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Association between COVID-19 vaccination during pregnancy and SGA in a rural area

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Abstract

Vaccines were the most crucial factor in ending the COVID-19 pandemic. Different types of COVID-19 vaccines were administered worldwide to all ages, including pregnant women. This study aimed to evaluate if different types of COVID-19 vaccines applied during pregnancy affect the "Small for Gestational Age" (SGA) incidence in a rural area of Turkey. A retrospective cohort study was performed with 146 completed pregnancies between 2021 and 2022. The health repository was scanned to obtain COVID-19 vaccination status during pregnancy, the type of COVID-19 vaccine administered and fetal birth weight. The presence of SGA was detected by using a gender-specific Fenton growth chart in newborns. We investigated the incidence of SGA for the whole study population and vaccinated group, as well as the types and trimesters of COVID-19 vaccination during pregnancy. There was no statistical significance between all pregnancies and vaccinated women during pregnancy in terms of SGA incidence ($p>0.05$). Either COVID-19 vaccination during pregnancy or type of COVID-19 vaccines or trimester of application did not statistically change the incidence of SGA ($p>0.05$). Pregnant women are skeptical about the COVID-19 vaccine, but inactivated and mRNA COVID-19 vaccine administration during pregnancy seems safe in terms of SGA incidence.

Keywords: COVID-19, small for gestational age, vaccination, COVID-19 vaccines, pregnancy

1. Introduction

Infectious diseases that spread around the world, known as pandemics, have been remembered with COVID-19. The novel coronavirus disease, which spreads quickly due to its human-to-human transmission feature, has affected all countries around the world (1, 2).

Data collected about "New Coronavirus Disease" revealed that the disease threatens not only the respiratory system but also many systems, including the genital system and related organs. The main reason why the virus acts in such a wide range is ACE 2 receptors, which is a way to enter the cell. It is believed that with high expression of ACE 2 receptors in the female genital system, COVID-19 may damage reproductive functions and can cause infertility, menstrual irregularity and fetal problems (3-5).

Vaccination is the most important and effective way to protect health and prevent infectious diseases (6). To defeat the COVID-19 epidemic, a large part of the population, including pregnant women, has been vaccinated. As the virus spread and the distribution of viral variants changed, the types of COVID-19 vaccines varied over time, including inactivated, live-attenuated, viral vector, protein subunit, and DNA and mRNA vaccines (7). Inactivated virus vaccines are a conventional protein-based approach which is made from whole viruses inactivated by chemical agents to activate the host's immune response. Messenger RNA (mRNA) vaccines are a gene-based approach which delivers a transcript that encodes a target antigen or immunogen (8).

In the literature, COVID-19 during pregnancy is associated with higher rates of fetal death, preterm birth, preeclampsia and emergency cesarean section (9, 10). There is little data on pregnancy outcomes and the safety of COVID-19 vaccines in pregnancy because pregnant women were excluded from first phase III clinical trials (11). The possible future harms and side effects of COVID-19 vaccination on pregnant women and fetuses are not yet fully known (6, 11, 12).

The incidence of morbidity and mortality is high in small for gestational age (SGA) infants. Although the definition of SGA is birth weight under the 10th percentile for a given gestational age, regardless of any pathology, SGA is associated with neurodevelopmental delay (13). Neurological diseases, close follow-up or hospitalization requiring morbidities are five to ten times higher in SGA babies than in appropriate for gestational age (AGA) babies (14).

Our study aims to evaluate if COVID-19 vaccination affects birth weight according to gestational age and to see if SGA incidence changes with different types of COVID-19 vaccines.

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2. Materials and Methods

This retrospective cohort study was conducted between 01.03.2021 and 01.03.2022 in Manisa Demirci district. This rural area's health repository was scanned to obtain COVID-19 vaccination status among pregnant women. Additionally, the types of COVID-19 vaccines and vaccine administration trimesters were noted. To determine SGA, birth weight according to gestational age was calculated using a gender-specific Fenton percentile curve. Pregnant women who applied to Manisa Demirci State Hospital were divided into two groups according to COVID-19 vaccination status. SGA incidences were found for vaccinated and non-vaccinated groups during pregnancy. In the study, the mother's age, type and doses of COVID-19 vaccines, trimester of vaccine application, gestational week of birth, mode of birth, birth weight and the gender of the babies were noted. Babies who were below the 10th percentile according to the Fenton percentile curve were defined as SGA (15). Low birth weight was determined using gender-specified Fenton growth charts and calculated by looking at the weeks of gestation (16). Statistical analyses were made by assigning the number 1 to SGA and number 2 to AGA. LGA babies, multiple gestations, neonates with congenital anomalies, aneuploidies and women with antenatal COVID-19 were excluded from the study. SGA presence was searched if it was related to COVID-19 vaccination during pregnancy and the type of vaccines. The relationship between SGA and COVID-19 vaccination during pregnancy was evaluated.

The study was conducted in accordance with the declaration of Helsinki. The approval for the study was obtained from the ethics committee of the University of Health Sciences, İstanbul Kanuni Sultan Süleyman Training and Research Hospital, with the number 2021.12,336. For the implementation of the study, permission was obtained from the Ministry of Health of the Republic of Türkiye.

Study data was evaluated with IBM Statistical Package for the Social Sciences for Windows, Version 23.0 (IBM Corp., Armonk, NY). In the analysis of the data, descriptive statistics (mean, standard deviation, median, minimum, maximum) for numerical variables and frequency distributions (number, percentage) for categorical variables were given. If there was a difference between two independent groups, the Mann-Whitney U test or independent sample t-test was used, depending on whether the variables were compatible with normal distribution. The Kruskal Wallis test or the One-Way ANOVA test was used to determine whether there was a difference between more than two independent groups. The results were considered statistically significant with p-values of <0.05.

3. Results

A total of 146 pregnant women were included in the study. The mean age was 30.16±5.29. Of the study population, 13.7% had advanced maternal age, 62.3% were vaccinated with mRNA, inactivated virus and combined vaccines, 47.3%, 13.7%, and 1.4%, respectively. In terms of vaccination periods, first-trimester, second-trimester, and third-trimester ratios were 20.5%, 15.8%, and 8.2%, respectively. The rest were vaccinated in combined trimesters. 84.9% delivered at 38th gestational weeks and above, 65.1% had a cesarean section, and 89.7% gave birth to 2500 to 4000 gr babies. Of the 84 male babies and 62 female babies, SGA ratios were 2% and 2.8%, respectively (Table 1).

Table 1. Distribution of participants' socio-demographic, obstetric characteristics, types and time of COVID-19 vaccination and neonatal characteristics

Age (years)		30.16±5.29	
		n	**%**
Age distribution	<21	5	3.4
	21-35	121	82.9
	>35	20	13.7
Vaccination during pregnancy	None	55	37.7
	1 dose	30	20.5
	2 or more doses	61	41.8
Type of vaccines	Inactive	20	13.7
	mRNA	69	47.3
	Inactive+mRNA	2	1.4
Trimester of vaccination	1.trimester	30	20.5
	2.trimester	23	15.8
	3.trimester	12	8.2
	1. and 2. trimester	20	13.7
	2. and 3. trimester	5	3.4
	1. and 3. trimester	1	0.7
Gestational week at birth	<38	22	15.1
	≥38	124	84.9
Mode of delivery	Normal vaginal delivery	51	34.9
	C-Section	95	65.1
Birth weight of infant	<2500 gr	6	4.1
	2500-4000 gr	131	89.7
	>4000 gr	9	6.2
Gender	Male	84	57.5
	Female	62	42.5
Percentile curve (male infant)	SGA	3	2.0
	AGA	81	55.5
Percentile curve (female infant)	SGA	4	2.8
	AGA	58	39.7

*n: number, %: ratio, SGA: small for gestational age, AGA: appropriate for gestational age

According to COVID-19 vaccination during pregnancy, SGA presence was not statistically different between the vaccinated and non-vaccinated groups (p=0.772). Furthermore, there was no statistical significance for SGA incidence between the application of inactivated vaccine only, mRNA vaccine only and the combination of both types (p=0.349) (Table 2).

SGA incidence was not different between the non-vaccinated and the inactivated vaccine-only groups and the mRNA vaccine-only and the combination of both types of vaccine groups, respectively (p=0.290, p=0.935, p=1.000). Furthermore, trimester of COVID-19 vaccine administration did not affect the SGA incidence (p=0.989) (Table 3).

Table 2. Comparison of SGA in neonatals between vaccinated and non-vaccinated group and COVID-19 vaccine types administered during pregnancy

SGA	**Vaccinated, n**	**Non-vaccinated, n**		**Total, n**	**p**
	91	55		146	0.772
	Inactive, n	**mRNA, n**	**Inactive+ mRNA, n**	**Total, n**	**p**
	20	69	2	91	0.349

*inactive: COVID-19 vaccine containing inactivated virus, *mRNA: mRNA (Messenger RNA) based COVID-19 vaccine, *SGA: small for gestational age *n: number of individuals

Table 3. Comparison of SGA between non-vaccinated and vaccinated with different COVID-19 vaccine types, and between trimester of administration

	SGA n (%)	**p**
Non-vaccinated, n (%) 55 (37.7)	3 (2)	0.290
Inactive, n (%) 20 (13.7)	0 (0)	
Non-vaccinated, n (%) 55 (37.7)	3 (2)	0.935
mRNA, n (%) 69 (47.3)	4 (2.7)	
Non-vaccinated, n (%) 55 (37.7)	3 (2)	1.000
Inactive+mRNA, n (%) 2 (1.4)	0 (0)	
First trimester, n (%) 30 (20.5)	1 (0.7)	0.989
Second trimester, n (%) 23 (15.8)	2 (1.4)	
Third trimester, n (%) 12 (8.2)	1 (0.7)	

*inactive: COVID-19 vaccine containing inactivated virus, *mRNA: mRNA (Messenger RNA) based COVID-19 vaccine *SGA: small for gestational age *n: number of individuals, %: ratio

SGA incidence was not statistically different between the whole population and the vaccinated group (p=1.000) (Table 4).

Table 4. Comparison of SGA incidence in the community and in those who had been vaccinated against COVID-19 during pregnancy

	SGA, n	**SGA incidence, %**	**p**
Vaccinated, n=91	4	4.3	1.000
Community, n=146	7	4.7	

*Community: Indicates the entire study population *SGA: small for gestational age *n: number of individuals, %: incidence are presented as ratio

4. Discussion

The connection between gestational week and birth weight provides information about intrauterine life and the health of the baby. Mortality and morbidities are 5 to 10 times higher in SGA babies than in babies with appropriate weight for gestational age (14).

While it is unclear to what extent COVID-19 vaccines prevent getting infected and the spreading of the virus, initial data have shown that vaccines reduce the duration and severity of new coronavirus illness. Of these different types, mRNA vaccines were first administered to pregnant women in the United States. The results, including completed pregnancies, have been published in the Centers for Disease Control and Vaccine Safety Monitoring program database (17).

To date, no unexpected results have been observed in terms of gestational diabetes mellitus, preeclampsia, intrauterine growth restriction, miscarriage rates, stillbirth rates, premature birth and neonatal deaths related to mRNA COVID-19 vaccines administered during pregnancy (18). According to a multicenter study that supports our study results, mRNA vaccines did not increase the incidence of SGA in the population (19). Additionally, our study reveals that the first trimester of COVID-19 vaccination is also safe in terms of SGA. Similar to our study, a prospective study designed with inactivated COVID-19 vaccines revealed that first-trimester vaccination did not increase the risk for SGA babies (20).

In a recent review, similar to our data, there was no evidence of a higher risk for SGA babies and additionally other adverse perinatal outcomes, including miscarriage and neonatal fetal abnormalities (21). Moreover, a different study conducted with mRNA and viral vector vaccines found that SGA incidence did not change with COVID-19 vaccination (22).

This study may have some weak points. Since it is a rural area study, it was held by one center with a limited population. However, it has a major strength in that it covers the results of two different COVID-19 vaccine types (mRNA and inactivated virus vaccines) in pregnant women.

As a result, the administration of inactivated and mRNA COVID-19 vaccines during pregnancy is safe in terms of SGA incidence. Considering the effects of severe COVID-19 disease in pregnancy and newborns, COVID-19 vaccines should be recommended during pregnancy.

Ethical Statement

The study was conducted in accordance with the declaration of Helsinki. The approval for the study was obtained from the ethics committee of the University of Health Sciences, İstanbul Kanuni Sultan Süleyman Training and Research Hospital, with the number 2021.12,336. For the implementation of the study, permission was obtained from the Ministry of Health of the Republic of Türkiye.

Conflict of interest

Authors declare no conflict of interest.

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Authors' contributions

Concept: P.Ö.K., Design: P.Ö.K., Data Collection or Processing: P.Ö.K., G.S., Analysis or Interpretation: G.S., Literature Search: P.Ö.K., G.S., Writing: P.Ö.K., G.S.

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