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Covid-19 vaccination in pregnancy and placental pathology

Leo Simanjuntak✉

Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas HKBP Nommensen, Medan, Indonesia

ABSTRACT

Objective: To describe and determine the association between Covid-19 vaccination in pregnancy and placental pathology.

Methods: Conducted in a tertiary hospital in Medan, Indonesia, from April 30th 2022 to June 30th 2022, this single-center cross-sectional study involved Covid-19 vaccinated and unvaccinated women with singleton full-term pregnancies delivering live fetuses *via* cesarean section. Maternal characteristics, placental pathologies, and the placental index were documented at enrollment. The association between Covid-19 vaccination status and placental pathology was assessed.

Results: The study enrolled 200 pregnant women, including 110 vaccinated women and 90 unvaccinated women. No significant differences were observed in birthweight ($P=0.48$), placental index ($P=0.48$), and placental pathology findings [intervillous bleeding ($P=0.20$), increased syncytial knots ($P=0.83$), chorangiosis ($P=0.13$), villous stromal edema ($P=0.13$), vascular dilation and congestion ($P=0.13$), and vascular wall thrombus ($P=0.71$)] between the vaccinated and unvaccinated groups.

Conclusions: This study revealed no statistically significant association between Covid-19 vaccination and placental pathology. The findings support the safety of Covid-19 vaccination during pregnancy, in regards to changes of the placental pathology.

KEYWORDS: Covid-19; Vaccination; Pregnancy; Women; Placenta

1. Introduction

The World Health Organization (WHO) declared a global pandemic of coronavirus disease 2019 (Covid-19) in March 2020, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Evidence suggests that pregnant women with Covid-19 are more susceptible to severe disease with a higher risk of preeclampsia/eclampsia, severe infections, admission to intensive care units, maternal death, preterm birth, as well as higher risk of maternal and/or fetal death[1]. Indonesian Obstetricians and Gynecologists Association reviewed 536 cases of Covid-19 in pregnancy during April 2020 to April 2021. As many as 4.5% required treatment in the intensive care unit and 3% died due to complications from the case[2]. Meanwhile, Royal College of

Obstetrics & Gynaecologists reported that more than two-thirds of pregnant women with Covid-19 are actually asymptomatic, but of those with symptoms, around 5% require intensive treatment, and require further breathing assistance[3].

Placental anatomy, physiology, and molecular structure remain some of the most intriguing and understudied topics in obstetrics[4]. The placenta is critical in protecting the fetus from maternal infections and chemical toxins. Transplacental transmission of SARS-CoV-2 has been substantiated in a documented case involving a pregnant woman with Covid-19 in late pregnancy[5]. Genomic material of SARS-CoV-2 has been identified in umbilical cord blood, the vaginal mucosa of pregnant individuals, and full-term placentas. The presence of specific anti-SARS-CoV-2 IgM and IgG antibodies in umbilical cord blood and milk specimens suggests in utero vertical transmission in SARS-CoV-2-positive pregnant individuals[6].

The ACE2 receptors which are mostly targeted by SARS-CoV-2

Significance

This study addresses a critical gap in knowledge regarding the impact of Covid-19 vaccination on placental pathology in pregnant women. Existing information is limited due to the exclusion of pregnant women from initial vaccine trials. By elucidating the relationship between vaccination and placental pathologies, this research contributes essential insights to reproductive science. This study provides and supports the evidence about the safety of Covid-19 vaccination to the placenta at least two weeks before delivery and shows vaccination does not exert the adverse effect to the growing fetus. Understanding these associations is crucial for guiding recommendations on Covid-19 vaccination in pregnant individuals, thus enhancing reproductive health practices and decision-making.

✉To whom correspondence may be addressed. E-mail: leosimanjuntak@uhn.ac.id

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is widely expressed in the fetal and maternal placental tissue[7]. Transplacental transmission of Covid-19 is one of the topics that have raised conflicting evidence across the globe[8]. Smithgall *et al* further reported several placental pathologies associated with Covid-19 such as villous agglutination, and T-cell vasculitis. Intrauterine growth restriction and preeclampsia has been found significantly in women with identified placental pathologies[9].

Multiple studies have confirmed that mRNA vaccines for Covid-19 are effective when given during pregnancy and are highly effective in reducing maternal morbidity and mortality from SARS-CoV-2 infection. Maternal vaccination boosts systemic and mucosal immunity, reducing viral cell entry and the risk of SARS-CoV-2 infection. Covid-19 vaccination during pregnancy results in maternal antibodies that are not only detectable in maternal sera at delivery and in breast milk, but are also present in infant sera, indicating that maternal antibodies were transferred prior to delivery[10]. Placental findings may indicate a potential clinical risk and may be an early warning sign of a rare lesion seen only after extensive use in pregnant women[11].

The increasing number of pregnant women infected with Covid-19 and the high risk for pregnant women if the infection with Covid-19 becomes severe and affects their pregnancy and their babies, efforts are needed to provide Covid-19 vaccinations for pregnant women. The Covid-19 vaccines in pregnancy are the mRNA based (Pfizer and Moderna) and inactivated-vaccine (Sinovac), subject to availability. The administration of the first dose of the Covid-19 vaccination begins in the second trimester of pregnancy, and the second dose is given according to the interval of the vaccine type. While the incidence of miscarriage and congenital anomalies does not seem to be elevated in pregnancies affected by Covid-19, pregnant women with this viral infection may face an augmented susceptibility to complications, including stillbirth and pregnancy loss[10].

WHO recommends giving Covid-19 vaccination to pregnant women if the benefits outweigh the risks, for example in pregnant women with comorbidities such as diabetes, hypertension, and cardiovascular diseases, since the people with preexisting comorbidities prone to have severe Covid-19 disease. American College of Obstetricians and Gynecologists (ACOG) stated that there were no complications in pregnant women or fetuses in pregnant women who received the Covid-19 vaccination[12]. However, to our knowledge this is the first study that elucidated histopathologic features of placenta following Covid-19 vaccination particularly in Indonesia. Hence, it is necessary to explore a more regional perspective which may contribute to a broader scientific understanding.

Pregnant women were excluded from initial clinical trials for Covid-19 vaccines; thus the understanding of the immunologic response to vaccination in pregnancy and the transplacental transfer of maternal antibodies is limited worldwide. This limited data also can be explained due to placental examination not being a component of epidemiologic clinical investigations. Therefore, this aims to describe and determine the association between Covid-19 vaccination in pregnancy and placental pathology.

2. Materials and methods

2.1. Study design

This single-centre and cross-sectional study was conducted in tertiary hospital in Medan, Indonesia from April 30th 2022 to June 30th 2022.

2.2. Sample and eligibility criteria

The study encompassed a sample of 200 placental specimens, recruited by total sampling which met the inclusion and exclusion criteria during the study period. The inclusion criteria of this study were women with singleton full-term pregnancy aged 18-35 years, well-documented Covid-19 vaccination status, and willing to participate in this study. These women had no history of positive reverse transcription-polymerase chain reaction (RT-PCR) testing for SARS-CoV-2. Among the 200 included subjects, 90 were unvaccinated individuals who had not received any dose of a SARS-CoV-2 vaccine before delivery, and their negativity was confirmed. while the other 110 were vaccinated women who had received a minimum of one dose of either a SARS-CoV-2 mRNA vaccine (Pfizer-BioNTech) or an inactivated vaccine (Sinovac) more than two weeks prior to delivery.

Exclusion criteria encompassed medical conditions such as preeclampsia, gestational hypertension, premature rupture of membranes, antenatal hemorrhage, anemia, diabetes mellitus, pregnancies involving fetal anomalies, and incomplete medical records. This stringent inclusion and exclusion criteria framework was employed to ensure a homogeneous and well-defined study population, enhancing the reliability and validity of the research findings.

2.3. Data collection and variables

Maternal attributes were documented upon enrollment, encompassing maternal age at delivery in years, maternal weight in kilograms, and details of pregnancy history and parity level. Subsequently, neonatal assessments were performed immediately post-delivery using electronic scales to measure the newborn's weight. Placentas, inclusive of membranes and umbilical cord, were promptly weighed after delivery, following the removal of blood and clots using absorbable cotton pads. The calculation of the placental index, defined as the ratio of placental weight to fetal weight, was carried out. It is noteworthy that previous research from our group established a correlation between elevated placental index values and adverse pregnancy outcomes[13]. Post-weighing, the placentas underwent thorough histopathological evaluation.

2.4. Statistical analysis

The statistical analyses were done using SPSS version 20. The numerical data normality was determined by Kolmogorov-Smirnov test, and data were presented in mean±standard deviation (mean±SD). The comparisons in maternal age, neonatal birth weight and placental weight between vaccinated and unvaccinated women were

determined using Student's *t* test. The association between Covid-19 vaccination status and placental pathology was examined through *Chi*-square testing for categorical variables. *P* value <0.05 was considered to be statistically significant.

2.5. Ethics statement

This research received ethical clearance from the Faculty of Medicine's ethical committee at Universitas Huria Batak Kristen Protestan Himmensen in Medan, Indonesia (Approval No: 336A/KEPK/FK/IV/2022).

3. Results

3.1. Demographic data

The demographic, maternal, and neonatal findings based on vaccination status are shown in Table 1. In this study, mean maternal age at delivery was (29.4±4.4) years (range 17-37 years). Mean newborn weight was (3248.0±334.6) g. 110 Out of the 200 pregnant women were vaccinated at least first dose of vaccination. Based on Table 1, there was no statistically significant demographics and maternal findings difference between the vaccinated and unvaccinated groups, thus both groups had similar characteristics.

3.2. Maternal and neonatal findings

Based on placental pathology, 116 of the pregnant women had placental insufficiency (58%), of which 55 (50%) were vaccinated and 61(68.2%) were unvaccinated. There were no significant differences in the birthweight, placental index, and placental pathology findings (intervilous bleeding, increased syncytial knots, chorangiosis, villous stromal edema, vascular dilation and

congestion, and vascular wall thrombus) between the vaccinated and unvaccinated groups. Most of the vaccinated women (89.3%) received Sinovac vaccine (inactivated vaccine), since it is the first and most widely available in Indonesia.

4. Discussion

The study revealed there was no placental pathology difference between Covid-19 vaccinated and unvaccinated groups. Recent study conducted by Smithgall *et al*[9] included 431 placentas from both fully vaccinated and unvaccinated groups, and found that the vaccinated and unvaccinated groups had similar demographics, including maternal age, gestational age at birth, and mode of delivery. There was no statistically significant demographics and maternal findings difference between the vaccinated and unvaccinated groups. These results are similar to our study findings.

Smithgall *et al*[9] also found that there was no significant difference in the placental findings, and birthweight between the vaccinated and unvaccinated groups. This study results are similar to ours. There were no significant differences in the birthweight or placental pathology findings (intervilous bleeding, increased syncytial knots, chorangiosis, villous stromal edema, vascular dilation and congestion, and vascular wall thrombus) between the vaccinated and unvaccinated groups. In contrast to recent study, we found that most pregnant women received the Sinovac vaccine because Sinovac is the first and most widely available Covid-19 vaccine in Indonesia to date[14]. Earlier cohort study of vaccinated pregnant patients conducted by Shanes *et al*[11], placental examination in women with vaccination showed no increased incidence of decidual arteriopathy, fetal vascular malperfusion, low-grade chronic villitis, or chronic histiocytic intervillitis compared with women in the control group. These findings support the safety of SARS-CoV-2 vaccination in pregnancy. There were also no significant differences

Table 1. Demographic, maternal, and neonatal findings based on vaccination status.

Characteristics	Total, n=200	Vaccinated, n=110	Unvaccinated, n=90	<i>P</i> value
Maternal age, years, mean±SD	29.4±4.4	30.3±3.8	28.3±4.8	0.10
Neonatal birth weight, g, mean±SD	3248.00±334.56	3203.57±284.77	3304.55±388.49	0.47
Placental weight, g, mean±SD	645.00±108.91	626.79±114.24	668.18±99.45	0.14
Placental index, mean±SD	0.20±0.03	0.19±0.03	0.20±0.03	0.47
Gravida, n(%)				0.45
Primigravida	80 (40)	39 (35.7)	41 (45.5)	
Secundigravida	52 (26)	24 (21.4)	28 (31.8)	
Multigravida	68 (34)	47 (42.9)	21 (22.7)	
Placental findings, n(%)				
Intervilous bleeding	32 (15.9)	23 (20.6)	10 (10.9)	0.20
Increased syncytial knots	29 (14.4)	18 (16.2)	11 (12.5)	0.83
Chorangiosis	42 (21.2)	21 (19.1)	21 (23.4)	0.12
Villous stromal edema	42 (21.2)	21 (19.1)	21 (23.4)	0.12
Vascular dilation and congestion	42 (21.2)	21 (19.1)	21 (23.4)	0.12
Vascular wall thrombus	12 (6.1)	6 (5.9)	6 (6.3)	0.71
Placental pathology conclusion, n(%)				0.20
Normal placental	84 (42)	55 (50)	29 (31.8)	-
Placental insufficiency	116 (58)	55 (50)	61 (68.2)	-
Vaccine type, n(%)				
Sinovac	179 (89.3)	98 (89.3)	81 (90)	-
Pfizer	21 (10.7)	12 (10.7)	9 (10)	-

in placental pathology findings (intervillous bleeding, increased syncytial knots, chorangiosis, villous stromal edema, vascular dilation and congestion, and vascular wall thrombus) between the vaccinated and unvaccinated groups, thus supporting the Covid-19 vaccination safety in pregnancy.

This study holds notable strength as it stands among the few investigations in Indonesia aimed at elucidating the relationship between Covid-19 vaccination and placental pathology. A robust aspect of this research lies in its comprehensive approach, wherein various placental pathologies are thoroughly evaluated to enhance the depth of understanding. However, certain limitations warrant acknowledgment. Notably, the study did not incorporate antibody testing for anti-Covid-19 levels (specifically IgM and IgG) to ascertain the subjects' complete immunization status. This limitation is attributed to the absence of routine antibody level testing in the standard medical practices of Indonesia. Despite this constraint, the study capitalizes on other methodological strengths, such as an ample and representative sample size, ensuring a robust foundation for statistical analyses and generalizability of findings to the broader population.

In conclusion, this study reveals no statistically significant association between Covid-19 vaccination and placental pathology. This study supports the result of previous studies about the safety of Covid-19 vaccination during pregnancy

Conflict of interest statement

Author declares no conflicts of interest in this study.

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Author's contributions

The author is responsible in the following task: conceiving and designing of the study, collecting data, analyzing and interpretation of the data, drafting the manuscript, and doing revision and proofreading the article.

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