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Impact of COVID-19 and vaccination on first and second trimester screening results

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ABSTRACT

COVID-19 has been shown to affect pregnant women. Since pregnant women are at risk of this infection, vaccination against COVID-19 has been suggested as an imperative way to diminish rate of COVID-19 in this population. In the current observational study, we have collected data of first and second trimester screening (FTS and STS) from pregnant women who were infected with SARS-CoV-2 and/or vaccinated against COVID-19 during their pregnancy, and compared this data with a group of control pregnant women. The cohort included 4612 and 2426 women referred for FTS and STS, respectively. There was no significant difference in median values of Pregnancy-associated plasma protein A (PAPP-A) and human chorionic gonadotropin-beta subunit (βHCG) between infected women and controls. Moreover, these levels were not different between "Infected + vaccinated" and "Only vaccinated" groups. However, median values of PAPP-A and βHCG were higher in "Infected + vaccinated" and "Only vaccinated" groups compared with "Infected" and "Control" groups ($P < 0.001$). Median values of unconjugated Estriol (uE3) and βHCG markers were not different between "Only vaccinated" and "Control" groups, yet both markers were elevated in "Infected" and "Infected + vaccinated" groups compared with other groups. AFP values were higher in "Infected" group ($P = 0.012$). However, multiple of the median (MoM) and risk of open spina bifida (OSB) were not affected. Finally, median of calculated risk of trisomy 18 was lower in "Infected" and "Vaccinated" groups compared with controls ($P = 0.007$). Moreover, AstraZeneca and Sinopharm vaccines were associated with elevation of the calculated risk values of trisomy 21 and trisomy 18 ($P < 0.001$). While Sinopharm did not affect nuchal translucency (NT) and NT MoM ($P = 0.13$), AstraZeneca and Barakat increased and decreased these values, respectively (P values = 0.0027 and 0.015, respectively). Taken together, COVID-19 during pregnancy might be associated with some adverse obstetric outcomes. Besides, vaccination against this infection might affect the results of STS or FTS.

1. Introduction

Pregnant women are at higher risk of being hospitalized, particularly in the ICU ward when infected with SARS-CoV-2. Moreover, they are more susceptible for needing mechanical ventilation compared with non-pregnant women at reproductive age [1]. Thus, it is necessary to consult these women about the possible threat for severe COVID-19 and implement actions to avoid infection with SARS-CoV-2 in pregnant women. Vaccination is an imperative way to diminish rate of COVID-19 in this population. Yet, data regarding the safety of vaccination in this

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group is scarce. Few studies have assessed the maternal, neonatal, and obstetrical consequences of vaccination against COVID-19. For instance, a preliminary study of safety of mRNA vaccines in pregnant women has not reported noticeable safety signals [2]. Consistent with this finding, another descriptive study of pregnant women who received an mRNA COVID-19 vaccine has reported no stillbirths, no increased risk of spontaneous abortions and lower rate of preterm birth compared with the national average rates [3]. Vaccination with the BNT162b2 vaccine has also been shown to be safe at all stages of pregnancy, due to the results of another observational case-control investigation [4]. Thus, the available data indicates safety of vaccination in this group of women.

However, the impact of COVID-19 vaccination or infection with SARS-CoV-2 on the results first/second trimester screening (FTS/STS) is less studied. In the current observational study, we have collected data of FTS and STS results from pregnant women who were infected with SARS-CoV-2 and/or vaccinated against COVID-19 during their pregnancy, and compared this data with a group of control pregnant women.

2. Patients and methods

2.1. Cases

The current investigation was implemented on pregnant women referred to Nilou Laboratory for FTS/STS during August 2021 to December 2021. The study protocol was approved by the institutional ethical committee. All included cases and controls signed the informed consent forms.

2.2. Statistical methods

Statistical analyses were performed using SPSS software version 21 (IBM Corporation, Armonk, NY, USA). Chi-2 test was used for assessment of association between categorical variables. The relationships between quantitative variables were evaluated using ANOVA test. P values < 0.05 were considered as significant. Tukey test was used as a non-parametric equivalent for ANOVA for comparing two or more subgroups within each group. This test was used for comparison of median values of circulatory markers.

3. Results

3.1. General data

The cohort included 4612 women referred for FTS (mean age (SD): 32.53 (4.67)). A total of 816 cases reported history of COVID-19 during pregnancy. Besides, 867 cases had history of both COVID-19 and vaccination. Thus, a total of 1683 had history of COVID-19 during pregnancy. Furthermore, 1018 cases were vaccinated against this virus and had no history of COVID-19. Taken together, a total of 1885 cases were vaccinated.

Totally, 2426 pregnant women were referred for STS (mean age (SD): 32.4 (4.58)). Among them, 600 cases had history of COVID-19 without vaccination. A total of 345 pregnant women of this group had history of both COVID-19 and vaccination. In addition, 422 cases had only history of vaccination. Thus, 945 pregnant women who came for STS had history of COVID-19 in pregnancy. Total number of vaccinated women in this group was 767. Control group consisted of pregnant women without history of COVID-19 and vaccination against SARS-CoV-2. This group included 1925 and 1059 cases referred for FTS and STS, respectively. Table 1 summarizes this information.

Patients received different drugs for management of COVID-19. Among those referred for FTS, combination of azithromycin and ReciGen® (interferon beta-1a), azithromycin alone, levofloxacin, combination of azithromycin and acetaminophen and combination of amoxicillin and ReciGen® were the most frequent therapeutic options with frequencies of 11%, 9.5%, 4.4%, 4.3% and 3.5%, respectively.

Table 1
Summary of number of included cases and their history of vaccination and COVID-19.

Groups	FTS		STS	
	Number	Percent	Number	Percent
Infected	816	17.6	600	24.7
Infected + vaccinated	867	18.7	345	14.2
Only vaccinated	1018	22.0	422	17.3
Controls	1925	41.6	1059	43.6
Total	4626	100.0	2426	100.0

In the STS group, azithromycin, favipiravir and remdesivir were prescribed for 2.9%, 0.7% and 0.5% of patients, respectively. Totally, 2.4% and 3.1% of patients in FTS and STS groups had history of hospitalization. Mean duration of hospitalization was 3 and 7 in FTS and STS groups, respectively. Two cases from FTs group were admitted in ICU.

Table 2 shows the number of vaccine doses administered in each group.

A total of 68.5% of cases took their vaccines more than 8 weeks before coming for FTS. Moreover, 27.1% and 4.4% of cases took vaccines between 4 and 8 weeks before FTS tests and <4 weeks prior to FTS, respectively. In the STS group, these percentages were 59.7%, 10.1% and 30.2%, respectively.

Table 3 shows the kinds of vaccines injected in each group.

3.2. Comparison of FTS markers

Based on the results of ANOVA test, there was no significant difference in median values of PAPP-A and βHCG between infected women and controls. Moreover, these levels were not different between "Infected + vaccinated" and "Only vaccinated" groups. However, median values of PAPP-A and βHCG were higher in "Infected + vaccinated" and "Only vaccinated" groups compared with "Infected" and "Control" groups ($P < 0.001$) (Table 4). Since MoM values were not different between these groups, FTS results were not affected.

Based on the results of ANOVA and Tukey tests, median values of uE3 and βHCG markers were different between groups (Table 5). While these values were not different between "Only vaccinated" and "Control" groups, both markers were elevated in "Infected" and "Infected + vaccinated" groups compared with other groups. However, these differences were not detected in MoM values.

Alpha fetoprotein (AFP) values were higher in "Infected" group ($P = 0.012$). However, MoM and risk of open spina bifida (OSB) were not affected.

Finally, median of calculated risk of trisomy 18 was lower in "Infected" and "Vaccinated" groups compared with controls ($P = 0.007$).

Then, we assessed associations between the kind of vaccines and levels of FTS markers (Table 6).

Then, we compared the median values of these markers between those were vaccinated with AstraZeneca, Sinopharm or Barakat with control group (Table 7).

Based on the results of ANOVA and Tukey tests, after adjustment for gestational age, all three kinds of vaccines were associated with elevation of βHCG, βHCG MoM, PAPP-A and PAPP-A MoM. Moreover,

Table 2
The number of vaccine doses administered in each group.

Number of doses	Frequency in FTS	Valid Percent in FTS	Frequency in STS	Valid Percent in STS
1	631	33.5	389	50.7
2	1219	64.7	362	47.2
3	22	1.2	8	1.0
Missing	13	0.7	8	1.0
Total	1885	100.0	767	100.0

Table 3
Kinds of vaccines in each group.

	Frequency in FTS	Valid Percent in FTS	Frequency in STS	Valid Percent in STS
Baharat	14	0.7	5	0.6
AstraZeneca	218	11.6	76	10.0
Sinopharm	1417	75.5	608	79.9
Pfizer	27	1.4	11	1.4
Barakat	118	6.3	33	4.3
Sputnik	54	2.9	24	3.2
Johnson & Johnson	4	0.2	1	0.1
Razi Cov Pars	3	0.2	1	0.1
Spikogen	1	0.1	0	0
Pastocovac	1	0.1	0	0
Unknown	12	0.7	6	0
Mix	8	0.3	2	0.3
Total	1885	100.0	767	100.0

Table 4
Comparisons of FTS markers between four groups of pregnant women (NT: nuchal translucency). ANOVA and Tukey tests were used for comparisons.

Groups	Infected	Infected + vaccinated	Control	Only vaccinated	P value
βHCG	27	31	29	32	<0.001
βHCG MoM	0.99	0.95	0.95	0.97	0.715
PAPP-A	26	2304	1290	2395.5	<0.001
PAPP-A MoM	1	1.03	0.99	1.02	0.278
NT	1.6	1.6	1.6	1.6	0.519
NT MoM	1.18	1.17	1.17	1.18	0.85

Table 5
Comparisons of STS markers between four groups of pregnant women (AFP: alpha fetoprotein, uE3: unconjugated Estriol, DIA: dimeric inhibin A, OSB: open spina befida, SLOS: Smith-Lemli-Opitz syndrome, T21: trisomy 21, T18: trisomy 18, ANOVA and Tukey tests were used for comparisons).

Groups	Infected	Only vaccinated	Control	Infected + vaccinated	P value
AFP	35	33	32	32	0.012
AFP MoM	1.06	1.03	1.04	1.04	0.732
uE3	0.6	0.89	0.635	0.84	<0.001
uE3 MoM	1	1.02	0.98	0.97	0.361
βHCG	28.7	29.6	27.7	31.7	0.008
βHCG MoM	0.95	0.97	0.94	1.02	0.489
DIA	269	267	271	283	0.556
DIA MoM	0.98	0.95	0.98	0.97	0.781
OSB Risk	13,700	15,100	15,100	14,400	0.649
T21 Risk	8120	6870	10,350	8570	0.086
T18 Risk	42,900	48,400	56,850	41,900	0.007
SLOS Risk	347,000	348,000	360,000	330,000	0.482

AstraZeneca and Sinopharm vaccines were associated with elevation of the calculated risk values of trisomy 21 and trisomy 18 ($P < 0.001$). While Sinopharm did not affect NT and NT MoM ($P = 0.13$), AstraZeneca and Barakat increased and decreased these values, respectively (P values = 0.0027 and 0.015, respectively).

We also assessed associations between the kind of vaccines and levels of STS markers (Table 8). AFP median and AFP MoM were lower in AstraZeneca group compared with controls ($P < 0.001$), thus the risk of OSB was lower in this group ($P = 0.016$). Sinopharm vaccine did not affect these values. Median of uE3 was elevated in both groups compared with controls ($P = 0.001$). However, uE3 MoM and risk of Smith-Lemli-Opitz syndrome (SLOS) were not affected by these vaccines. βHCG median and MoM were increased in both groups compared with controls ($P < 0.001$). DIA median and DIA MoM were lower in AstraZeneca group ($P = 0.001$). However, DIA median was increased in Sinopharm group ($P = 0.001$), without any impact on DIA MoM.

The reported risk of tisomy 21 was increased in both groups ($P < 0.001$), possibly enhancing false positive rates. However, no difference was detected in the reported risk of trisomy 18 ($P = 0.209$).

Then, we compared these values in different groups of pregnant women infected with COVID-19 based on the time of infection during pregnancy. In those came for STS, median of trisomy 18 risk was higher in those infected between 4 and 8 weeks before sampling ($P = 0.027$). Other markers were not different between groups.

Notably, in "Infected + vaccinated" group, the NT MoM was increased until 8 weeks from injection of vaccine ($P = 0.039$). There was no difference in other FTS markers and calculated risks based on the time of infection in the first trimester.

uE3 median was lower in those infected<8 weeks before sampling ($P = 0.025$). Yet, uE3 MoM was not affected, thus no difference was reported in calculated risks for trisomies and SLOS.

Mean AFP and AFP MoM as well as SLOS risk were increased in those vaccinated and not infected with COVID-19 during 4 weeks after vaccination ($P < 0.001$). However, these values were decreased after 4 weeks and did not affect calculated risk of OSB and trisomy 21. Mean value of uE3 was increased in those coming for tests more than 8 weeks after vaccination ($P = 0.001$). However, uE3 MoM was not affected. Calculated risk of SLOS was lower in those coming for tests<4 weeks after vaccination ($P = 0.021$). Other markers were not affected by the time of vaccination.

4. Discussion

COVID-19 during the late pregnancy has been shown to be associated with elevation of the risk of adverse birth outcomes, particularly iatrogenic preterm birth and cesarean section delivery [5]. Another study has shown association between COVID-19 pandemic and insufficient or excessive gestational weight gain, occurrence of premature rupture of membranes and fetal distress [6]. Moreover, a recent retrospective study has indicated higher occurrence of premature delivery in pregnant women affected with COVID-19 [7]. A systematic review and *meta*-analysis has reported association between COVID-19 and elevated risk of preeclampsia, preterm birth and other adverse obstetric outcomes [8]. An overview of systematic reviews has shown that COVID-19 might

Table 6
Associations between the kind of vaccines and levels of FTS markers.

Kind of vaccine	βHCG	BHCG MoM	PAPP-A	PAPP-A MoM	NT	NT MoM	T21 Risk	T18 Risk
Baharat	41.50	1.2550	2978.00	1.0050	1.700	1.2250	1765.00	1195000.00
AstraZeneca	29.70	0.9600	2289.50	1.1000	1.660	1.2000	3910.00	1845000.00
Sinopharm	32.00	0.9700	2373.50	1.0200	1.600	1.1700	4300.00	1930000.00
Pfizer	31.00	1.1100	1689.00	1.0700	1.700	1.1800	2090.00	625000.00
Barakat	31.00	0.9400	2394.00	1.0800	1.500	1.1500	6130.00	2810000.00
Spotnik	32.00	0.9500	992.50	0.9900	1.635	1.1650	2390.00	1185000.00
Control	29.00	0.9500	1290	0.9900	1.600	1.1700	4680	1,650,000
P value	0.003	0.007	0.004	0.0050	0.006	0.046	0.021	0.003

Table 7
Comparison of median values of FTS markers between those were vaccinated with AstraZeneca, Sinopharm or Barakat with control group (ANOVA and Tukey tests were used for comparisons).

Kind of vaccine	βHCG	βHCG MoM	PAPP-A	PAPP-A MoM	NT	NT MoM	T21 Risk	T18 Risk
AstraZeneca	29.70	0.9600	2289.50	1.1000	1.660	1.2000	3910.00	1845000.00
Sinopharm	32.00	0.9700	2373.50	1.0200	1.600	1.1700	4300.00	1930000.00
Barakat	31.00	0.9600	2394.00	1.0800	1.500	1.1500	6130.00	2810000.00
Control	29.00	0.9500	1290	0.99	1.600	1.1700	4680	1,650,000
P value	0.002	0.018	<0.001	<0.001	0.015	0.027	<0.001	<0.001

Table 8
Association between kind of vaccine and levels of STS markers.

Kind of vaccine/markers	AstraZeneca	Sinopharm	Control	P value
AFP	29	33	32	<0.001
AFP MoM	0.94	1.05	1.04	0.004
uE3	0.81	0.895	0.635	0.001
uE3 MoM	0.96	0.995	0.98	0.224
βHCG	29.1	30.75	27.7	0.001
βHCG MoM	1	1	0.94	<0.001
DIA	245	279.5	271	0.001
DIA MoM	0.87	0.97	0.98	0.001
OSB Risk	18,200	13,900	15,100	0.016
T21 risk	5840	7565	10,350	<0.001
T18 risk	45,400	45,500	56,850	0.209
SLOS risk	348,000	341,500	360,000	0.568

results in adverse birth outcomes, such as preterm delivery, low birth weight and admission of neonates in ICU [9]. Thus, the impact of this disorder on adverse pregnancy outcomes has been well studied. However, the impact of COVID-19 on STS and FTS results has been less studied. In the current study, we compared FTS and STS results between four groups of pregnant women, which were classified based on the infection with COVID-19 and vaccination against this disorder. We detected higher median values of PAPP-A and βHCG in "Infected + vaccinated" and "Only vaccinated" groups compared with "Infected" and "Control" groups. Since MoM values were not different between these groups, FTS results were not affected. However, future studies should assess whether changes in median values of these markers is associated adverse obstetric outcomes.

Similarly, COVID-19 infection has been associated with higher AFP values. Although MoM and risk of OSB were not affected, the association between high AFP values and adverse obstetric outcomes should be assessed in future studies. Besides, high AFP levels might be an indicator of adverse effects of COVID-19 on placenta.

In the STS, median of calculated risk of trisomy 18 was lower in "Infected" and "Vaccinated" groups compared with controls. This finding indicates the impact of both infection and vaccination on STS results, necessitating considering this point in the interpretation of STS. We also reported the impact of AstraZeneca, Sinopharm or Barakat vaccines on FTS markers. Notably, AstraZeneca and Sinopharm vaccines were associated with elevation of the calculated risk values of trisomy 21 and trisomy 18. Besides, AstraZeneca and Barakat increased and decreased NT and NT MoM values. Therefore, our results indicate the impact of vaccination against COVID-19 on calculated risk of trisomies. Similarly, AFP as an STS marker was affected by AstraZeneca vaccine, resulting in reduction of the calculated risk of OSB. Moreover, the reported risk of tisomy 21 was increased in pregnant women vaccinated with AstraZeneca or Sinopharm vaccines. This might result in increase in false positive rates.

Finally, the time of vaccination during the pregnancy has been shown to affect markers, possibly due to changes in the immune responses.

Taken together, our results suggest that COVID-19 during pregnancy might be associated with some adverse obstetric outcomes. Besides, vaccination against this infection might affect the results of STS or FTS, increasing the false positive rates.

Declarations

Ethics approval and consent to Participant.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences. All methods were performed in accordance with the relevant guidelines and regulations.

Consent of publication

Not applicable.

Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

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Not applicable.

Authors' contributions

SGF wrote the manuscript and revised it. SH, SY, MMTA, PS, SJ and SN performed the data collection. MHM designed and supervised the study. SS, SD, ZSM, SA, FN, BY, AKF and MS analyzed the data. All authors read and approved the submitted version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgement

Not applicable.

References

[1] S. Ellington, P. Strid, V.T. Tong, K. Woodworth, R.R. Galang, L.D. Zambrano, et al., Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status—United States, January 22–June 7, 2020, Morb. Mortal. Wkly Rep. 69 (25) (2020) 769.

[2] T.T. Shimabukuro, S.Y. Kim, T.R. Myers, P.L. Moro, T. Oduyebo, L. Panagiotakopoulos, et al., Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons, The New England J. Med. 384 (24) (2021) 2273–2282.

[3] M.E. Trostle, M.A. Limaye, V. Avtushka, J.L. Lighter, C.A. Penfield, A.S. Roman, COVID-19 vaccination in pregnancy: early experience from a single institution, Am J Obstet Gynecol MFM. 3(6) (2021).

[4] S. Bookstein Peretz, N. Regev, L. Novick, M. Nachshol, E. Goffer, A. Ben-David, et al., Short-term outcome of pregnant women vaccinated with BNT162b2 mRNA COVID-19 vaccine, Ultrasound Obstetr Gynecol: Off. J. Int. Soc. Ultrasound Obstetrics Gynecol. 58 (3) (2021) 450–456.

[5] R. Yang, H. Mei, T. Zheng, Q. Fu, Y. Zhang, S. Buka, et al., Pregnant women with COVID-19 and risk of adverse birth outcomes and maternal-fetal vertical transmission: a population-based cohort study in Wuhan, China, BMC Med. 18 (1) (2020) 1–7.

[6] M. Du, J. Yang, N. Han, M. Liu, J. Liu, Association between the COVID-19 pandemic and the risk for adverse pregnancy outcomes: a cohort study, BMJ Open 11 (2) (2021) e047900.

[7] S.-A. Taghavi, S. Heidari, S. Jahanfar, S. Amirjani, A. Aji-Ramkani, M. Azizi-Kutenaee, et al., Obstetric, maternal, and neonatal outcomes in COVID-19 compared to healthy pregnant women in Iran: a retrospective, case-control study, Middle East Fertility Society J.. 26 (1) (2021) 1–8.
[8] S.Q. Wei, M. Bilodeau-Bertrand, S. Liu, N. Auger, The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis, CMAJ 193 (16) (2021) E540–E548.
[9] A. Ciapponi, A. Bardach, D. Comandé, M. Berrueta, F.J. Argento, F. Rodriguez Cairoli, et al., COVID-19 and pregnancy: An umbrella review of clinical presentation, vertical transmission, and maternal and perinatal outcomes, PLoS one. 16 (6) (2021) e0253974.