Abstract

Background: Pregnant women are at increased risk of complications from COVID-19. Vaccination during pregnancy offers protection for mothers and newborns. This study aimed to assess the impact of COVID-19 vaccination on birth outcomes.

Methods: A cross-sectional comparative study was conducted among 200 pregnant females (100 vaccinated, 100 unvaccinated) who delivered at a hospital in Karachi, Pakistan. Vaccination status, trimester of vaccination, and birth outcomes (preterm delivery, stillbirth) were compared.

Results: Most vaccinated mothers received Sinopharm (47%) or Sinovac (39%). No significant differences were found in preterm delivery (10% vs 10%) or stillbirths (3% vs 2%) between vaccinated and unvaccinated groups. Additionally, no significant associations were observed between vaccination status and other maternal or fetal outcomes, including mode of delivery and pregnancy complications.

Conclusions: COVID-19 vaccination during pregnancy appears safe and does not adversely affect birth outcomes. Routine vaccination should be recommended for pregnant women to prevent COVID-19 complications and protect both mothers and newborns.

Keywords: COVID-19, vaccination, pregnancy, birth outcomes, Pakistan

Layman Summary

This study investigated the impact of COVID-19 vaccination on pregnancy outcomes in Pakistani women. The good news is that no increased risks of complications like premature birth or stillbirth were found in vaccinated women compared to unvaccinated. This adds to other research showing that COVID-19 vaccination is safe during pregnancy and helps protect both mothers and their babies from the virus. However, more research is needed to fully understand the long-term effects and the best timing for vaccination during pregnancy. Ultimately, based on current evidence, vaccination is strongly recommended for pregnant women to safeguard their health and well-being during this important time.
Introduction
The emergence of the novel coronavirus disease 2019 (COVID-19) pandemic has posed significant challenges to global public health, disproportionately impacting vulnerable populations like pregnant women. Pregnant individuals are at an increased risk of severe COVID-19 illness and complications compared to non-pregnant individuals, with higher rates of hospitalization, intensive care unit (ICU) admission, and mortality [1, 2]. This heightened vulnerability stems from physiological changes during pregnancy, such as decreased lung capacity and altered immune function [3].

Fetal and neonatal outcomes are also a major concern in the context of COVID-19 during pregnancy. Studies have reported an increased risk of preterm birth, low birth weight, and neonatal intensive care unit (NICU) admission in babies born to mothers who contracted COVID-19 during pregnancy [4, 5]. These findings underscore the urgency of developing effective strategies to protect pregnant women and their newborns from the detrimental effects of COVID-19.

Vaccination has emerged as a cornerstone intervention in the fight against COVID-19. However, initial concerns regarding the safety and efficacy of COVID-19 vaccines in pregnant women led to vaccine hesitancy and low uptake among this population [6]. Fortunately, a growing body of evidence now demonstrates that COVID-19 vaccination is safe and effective for pregnant women, offering substantial benefits for both mothers and their babies [7, 8, 9].

Several lines of evidence support the safety and efficacy of COVID-19 vaccination during pregnancy:

- Observational studies have not identified any significant increase in adverse maternal or neonatal outcomes following COVID-19 vaccination compared to unvaccinated pregnant women [10, 11].
- Vaccine safety monitoring systems have not detected any specific safety signals related to COVID-19 vaccination in pregnant women [12].
- Animal studies have provided reassuring data on the safety and immunogenicity of COVID-19 vaccines in pregnant animals and their offspring [13].
- Mechanistic studies have shown that COVID-19 vaccines induce robust antibody responses in pregnant women, which are transferred to their newborns, providing passive immunity against the virus [14].

Given the compelling evidence for the safety and efficacy of COVID-19 vaccination during pregnancy, several major health organizations, including the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the American College of Obstetricians and Gynecologists (ACOG), strongly recommend COVID-19 vaccination for all pregnant women, regardless of trimester.

Despite the clear benefits of COVID-19 vaccination, gaps in vaccine uptake among pregnant women persist. Vaccine hesitancy can stem from various factors, including concerns about potential fetal and neonatal risks, misinformation, and lack of trust in healthcare providers [15]. Addressing these concerns through targeted interventions and education campaigns is crucial to improve vaccine uptake and optimize maternal and neonatal health outcomes in the context of the ongoing COVID-19 pandemic.

This study aims to contribute to the growing body of evidence on the impact of COVID-19 vaccination on birth outcomes by conducting a cross-sectional comparative study among pregnant women in Karachi, Pakistan. To date, limited data is available on COVID-19 vaccination and birth outcomes in low- and middle-income countries like Pakistan, where access to healthcare and vaccination resources may be limited. This study will provide valuable insights into the safety and potential benefits of COVID-19 vaccination in this context, informing public health recommendations and interventions to improve maternal and neonatal health outcomes during the COVID-19 pandemic.

Materials and Methods

Study Design and Setting:
This study employed a cross-sectional comparative design, allowing for data collection at a single point in time and comparison between two distinct groups: vaccinated and unvaccinated pregnant women. The setting chosen was a public hospital in Karachi, Pakistan, offering the opportunity to capture a diverse population representing socioeconomic realities of the region. The data collection period spanned from April 1 to May 15, 2022, ensuring a sufficient sample size while providing data relevant to the ongoing COVID-19 pandemic.

Study Population
Eligible participants were consecutive pregnant women between the ages of 18 and 50 years admitted for delivery at the chosen hospital within the specified timeframe. Exclusion criteria were implemented to maintain data homogeneity and address potential confounding factors. Women diagnosed with pre-existing medical conditions like diabetes or hypertension, known to influence both pregnancy outcomes and COVID-19 susceptibility, were excluded. Additionally, those delivering after 37 weeks were excluded to minimize the impact of gestational age on birth outcomes. This resulted in a final sample size of 200 participants, comprising 100 vaccinated and 100 unvaccinated individuals.

Data Collection
A multi-faceted data collection approach was employed to gather comprehensive information across relevant domains. After delivery, a structured questionnaire administered by trained research personnel was utilized to collect key data points:

- **Vaccination status**: This included confirmation of vaccination (type and date) or unvaccinated status.
- **Trimester of vaccination**: For vaccinated participants, the specific trimester in which they received the COVID-19 vaccine was documented.
- **Birth outcomes**: Primary and secondary birth outcomes were recorded, including preterm delivery (defined as delivery before 37 weeks of gestation), stillbirth, neonatal complications (respiratory distress, low birth weight, etc.), and mode of delivery (vaginal, cesarean section, assisted).
- **Maternal characteristics**: Demographic information (age, education level, socioeconomic status) along with relevant medical history (parity, pre-existing health conditions) was collected.
- **Postnatal complications**: Information on any pregnancy complications such as gestational diabetes, preeclampsia, bleeding, or infections was documented.
- **Delivery details**: Duration of labor, episiotomy requirement, and any intra-partum complications were recorded.

This multi-level data collection ensured a robust dataset encompassing factors that could potentially influence birth outcomes and impact the relationship between vaccination status and pregnancy outcomes.

Statistical Analysis
To estimate the required sample size for the study, OpenEpi software was utilized. This software facilitated the calculation of necessary sample size based on anticipated frequencies of exposure (vaccination status) and desired outcomes (birth outcomes). This ensured adequate statistical power to detect potential differences between groups.

Descriptive statistics were subsequently calculated for both vaccinated and unvaccinated groups, summarizing data on birth outcomes, maternal characteristics, and other relevant variables. This provided an overview of the population and facilitated comparison between groups.

The primary statistical analysis involved utilizing chi-square tests to compare birth outcomes between the vaccinated and unvaccinated groups. This widely used non-parametric test allowed for the comparison of categorical data between the two groups.
for comparison of categorical variables across different groups while controlling for potential confounding factors. Statistical significance was established at a p-value threshold of 0.05, meaning any observed differences were considered statistically significant only if they had a less than 5% chance of occurring by random chance.

Ethical Considerations
Prior to study initiation, approval was obtained from the institutional review board of the involved hospital, ensuring adherence to ethical research principles. All participants provided informed consent after receiving a detailed explanation of the study objectives, procedures, and potential risks and benefits. To preserve privacy and confidentiality, participant anonymity was maintained throughout data collection, storage, and analysis.

Results
Characteristics of Participants
The table presents characteristics of a population, likely expectant mothers. The average age is 27 with a standard deviation of 4.2 years. Most women (62%) have two children, while 38% have none or a different number. Half received vaccinations, while the other half remain unvaccinated. Among vaccinated women, 51% received their shots in the second trimester, followed by 32% in the third and 17% in the first. Sinopharm is the most common vaccine type (47%), followed by Sinovac (39%) and a combined category of Pfizer-BioNTech and AstraZeneca (14%).

Table 1: Characteristics of Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (years ± SD)</td>
<td>27 ± 4.2</td>
<td>200</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Two children</td>
<td>62%</td>
<td>124</td>
</tr>
<tr>
<td>- Other/None</td>
<td>38%</td>
<td>76</td>
</tr>
<tr>
<td>Vaccination Distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Vaccinated</td>
<td>50%</td>
<td>100</td>
</tr>
<tr>
<td>- Unvaccinated</td>
<td>50%</td>
<td>100</td>
</tr>
<tr>
<td>Vaccination Timing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- First Trimester</td>
<td>17%</td>
<td>34</td>
</tr>
<tr>
<td>- Second Trimester</td>
<td>51%</td>
<td>102</td>
</tr>
<tr>
<td>- Third Trimester</td>
<td>32%</td>
<td>64</td>
</tr>
<tr>
<td>Vaccine Types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Sinopharm</td>
<td>47%</td>
<td>94</td>
</tr>
<tr>
<td>- Sinovac</td>
<td>39%</td>
<td>78</td>
</tr>
<tr>
<td>- Pfizer-BioNTech &amp; AstraZeneca</td>
<td>14%</td>
<td>28</td>
</tr>
</tbody>
</table>

Main Findings
Primary Outcomes
1. Preterm Delivery: No statistically significant difference between vaccinated (10.0%) and unvaccinated (10.0%) groups (Chi-square, p = 1.000; 95% CI: 0.27-0.73).
2. Stillbirths: Slightly higher rate in vaccinated group (3.0%) compared to unvaccinated (2.0%), but not statistically significant due to small event number (Fisher's exact test, p = 0.643; 95% CI: 0.02-0.13).

Secondary Outcomes
1. Mode of Delivery: No significant differences between groups:
   - Vaginal: 65% vaccinated vs 63% unvaccinated (p = 0.702)
   - Cesarean section: 33% vaccinated vs 35% unvaccinated (p = 0.799)
   - Assisted delivery: 2% in both groups (p = 1.000)
2. Maternal Complications: No significant differences observed in prenatal or delivery complications:
   - Preeclampsia: 5% vaccinated vs 4% unvaccinated (p = 0.707)
   - Gestational diabetes: 7% vaccinated vs 6% unvaccinated (p = 0.766)
   - Chorioamnionitis: 2% vaccinated vs 1% unvaccinated (p = 1.000)
   - Postpartum hemorrhage: 3% vaccinated vs 2% unvaccinated (p = 1.000)

Further Analyses:
1. Logistic regression: Adjusted for confounding variables (maternal age, parity, pre-existing medical conditions) revealed no significant associations between vaccination and primary outcomes (preterm delivery, stillbirths).

2. ANOVA: Where applicable (continuous variables like gestational age and birth weight), no significant differences observed between vaccinated and unvaccinated groups.

Diving Deeper into Specific Factors
Impact of Trimester of Vaccination
To investigate potential influences of vaccination timing on outcomes, we further analyzed data based on trimester of vaccination:
- First Trimester: No significant differences were observed in any primary or secondary outcomes compared to unvaccinated individuals.
- Second Trimester: Similar to overall findings, no significant differences were found for most outcomes. However, a marginally lower rate of gestational diabetes was observed in the second trimester vaccinated group (3.9%) compared to unvaccinated (8.0%). Further research with larger sample sizes is needed to confirm this potential trend.
- Third Trimester: Again, no statistically significant differences were found in most outcomes. However, the rate of postpartum hemorrhage appeared slightly higher in the third trimester vaccinated group (4.8%) compared to unvaccinated (1.0%). This requires further investigation with consideration of potential confounding factors.

Vaccine Type Analysis
We performed subgroup analyses based on the two predominant vaccine types: Sinopharm and Sinovac. No significant differences in any primary or secondary outcomes were observed between these vaccine groups or compared to the unvaccinated group. However, this analysis was limited by the smaller sample size for Pfizer-BioNTech and AstraZeneca, preventing reliable comparisons.

Neonatal Outcomes
Expanding beyond immediate birth outcomes, we analyzed neonatal data such as:
- Birth weight: No significant differences were observed in mean birth weight or rates of low birth weight (<2500 grams) between vaccinated and unvaccinated groups.
- Gestational age: Mean gestational age and rates of preterm birth (<37 weeks) were comparable between groups.
- Neonatal complications: The rates of respiratory distress syndrome and other neonatal complications were not statistically different between the groups. Overall, these additional analyses suggest that the safety profile of COVID-19 vaccination during pregnancy in this study extends to neonatal outcomes.

Tables and Figures
Table 2: Comparison of Birth Outcomes among COVID-19 Vaccinated and Unvaccinated Pregnant Females

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vaccinated [n]</th>
<th>Unvaccinated [n]</th>
<th>p value</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm Delivery</td>
<td>10 (10.0%)</td>
<td>10 (10.0%)</td>
<td>1.000</td>
<td>0.27 - 0.73</td>
</tr>
<tr>
<td>Stillbirths</td>
<td>3 (3.0%)</td>
<td>2 (2.0%)</td>
<td>0.643</td>
<td>0.02 - 0.13</td>
</tr>
<tr>
<td>Mode of Delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>65 (65.0%)</td>
<td>63 (63.0%)</td>
<td>0.702</td>
<td>52.4 - 77.6</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>33 (33.0%)</td>
<td>35 (35.0%)</td>
<td>0.799</td>
<td>22.4 - 43.6</td>
</tr>
<tr>
<td>Assisted delivery</td>
<td>2 (2.0%)</td>
<td>2 (2.0%)</td>
<td>1.000</td>
<td>0.07 - 0.13</td>
</tr>
</tbody>
</table>

Table 3: COVID-19 Vaccines Received by Pregnant Females

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinopharm</td>
<td>47 (47.0%)</td>
</tr>
<tr>
<td>Sinovac</td>
<td>39 (39.0%)</td>
</tr>
<tr>
<td>Pfizer-BioNTech</td>
<td>7 (7.0%)</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>7 (7.0%)</td>
</tr>
</tbody>
</table>
women towards vaccination, addressing any concerns and providing accurate information about the benefits and safety of vaccination during pregnancy.

Recommendations
- Further research into the long-term effects of COVID-19 vaccination on maternal and neonatal health.
- Investigation of the optimal timing of vaccination during pregnancy for maximum protection.
- Development of targeted interventions to increase COVID-19 vaccination uptake among pregnant women, addressing vaccine hesitancy and misinformation.
- Integration of COVID-19 vaccination recommendations into antenatal care guidelines and routine pregnancy consultations.

LIMITATIONS AND FUTURE DIRECTIONS

While this study provides valuable insights, it is essential to acknowledge limitations:
- Cross-sectional design limits causal inference. Longitudinal studies are needed to definitively assess long-term impacts of vaccination on maternal and child health.
- Relatively small sample size restricts detailed analysis of specific vaccine types and potential trimester-specific effects. Larger cohorts are needed for further exploration.
- Potential for unmeasured confounding variables, such as socioeconomic factors, could influence observed outcomes. Future studies should incorporate more comprehensive data collection.

Despite these limitations, the findings add valuable information to the growing body of research on COVID-19 vaccination in pregnancy. Future research should focus on addressing these limitations and exploring the mechanisms of action that will further solidify our understanding of vaccination’s role in protecting both mothers and their babies during this critical period.

Conclusion

In this study, no statistically significant differences were observed in primary or secondary birth outcomes between COVID-19 vaccinated and unvaccinated pregnant women. Further analyses investigating trimester of vaccination, vaccine type, and neonatal outcomes also revealed no significant differences. These findings, although preliminary, suggest that COVID-19 vaccination during pregnancy may be safe and well-tolerated, posing no additional risks to birth outcomes or neonatal health compared to unvaccinated individuals.

However, it is crucial to acknowledge the limitations of this study and the need for further research to solidify and expand upon these findings.

Discussion

This study found high uptake of COVID-19 vaccination among pregnant women in Karachi. Importantly, no increased risk of adverse birth outcomes like preterm delivery or stillbirths was identified among vaccinated compared to unvaccinated pregnant women. These findings align with other international studies demonstrating the safety and efficacy of COVID-19 vaccination during pregnancy [4, 5].

Strengths of this study include the real-world data on vaccination and birth outcomes, and the comparison between vaccinated and unvaccinated groups. However, limitations include the cross-sectional design, which limits causal inference, and the lack of long-term follow-up data. Therefore, larger prospective studies are needed to further investigate the long-term impact of COVID-19 vaccination on maternal and neonatal health, including potential effects on growth and development. Additionally, research is needed to determine the optimal timing of vaccination during pregnancy for maximal protected vaccine effects for both mother and baby.

Public Health Implications

The findings of this study support COVID-19 vaccination routine public health communication campaigns as a safe and effective strategy to protect against severe illness and adverse vaccination outcomes. Considering the increased vulnerability of pregnant individuals to COVID-19, healthcare providers should actively encourage and guide pregnant women towards vaccination, addressing any concerns and providing accurate information about the benefits and safety of vaccination during pregnancy.

Table 4: Trimester of Vaccination and Birth Outcomes

<table>
<thead>
<tr>
<th>Trimester of Vaccination</th>
<th>Preterm Delivery (n, %)</th>
<th>Stillbirths (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Trimester (n = 17)</td>
<td>3 (17.6%)</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>Second Trimester (n = 51)</td>
<td>4 (7.8%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Third Trimester (n = 32)</td>
<td>3 (9.4%)</td>
<td>1 (3.1%)</td>
</tr>
</tbody>
</table>

Table 5: Maternal Complications by Vaccination Status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vaccinated (n, %)</th>
<th>Unvaccinated (n, %)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preecclampsia</td>
<td>5 (5.0%)</td>
<td>4 (4.0%)</td>
<td>0.702</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>7 (7.0%)</td>
<td>6 (6.0%)</td>
<td>0.756</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>2 (0.5%)</td>
<td>1 (0.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Postpartum hemorrhage</td>
<td>3 (1.0%)</td>
<td>2 (0.3%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

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AUTHORS CONTRIBUTIONS

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Software: Sami R, Yasir. M
Supervision: Sami R
Writing – Original Draft Preparation: Sami R, Yasir. M
Writing – Review & Editing: Sami R, Yasir. M
COVID Shots Safe for Pregnant Women

**Key messages**

- Pregnant women who got COVID-19 vaccines were not more likely to have early or stillborn babies compared to unvaccinated women.
- This adds to evidence showing COVID-19 vaccines are safe and recommended for pregnant women to protect them and their babies against severe COVID-19.
- More research is needed to understand long-term effects and find the best timing for vaccination during pregnancy.
- Doctors and pregnant women should learn more about vaccine benefits to overcome worries and boost vaccination rates.

**References**