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A potential impact of the immunological profile of current covid-19 vaccines on pregnancy outcomes

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Abstract

The potential impact of COVID-19 vaccination on pregnancy is still a topic of question in clinical practice. This short communication briefly presents the impact of immunological aspects of current covid-19 vaccines on pregnancy outcomes.

Keywords: COVID-19; Vaccination; Pregnancy; Immunological aspects

1. Introduction

1.1. Potential Impact of COVID-19 and Vaccination on Pregnancy

While previous studies have shown that complications such as lung injury, diabetes mellitus, and cardiovascular diseases are more common in pregnant women after SARS-CoV-2 infection compared to non-pregnant women [1] recent data have raised concerns about adverse events, including abortion or fetal malformation, occurring after COVID-19 vaccination [2]. A recent study [3], estimated the effects of COVID-19 vaccination on pregnant women and fetuses using the V-safe monitoring and VERS systems. The results indicated a higher rate of adverse reactions in pregnant women compared to non-pregnant women. Following mRNA vaccination, 13.9% of pregnant women experienced pregnancy loss, and 9.4% had premature delivery, suggesting a relatively substantial probability of these adverse events. Additional recent data also indicate that pregnant patients may require hospitalization due to potential vaccine-related adverse events [4]. After receiving COVID-19 vaccines during pregnancy, a high rate of adverse events (87.82%) was observed, particularly in pregnant women, who are considered a vulnerable or special population. Most of these cases are categorized as serious [5]. COVID-19 vaccination during pregnancy does not appear to prevent infection with the omicron variant [6]. Very frequent local and systemic side effects were described after exposure to mRNA COVID-19 vaccines during pregnancy, as well as severe events like pulmonary embolism, membranes preterm premature rupture, isolated fever with hospitalization, and herpes zoster, albeit infrequently [7]. Post-COVID-19 vaccination, elevated coagulation indexes (D-Dimer levels) may be associated with infrequent thromboembolic events during

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pregnancy [8-10]. Furthermore, beyond the pediatric population, pregnancy may be linked to infrequent covid-19 vaccine-induced potentially fatal complications, including myocarditis and/or thrombocytopenia, although these are infrequent and require further clarification [11].

1.2. Potential Impact of Immunological Profile on COVID-19 Vaccination-Related Pregnancy Outcomes

From an immunological perspective, the ethical considerations of testing vaccines in pregnant women have been a topic of debate for several years [12] and pregnant women initially were excluded from the phase 3 clinical trials of COVID-19 vaccines [13] thereby signifying limited data available concerning pregnancy.

Some data suggest that women infected with SARS-CoV-2 during pregnancy are at a higher risk of preterm birth [14] thus may warranting vaccination. Certain related studies indicate that vaccination is not connected with significant side effects, such as negative fetal or neonatal outcomes, and is considered safe and may be recommended for pregnant patients [15]. Nevertheless, there are some concerns regarding the safety of initiating a SARS-CoV-2 vaccination program during pregnancy, as there have been reports of post-COVID-19 vaccination adverse events, such as abortion or fetal malformation [2].

Crucial knowledge gaps emerge from German and US trials of the BNT162b2 mRNA vaccine, indicating a broad immune response to the vaccine. This includes the induction of neutralizing antibody responses, helper T cell type 1 (Th1) CD4+ cells, and the expansion of effector memory CD8+ T cells in both men and non-pregnant women [16]. Th1-biased vaccine immune responses are crucial for durable protection and vaccine safety [17]. mRNA vaccines also induce robust Th1-biased T-cell responses [18]. Likewise, recent Matrix-M-adjuvanted vaccines induce a Th1-dominant immune response. Additionally, beyond Th1-immnune response, SARS-CoV-2 mRNA vaccines trigger an augmented Th17 immune response [19]. However, Moderna vaccines, in comparison to other vaccines, induce more adverse effects, partially due to the lower frequency of T regulatory (Treg) lymphocytes in Moderna vaccine recipients [20].

It remains unknown whether a similar immunophenotypic profile is detected in pregnant women. These data raise concerns because successful pregnancy outcomes largely depend on heightened helper Th2 and Treg activity, with decreased Th1 responses [21]. In contrast, for instance, preeclampsia is linked with an imbalance in both systemic and local pro-inflammatory Th1 and Th17 cytokines (e.g., tumor necrosis factor [TNF]-α and interleukin [IL)-17) and a decrease in suppressive Treg and Th2 cytokines (e.g., IL-10 and IL-4) [22]. The imbalance in Th1/Th2/Th17/Treg is observed in animal and human models of preeclampsia [22].

Beyond preeclampsia, when compared to healthy pregnant women, patients with recurrent pregnancy losses, a common reproductive disorder affecting 2–5% of reproductive-age women, exhibit fewer Treg cells [23] while more Th17 cells in the circulation and deciduas [24,25]. Pro-inflammatory Th17-related cytokines, including IL-17, can trigger embryo rejection, while Treg-regulated cytokines such as IL-10 and transforming growth factor beta could enhance immunological to clearance and improve pregnancy outcomes [25,26].

The disruption of the balance of CD4+ T cell responses during pregnancy is connected with adverse perinatal outcomes, including fetal loss and preterm birth [27]. There are also concerns that neonates born to mothers with altered CD4+ T cell responses may experience long-term sequelae [28].

Specifically, while a pro-inflammatory Th1-immune response is necessary during implantation to promote tissue remodeling and angiogenesis [29] an excessiveTh1 or Th17 immune response, also induced by the mentioned covid-19 vaccines [16-19], is linked to implantation failures, early pregnancy losses, and repeated implantation failures [30,31]. During the implantation window, pro-inflammatory Th1 cytokines promote the invasion of trophoblast cells and endometrial neovascularization. Nevertheless, prolonged or overexposure to pro-inflammatory cytokines could impair the pregnancy, potentially leading to miscarriage. After placentation, there is a shift from Th1 to Th2 immune responses, supporting a more anti-inflammatory state until parturition. Shortly after the placental implantation, the Th2 shift becomes apparent, which is critical for the maintenance and development of normal fetus and placenta [32] as well as the suppression of Th1 immunity at the maternal-fetal junction [33]. Treg cells play a key role in maternal-fetal tolerance [34] allowing an embryo, a semi-allograft, to thrive in the uterus without being rejected [35].

Th17 cells are another class of pro-inflammatory Th cells present at the maternal-fetal interface. Women with unexplained recurrent pregnancy losses (RPL) have shown an increased proportion of peripheral blood Th17 cells and their related cytokine levels (IL-17A) during the proliferative and secretory phases of the ovulatory cycle compared to normal controls [36]. IL-17, also induced by COVID-19mRNA vaccination [37], is a pro-inflammatory cytokine that promotes inflammation and maternal-fetal rejection. Moreover, IL-17, by interacting with Th1 cells, could further

contribute to the immune-related pathophysiology of RPL [24], clearly supporting that Th1–type and Th17-type of immune responses are incompatible with pregnancy.

Many maternal immune malfunctions are often present and contribute to immunopathogenesis of women with RPL [35,38]. These women exhibit increased T cell activation with systemic Th1 dominance compared to normal fertile women [39]. Moreover, dysfunction of natural killer activity [40,41] and a skewed Th1 over Th2 immune response are considered detrimental to pregnancy [32]. Uterine natural killer cells represent highly granulated natural killer cells identified in the endometrium with the phenotype of $CD56^{++}/CD16^{-}$. They display the capability to secrete a range of cytokines [42]. In normal pregnancy, augmented regulatory uterine natural killer cells are essential for maintaining reproductive success because they play an important role in trophoblast invasion, spiral artery remodeling, and appropriate placentation [43-45]. Their dysfunction is closely linked with RPL [46].

Besides, women with RPL have the propensity to Th17 over Treg cell immunity [47]. Beyond RPL, Th1, Th17, IL-17, and cytolytic natural killer cells are also increased in preeclampsia and contribute to fetal growth restriction [48].

On the contrary, Th2 cells can suppress Th17 activation through IL-10 secretion and inhibit Th1 activation through IL-4 production. Notably, Th1/Th2 cell ratios are introduced for diagnosing and monitoring women with RPL [49].

Interventions that regulate the shifted Th1 immune response, such as intravenous immunoglobulin G, blockers of TNF-α (a major Th1-related cytokine), or T cell activation inhibitors like etanercept or tacrolimus, have significantly improved pregnancy outcomes in women with RPL [49-51]. Moreover, pregnancy loss has been prevented when Th2 immunity was induced by the experimental administration of IL-10 to pregnant mothers [52]. Likewise, during experimental pregnancy, IL-10 appears to contribute to Treg-mediated protection of the fetus [53]. Thus, IL-10 or other type 2 cytokines may represent novel therapeutic approaches that could enhance pregnancy success. Time- and cytokine-specific regulation of Th1 immunity during pregnancy is crucial for achieving a successful pregnancy outcome, necessitating further research.

2. Conclusion

The issue of COVID-19 prevention during pregnancy primarily focuses on the safety of coronavirus vaccines for pregnant women. Despite of contradictory evidence, based on some data, the vaccine may be considered safe during pregnancy, with a low percentage of side effects similar to those observed in non-pregnant women. Serious adverse events have been documented, but at a low rate. However, a significant challenge in many of these studies was the lack of adequate matching for cases and controls. More recent data have provided different evidence, and the impact of side effects on the fetus has yet to be clearly determined. Data continues to evolve, and the vaccine remains under ongoing evaluation. The immune status of a pregnant woman is relatively complex and fragile. Certain concerns arise owing to the post-COVID-19-related dysfunction of the host's immunological profile, which may lead to potential adverse events in pregnancy. Taking into account all the available data, both positive and negative, and acknowledging the limited duration of vaccine studies (despite the large number of people vaccinated), it raises the question of what should guide us in making vaccination decisions, especially when confronted with unfavorable data. Pregnant women and their obstetricians must meticulously assess the immune-related concerns and employ the established data at their disposal to balance the benefits and risks of COVID-19 vaccines.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

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