower stillbirth in vaccinated women (p<0.01) [33]. Furthermore, they found patients who were vaccinated and boosted had significantly lower rates of preterm birth (p<0.05), stillbirth (p<0.01), small for gestational age (SGA) (p<0.05), and very low birthweight babies (VLBW) (p<0.01) when compared with those pregnant women who had been vaccinated for COVID-19 but had not receive a third booster dose 5 months after completing the initial vaccination series.

In Switzerland, Favre et al. evaluated the multicenter Swiss COVI-PREG registry to examine the associations between maternal COVID-19 vaccination and stillbirth [34]. They found that among 1012 women in Switzerland who had been administered at least 1 dose of mRNA vaccine between March 1 and December 27, 2021, there was no increase in adverse pregnancy or neonatal outcomes compared with historic data on background risks, and no stillbirths reported [34]. In a recent meta-analysis, Rahmati et al. evaluated the association between maternal COVID-19 vaccination and perinatal outcomes including 862 272 individuals (308 428 vaccinated and 553 844 unvaccinated) reported in the medical literature up to November 2022 [22]. Stillbirth risk showed a reduction of 45% (17%-63%) in association with vaccination. Maternal vaccination was associated with a decreased probability of preterm birth at levels of 15% (3%-25%), 33% (14%-48%), and 33% (17%-46%) before 37-, 32- and 28-weeks' gestation, respectively, when compared with unvaccinated mothers. The necessity for neonatal intensive care was significantly lower by 20% when pregnant mothers had received the COVID-19 vaccine (16%-24%). An important multicenter cohort study by Hui et al. has provided evidence that maternal vaccination against SARS-CoV-2 results in a decreased risk of stillbirth when compared with unvaccinated women [35]. This retrospective study conducted at 12 maternity hospitals in Melbourne, Australia and evaluated the clinical perinatal outcomes of 17 365 women who received ≥1 doses of the mRNA COVID-19 vaccine before or during pregnancy, comparing this data with 15 171 unvaccinated pregnant women during the period from July 1, 2021 to March 31, 2022. The vaccinated mothers had a lower rate of stillbirth compared with the unvaccinated cohort (0.2% vs 0.8%; adjusted odds ratio, 0.18; 95% CI, 0.09-0.37; *P*<.001). When these data were stratified for gestational age, this association was statistically significant only for preterm stillbirths [35]. Morgan et al. compared the frequency of perinatal death between 2069 pregnant patients who completed COVID-19 vaccination series with 13 796 unvaccinated patients within the Ochsner Health System in Louisiana between January 1st and December 31st 2021 [26]. The results demonstrated that vaccination was associated with a lower incidence of perinatal death (0.5% vaccinated group vs 0.8% unvaccinated group, aOR 0.20 0.05-0.88). Maternal COVID-19 vaccination was also associated with lower rates of preterm delivery (aOR 0.63, 0.48-0.82), VLBW (aOR 0.35, 0.15-0.84), and necessity for NICU (aOR 0.66, 0.52-0.85).

Placental Effects of COVID-19 Vaccine Refusal

It is important that the placenta, the largest of fetal organs, functions properly to ensure its ability to support oxygenation and nutritional support of fetal growth and development. In addition, the placenta serves as the first line of defense against infectious diseases. The maternal-fetal interface is a complex structure that regulates hormonal, biochemical, and maternal immunological factors that are necessary for fetal development. This interface consists of cytotrophoblasts which have a proliferative capability, and the syncytiotrophoblast, which are multinucleated and fused terminally differentiated cells. It is the syncytiotrophoblast that covers the surface of the chorionic villous trees, where it is in direct contact with maternal blood flowing through the intervillous space. The syncytiotrophoblast layer is the most important cellular component of the maternal-fetal interface, is strongly resistant to infection from numerous infectious agents, and provides a critically important function in protecting the fetus against viruses and other pathogens [4,36,37].

Multiple clinicopathological studies have established that SARS-CoV-2 can infect the placenta and result in significant pathological changes to that vital fetal organ [5,38-44]. The most common findings include chronic histiocytic intervillositis (CHIV), increased perivillous fibrin deposition that in the majority of placentas reaches the level of massive perivillous fibrin deposition (MPFD), and trophoblast necrosis. MPFD and CHIV are unusual placental abnormalities that were rarely observed in placentas prior to the COVID-19 pandemic. The simultaneous result of these three pathologic findings in placentas infected with SARS-CoV-2 from pregnant women with COVID-19 has been termed "SARS-CoV-2 placentitis" by Watkins et al. [40]. Additional pathological findings can accompany SARS-CoV-2 placentitis that include findings of maternal vascular malperfusion (MVM) and fetal vascular malperfusion (FVM), villitis, hemorrhages, and thrombohematomas [38]. Schwartz et al. examined

placentas from 64 stillborn fetuses and four early neonatal deaths from 12 countries that were confirmed using immunohistochemistry or nucleic acid methodology to have infection with SARS-CoV-2. In all 68 cases the mother had not received vaccination for COVID-19 [39]. Findings demonstrated that all 68 placentas had severe destructive pathology resulting from SARS-CoV-2 placentitis, and that there was coexistent CHIV, increased fibrin deposition or MPFD, and trophoblast necrosis in 97% of placentas. The severity of tissue necrosis was striking as the average infected placenta had 77.7% tissue destruction resulting from widespread involvement with SARS-CoV-2 placentitis; many placentas had >90% of the parenchyma destroyed. Placental tissue destruction to this extent must significantly impede the capability of the placental vascular network to deliver adequate oxygen and nutrients to the fetus to maintain its viability and is thus incompatible with fetal survival. It was concluded that the placental destruction and resulting insufficiency from SARS-CoV-2 placentitis and consequent severe fetal hypoxia produced a hypoxic-ischemic fetal or neonatal demise. Additional studies have confirmed that placental destruction from SARS-CoV-2 placentitis can result in stillbirth in pregnant women who have not received the COVID-19 vaccine. In Sweden, Zaigham et al. described five stillborn fetuses from unvaccinated mothers with COVID-19 in which all placentas were infected with SARS-CoV-2 and had developed SARS-CoV-2 placentitis and tissue destruction [42]. A report from Greece by Konstantinidou et al. described six stillborn fetuses from unvaccinated mothers with SARS-CoV-2 infection during pregnancy, with all placentas exhibiting SARS-CoV-2 placentitis [30].

When examined together, the placental pathology, clinical and epidemiologic studies strongly suggest that COVID-19 vaccination of pregnant women may prevent stillbirth. Vaccination probably does this via a mechanism of inhibiting maternal viremia and development of placental infection, thus preventing the formation of SARS-CoV-2 placentitis and placental insufficiency. It appears highly unlikely that the lack of maternal vaccination is coincidental in the multiple reports of SARS-CoV-2 placentitis associated with stillbirths and neonatal deaths.

Effects of COVID-19 Herd Immunity on Pregnancy and Vaccine Refusal

Following 4 years of global COVID-19 infections there are scant current data on the effects of herd immunity to SARS-CoV-2 and its relationship to pregnancy outcomes in unvaccinated persons. Recent data from the Centers for Disease Control and prevention indicate that the COVID-19 vaccine remains an effective method for prevention of neonatal morbidity and hospitalization during the Omicron subvariant predominance, a time when community herd immunity to SARS-CoV-2 is high [45]. The Omicron variants have produced large numbers of infections due to their highly contagious nature, and that plus continued distribution of COVID-19 vaccines including the BA.4/BA.5-Adapted Bivalent Booster has increased herd immunity to the virus. This has had the effect of reducing overall morbidity and mortality from COVID-19 during the Omicron variant surges among pregnant persons, and especially among unvaccinated individuals [46].

COVID-19 VACCINATION

Mechanism of Action Vaccine–mRNA

The *Coronaviridae* are a family of viruses that cause a range of upper respiratory tract illnesses in humans, with the most severe manifestations resulting in acute respiratory distress syndrome, pneumonia. and multiorgan disease syndrome. Human-to-human transmission occurs through close contact, respiratory secretions, and aerosols. SARS-CoV-2 is a coronavirus that is an enveloped, positive-sense, single-stranded RNA virus containing 12 open-reading frames encoding protein, including four structural proteins: envelope, membrane, nucleocapsid, and lastly, the spike protein [47]. The molecular mechanism of host entry is through the surface spike glycoprotein (S protein). The S protein is composed of a region that attaches to the ACE2 receptor found commonly in the respiratory epithelial cell, and which facilitates fusion of the host and virus membranes [48]. This spike protein represents the primary target for neutralizing antibodies and current vaccines. The two most popular COVID-19 vaccines are Moderna and Pfizer-BioNTech vaccines that are mRNA vaccines administered intramuscularly. They stimulate both cellular and humoral immunity. The mRNA codes for the spike protein of the virus and is included in a lipid nanoparticle that once injected intramuscularly into the human body, it attaches to host cells, inserts its mRNA into the cytoplasm, and synthesizes the viral spike proteins. The proteins are then recognized by antigen presenting cells (APCs), such as dendritic cells, macrophages, and B cells, which have MHC-1 and MHC-2 molecules on their surface. The binding of the protein acts as an antigen to the MHC molecules and leads to the immune recognition of cytotoxic T cells and helper T cells. This leads to production of cytokines that cause B cells antibodies that target the viral spike protein and memory T-cell proliferation [49,50]. Presentation of the spike proteins by MHC-1 proteins to the T-cell receptors of CD8+ T-cells also result in the production of cytotoxic T-cells which causes the death of virus-infected cells and helps further amplify the immune response [49,50]. Another popular vaccine was the Johnson & Johnson vaccine (Janssen) (no longer available as of May 2023), a DNA

vaccine that uses its recombinant human adenovirus serotype 26 (Ad26) to introduce a DNA sequence encoding the entire SARS-CoV-2 spike protein. The DNA sequence is not integrated and remains distinct from the host cells. Once the viral spike proteins present themselves on the surface of the host cell, they activate formation of CD4+ and CD8+ T cells, B-cells, plasma cells, and cytokines, resulting in both a cellular and humoral immune response [49]. However, this vaccine was less efficacious than the Moderna and Pfizer-BioNTech vaccines [49].

Speed of Creation and Mass Circulation

December 2019 was the first known human case of COVID-19 in Wuhan, China [3]. In December 2020, the FDA approved an emergency use authorization for the Pfizer vaccine [51]. One month later, the FDA issued an emergency use authorization for Moderna's vaccine [51]. Prior to the identification of SARS-CoV-2 there were no reports of a vaccine being developed in less than 1 year, and no there were no vaccines for preventing other coronavirus infections such as MERS and SARS-CoV in humans [49]. The previous record for development of a vaccine was the mumps vaccine, which took 4 years to develop in the 1960s. According to the WHO, there have been 770 875 433 confirmed cases of COVID-19 as of September 27th, 2023, including 6 959 316 reported deaths. As of September 19th, 2023, a total of 13 505 262 477 vaccine doses have been administered [52]. The high levels of coverage of the COVID-19 vaccine have been a significant reason for the declining rates mortality and morbidity of COVID-19. Encouraging mass circulation of the COVID-19 vaccine is key to mitigating the impact of the pandemic on the community, and especially pregnant mothers.

FDA Approval for Pregnant Patients

During the development of the COVID-19 vaccines, pregnant women and children were excluded from the pre-authorization clinical trials. There was initially insufficient evidence to support the use of COVID-19 vaccination in pregnant patients. As time went on, evidence showed that pregnant patients were more likely to suffer severe illness with COVID-19 infection. COVID-19 during pregnancy is associated with an increased risk of preterm delivery, maternal severe illness, admission to an intensive care unit, acute respiratory distress syndrome, and death [53,54].

Studies have revealed an association between COVID-19 vaccination and lower severity of COVID-19 infection in pregnant people [55]. Vaccinated individuals were also less likely to experience adverse pregnant outcomes [56,57]. Another study by Munoz et al. also revealed that COVID-19 vaccination or booster during pregnancy elicited an efficient transplacental antibody transfer to the newborn and significantly increased maternal and cord blood antibodies [58]. The CDC in collaboration with the American College of Obstetricians and Gynecologists (ACOG) have provided guidance strongly recommending that pregnant individuals be vaccinated against COVID-19 [59-61]. The Food and Drug Administration (FDA) issued a statement of support for COVID-19 vaccination for pregnant patients, breastfeeding women, and/or women of reproductive age [62]. Despite these recommendations, vaccine hesitancy is a major barrier to COVID-19 vaccine acceptance due to concerns about safety for the unborn child and mistrust of the vaccine [56,63]. Increased attention is needed to increase vaccination acceptance in pregnant patients by emphasizing the safety and benefits for the mother and the fetus.

COVID VACCINATION HESITANCY IN PREGNANCY

What is Vaccination Hesitancy?

Vaccination hesitancy is defined as the diffidence towards accepting and receiving vaccinations [16,64,65]. This hesitancy continues to transcend across time not only with the creation of new vaccines, but also vaccines that have been available since the early 20th century. The reluctance to vaccination persists despite vaccine availability, status, and high-quality evidence of efficacy and safety. The concept of vaccination hesitancy stems back to the origins of this process and the advent of Jennerian vaccination for smallpox. Such hesitancy threatens COVID-19 vaccination programs and wide-spread vaccination and potential for creation of a population benefit with herd immunity [64]. The importance of vaccination during the current global COVID-19 pandemic is paramount toward increasing herd immunity and stabilization of disease. There exists a drastic disparity in COVID-19 vaccination rates amongst populations, especially pregnant patients.

Concept of Vaccination Hesitancy in Pregnancy

COVID-19 vaccination in pregnancy is a severe health concern given the increased maternal mortality and severe disease possible with COVID-19 infection in pregnancy [1,2,66,67]. Evidence of vaccination hesitancy in pregnancy can be observed in the study by Germann et al. who conducted a multivariate Poisson regression analysis to estimate vaccination by baseline vaccination hesitancy status. In their study of 459 individuals surveyed, they found that 290 provided vaccination status and of those 40% reported vaccination hesitancy at initial survey and of those 52% reported subsequent vaccination

at follow-up. More importantly, they noted that only 10% of patients who identified as vaccination hesitant transitioned to vaccinated during the study period [16]. They noted that individuals who were older, parous, employed, and with higher educational degrees were more likely to be vaccinated vs non-Hispanic Black individuals; Medicaid patients being less likely to be vaccinated [16]. This highlights the significant ethnic and racial disparities that exist in COVID-19 vaccination access, education, and acceptance in pregnancy.

Kiefer et al. conducted a cross-sectional study in pregnant and postpartum patients from March to April of 2021 and found after adjusting for age, parity, race, and trimester and chronic conditions, that vaccination hesitancy was 46% in pregnant patients. They found that non-Hispanic Black patients, younger age, lower education, higher parity, and substance use were more likely to decline vaccination and experience hesitancy about becoming vaccinated [68]. Factors that were associated with high rates of vaccination: a family or friend receiving the vaccine, being concerned about contracting COVID-19, acceptance of tetanus or influenza vaccine, and reporting benefits of vaccination for COVID-19 for the baby. Levy et al. sent surveys to 1002 women from December 2020 to January of 2021 with a response rate of 66.1% and completion of the survey was after emergency authorization of the Pfizer vaccine. They found most respondents were >30 years (82.9%), had advanced degrees (87.7%), and were White (62.7%). Most respondents were already vaccinated to influenza during pregnancy; 77.9% and 58.3% stated they would accept the Pfizer vaccination. The main concern in declining vaccination in pregnant individuals was the effect of the vaccine on the fetus (45.8%) followed by how the vaccine would affect themselves (17.7%) [69]. Age, ethnic minority, educational status, and whether they received the seasonal influenza vaccine had a huge influence on vaccine hesitancy.

It is possible that COVID-19 vaccine hesitancy in pregnancy may change over time because of evolving knowledge about the vaccine and changes in vaccine-related attitudes and beliefs. However, significant vaccination hesitancy exists with other vaccines commonly recommended in pregnancy for pertussis and influenza, with reports showing that only 50% of pregnant patients are found to be vaccinated for these illnesses each year, despite widespread acceptance and safety, without a large influence and coverage within the media [68]. General factors that were found with other past vaccinations have mirrored the hesitancy associated with the initial vaccination to COVID-19 including social, political, religious, and other beliefs [70]. Although organizing these above factors into various categories surrounding a social-ecological framework can help guide policy change and interventions, each factor is potentially linked, thus necessitating a holistic approach to understanding vaccine hesitancy when counseling patients [10].

CAUSES OF COVID VACCINATION HESITANCY IN PREGNANCY

Knowledge and Information of Vaccination in Pregnancy

Vaccination rates in pregnant women remains low for a variety of well-known infections that are commonly preventable and/or mitigated by vaccination in the postpartum and intrapartum periods. These include influenza, pertussis, measles, mumps, rubella, COVID-19, and most recently respiratory syncytial virus (RSV). Although there is emerging safety data regarding all these vaccines, some which are more well studied then others, there are limited randomized controlled trials in pregnant patients given the ethical consideration of pregnant patients serving as research subjects. Vaccination hesitancy during the early pandemic was expected given that the CDC did not authorize pregnant individuals to receive the vaccine until the end of July, 2021 [9]. Initial data surrounding safety of COVID-19 vaccination during pregnancy were limited. Given the vaccine was an mRNA vaccination, their safety was hypothesized to be acceptable for use in pregnancy, but again pregnant patients were excluded from early trials.

Furthermore, lack of awareness of national recommendations and provider support for vaccination in pregnancy can impact acceptance. Maternal health providers including midwives, obstetricians/gynecologists, and advanced practitioners rely heavily on guidance from national organizations such as the Society for Maternal Fetal Medicine (sMFM) and the American College of Obstetrics and Gynecology (ACOG) for consensus statements supporting vaccination [71]. Some maternal health providers may be hesitant to endorse recommendations for vaccination based on political influence and current geographic location.

Society and Politics

The timely creation of the COVID-19 vaccine in less than 1 year drastically impacted wide-spread acceptance. The initial vaccine created against COVID-19, Pfizer-BioNTech COVID-19 vaccine, was created, evaluated, and authorized for emergency use in under a year [64]. The rapid need for a vaccination during a global pandemic was paramount and emergency authorization of federal funding as well as concerns about profits obtained from vaccine manufacturers competing to provide the initial COVID-19 mass-distributed vaccination only added to heightened vaccination hesitancy [64]. Furthermore, the negative relation between vaccination intentions and

anti-vaccine conspiracy beliefs is mediated by perceived dangers of vaccines, and feelings of powerlessness, disillusionment, and mistrust in political authorities [12].

Conspiracy Theories, Social Media

Conspiracy theories have continued to propagate despite evidence discrediting their existence. For example, many believe that the US government is covering up life outside of Earth or that the British government had Princess Diana murdered [12]. Conspiracy theories also transcend into vaccination where prior polls have shown at least 20% believe vaccination causes autism [12]. Anti-vaccine conspiracy theories are present in modern society and garner social media and popular attention with attempts to discredit safety, efficacy, and widespread acceptance. Some of these conspiracy theories surrounding vaccination stem from distrust in pharmaceutical companies and their ultimatums for capital gain. Likewise, these conspiracy theories also have foundations in general mistrust in science. Jolley et al. conducted an anti-vaccine conspiracy study with 89 British parents requiring them to fill out surveys regarding the perception of vaccines and found in regression analyses that anti-vaccine conspiracy beliefs reflected negatively towards vaccination intention, and this strongly correlated with "perceived danger of vaccines, and feelings of powerlessness, disillusionment and trust in authorities [12]."

Furthermore, the mass dissemination of social media in modern society allows for global circulation of vaccine conspiracy theories, especially in the age of COVID-19, which was a highly covered and debated media topic. During the COVID-19 pandemic, Twitter reported a COVID-19 tweet happened every 45 milliseconds making it the 2nd most used tweet hashtag in 2020 [72]. Social media platforms have created immediate access to non-editorial information and are widely distributed on platforms such as Facebook, Reddit, TikTok, and YouTube. These forums have not undergone editorial or scientific screening and the anonymous nature of such communities allows for propagation of unsolicited opinions for the masses. The instantaneous information processed through social media networks is further publicized by bot accounts and internet trolling. Puri et al. have found that certain social media users, those with cognitive impairments, older age, lower literacy, and less digital literacy, are more susceptible to the negative sensationalism of these topics [72]. Studies have shown that healthcare providers and national medical organizations, such as sMFM or ACOG, and their involvement in social platforms can help rewrite widely disseminated narratives. Social media platforms themselves have a morality to uphold by filtering and flagging harmful content [72]. Not only has social media impacted vaccine acceptance but there has been a public outcry over vaccine mandating in the public workplace and society.

Vaccine Policies, Mandates, Religious Objections

Vaccination policies at various institutions have impacted the requirement for employees to be vaccinated to COVID-19. A study by Townsel et al. showed that in a population of female healthcare workers including physicians, nurses, staff with patient contact etc. showed that compared to other women of reproductive age, pregnant women in the cohort were six times more likely to delay the vaccination and twice as likely to decline [73]. Not only has vaccination in the healthcare setting been mandated, but throughout the pandemic various restaurants and social settings implemented vaccine mandates for attendance. These vaccine mandates have caused concern amongst different governing bodies, such as religious affiliations, some of which are strongly against vaccination. The main concerns regarding objection to mandatory vaccination center on limiting freedom of choice. Conservative Christians and some other religions have had resistance toward vaccination with distrust in science and ideology of divine health and intervention [74]. Furthermore, a vast majority believe in the concept of herd immunity.

Herd Immunity

Herd immunity is the concept that one can obtain indirect protection from disease if a large portion of society is vaccinated against the disease. Herd immunity within the COVID-19 pandemic is present and some pregnant patients reluctant to become vaccinated for numerous reasons may have relied on herd immunity to assure them of possible viral protection. However, Kirkcaldy et al. note that the herd immunity to COVID-19 is not well understood and that the duration of neutralizing IgM antibodies is not well defined; detection of IgG within the immune system is not synonymous with future protection [75]. Specifically, with the rapid COVID-19 variant prevalence throughout the last 2 years, coverage and protection against COVID-19 will likely require yearly administration of a vaccine based on circulating variants globally, similar to influenza vaccination.

Concerns about Fetal Safety, Infertility

The major reason for maternal reluctance to COVID-19 vaccination is concern about safety and potential adverse outcomes for the fetus [71]. A multitude of large-scale studies have shown safety of the COVID-19 vaccine in pregnant patients and acceptance is increasing [9,53,55,58,59,76]. Yet, patients continue to be concerned about harming their fetus without factoring in the thrombogenic effect of COVID-19 to the placenta increasing risk of stillbirth [77]. Reproductive concerns

surrounding COVID-19 vaccination exists with early theories of leading to infertility or decreased egg quality, but are disproven in statements by sMFM and ACOG and the American Society for Reproductive Medicine (ASRM) with no clear evidence to support such claims [8]. For these reasons, a majority of pregnant patients indicate that they prefer to defer vaccination till after pregnancy. Increasing maternal acceptance and participation in vaccination will gain support with proven foundations that increase education, counseling, and awareness of disease severity in pregnancy.

PATIENT COUNSELING AND EDUCATION

Disparities in Minorities

Major racial disparities exist in COVID-19 access, vaccine dissemination, education, and treatment. Unrepresented minorities and populations with lower socioeconomic status are more severely affected from COVID-19 having more severe disease and likewise vaccination rates in these populations are some of the lowest. Part of the reason for low vaccination rates in minorities stems from increased fear surrounding vaccination. A systemic review by Abba-Aji found that there was consistent evidence of COVID-19 vaccine hesitancy among Black/Afro-Caribbean groups in the US and the UK. However, studies of Hispanic/Latino populations in the US and Asian populations in the UK had a variety of results with levels similar, less, and higher compared to their White counterparts [78]. Major factors associated with vaccine hesitancy in this population surround distrust in science and concerns for vaccine safety, and in migrant populations, language barriers, lack of access, and fear of deportation [78]. Improving provider-patient communication and increasing access and prompting awareness within religious communities can help reduce the disparities seen with migrants. Finney et al. highlight the importance of policy-level changes that can enhance vaccination rates with reducing cost for vaccines and increasing implementing vaccine mandates for daycares, schools, and public places [64].

Education and Policy

Increased vaccine acceptance and decreasing vaccine hesitancy is integral to improving vaccination rates in pregnant patients. Improving counseling and education amongst providers and patients and increasing government support for vaccination programs are vital steps toward prompting change in vaccination in pregnancy. A variety of studies have shown that provider endorsement and education surrounding the importance of vaccination has a tremendous impact on vaccine acceptance. An anonymous survey by Siegel et al. found that when providers recommended the COVID-19 vaccination, 58.4% of patients were more likely to accept immunization (OR 5.82, 95% (CI) 3.68-9.26, p <0.005) [79]. Additionally, provider support and recommendations outside of prenatal care during the preconception phase can highly impact vaccination. Such discussions can be addressed by primary care physicians (PCPs) and advanced practitioners who ideally provide longstanding global care for patients. Having a PCP who has a long-established relationship with their patient discuss recommended vaccines in pregnancy in the preconception phase, prior to their first visit with an OBGYN, can help spark the initial educational process and influence potential vaccine acceptance.

Motivational Counseling

Cultivating a culture of partnership with patients is fundamental to promoting change. Foundations in motivational interviewing are key to improving provider-patient communication and interactions surrounding conversations about vaccines. Various studies have shown that motivational interviewing increases vaccine acceptance [7]. In a study by Gagneur et al. in 2017, they instituted a motivational program to discuss childhood vaccinations with mothers in the postpartum period; incorporating these principles increased an intent to vaccinate from 78% to 89% [6,7,80]. Incorporation of open-ended questions, providing affirmation statements such as “The health of your unborn child seems to be your top priority,” and reflective listening can increase patient participation. Rather than providing a plethora of facts surrounding the benefits of vaccination, engaging the patient in conversation, and asking permission to discuss vaccination is vital to success. Leading phrasing for such conversations should start with open-ended questions. The conversational principles surrounding motivational interviewing encompasses four processes: engagement, focus, evoking, and planning [7].

CONCLUSIONS

Significant disparities exist in COVID-19 vaccine administration in specific populations who are most likely to acquire severe illness from COVID-19, namely pregnant patients. Historical vaccination hesitancy in pregnancy has complicated promoting vaccination in these populations. A variety of reasons for vaccine hesitancy exist including, but not limited to, perceived dangers of vaccines, mistrust in political authorities, social, religious, education, knowledge, and issues with access. Yet, the major contributing factor for vaccine hesitancy in pregnancy is ultimately concerns over fetal safety and risks to the unborn child. Multiple studies have shown safety of the COVID-19 vaccine in pregnant patients. Increasing maternal education and knowledge about vac-

cination in pregnancy is paramount. However, more important is improving provider education on motivational interviewing and increasing rapport with patient-provider interactions to decrease vaccination myths and hesitancy and prompt and inclusive environment of acceptance.

Support from the government is also key to increase access and lessen cost and from large organizations, such as sMFM and ACOG, to guide provider support and education. Such principles should be carefully considered for future vaccinations, such as the newly recommended RSV vaccine [81].

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