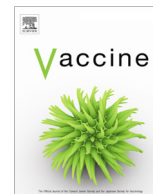




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



# Early exploration of COVID-19 vaccination safety and effectiveness during pregnancy: interim descriptive data from a prospective observational study



Inna Bleicher<sup>a,\*</sup>, Einav Kadour-Peero<sup>b</sup>, Lena Sagi-Dain<sup>c</sup>, Shlomi Sagi<sup>a</sup>

<sup>a</sup> Department of Obstetrics and Gynecology, Bnai -Zion Medical Center, Haifa, Israel

<sup>b</sup> Department of Reproductive Endocrinology and Infertility, McGill University Health Center, Montreal, QC, Canada

<sup>c</sup> Department of Obstetrics and Gynecology, Carmel Medical Center, Haifa, Israel

## ARTICLE INFO

### Article history:

Received 23 April 2021

Received in revised form 4 September 2021

Accepted 16 September 2021

Available online 25 September 2021

### Keywords:

Covid-19 vaccine

mRNA vaccine

Pregnancy vaccination

## ABSTRACT

**Objective:** During December 2020, a massive vaccination program was introduced in our country. The Pfizer-BioNTech, BNT162b2 vaccine was first offered exclusively to high-risk population, such as medical personnel (including pregnant women). In this study we compare short term outcomes in vaccinated vs. non-vaccinated pregnant women.

**Methods:** In this prospective observational cohort study, vaccinated and non-vaccinated pregnant women were recruited using an online Google forms questionnaire targeting medical groups on Facebook and WhatsApp. A second questionnaire was sent one month after the first one for interim analysis. Our primary outcome was composite complications in vaccinated and non-vaccinated groups, considered any of the following: vaginal bleeding, pregnancy loss, hypertension, gestational diabetes, and preterm birth. Secondary outcomes included: vaccine side effects, diagnosis of COVID-19 since the last questionnaire, prevalence of vaccinated participants, and reasons for refusal to be vaccinated.

**Results:** Overall, 432 women answered the first questionnaire, of which 326 responses were received to the second questionnaire. Vaccination rate increased from 25.5% to 62% within a month. Maternal age, gestational age at enrollment, nulliparity and number of children were similar in both groups. The rate of composite pregnancy complications was similar between vaccinated and non-vaccinated group (15.8% vs 20.1%,  $p = 0.37$ ), respectively. The risk for COVID-19 infection was significantly lower in the vaccinated group (1.5% vs 6.5%,  $p = 0.024$ , Odds Ratio: 4.5, 95% confidence interval 1.19–17.6).

**Conclusions:** mRNA vaccine during pregnancy does not seem to increase the rate of pregnancy complications and is effective in prevention of COVID-19 infection.

© 2021 Elsevier Ltd. All rights reserved.

## 1. Introduction

Three months following the first report of a novel coronavirus pneumonia in China, [1] the World Health Organization declared this outbreak as a pandemic [2]. The effect of coronavirus disease 2019 (COVID-19) on pregnant population remained in dispute. While some argued that pregnancy had no or minimal effect [3], others showed that pregnancy is a risk factor for severe maternal disease and for fetal and neonatal complications [4,5].

After the genetic sequence of the SARS-COV-2 was defined, the first mRNA vaccine development was initiated [6–8], and during July 2020 phases 2/3 of the leading vaccine (Pfizer-BioNTech,

BNT162b2) have begun. Six months later, the developers demonstrated that the vaccine is protective against COVID-19 [6]. On December 27th 2020, a massive vaccination program began in our country, prioritizing health care workers and high risk population such as elderly and people with comorbidities [9]. The vaccine was given in two doses, three weeks apart. No official recommendation was published to vaccinate pregnant women due to lack of evidence regarding safety, since this population was excluded from phase II/III trial. However, along with the discovery of the mutant variants of the virus, and due to a sudden increase in morbidity and intensive care unit admission in this population, the Israeli Ministry of Health has decided not to withhold vaccination from pregnant women. At first, the vaccine was available only to pregnant women at risk (i.e., medical personnel). However, within several weeks the recommendations have changed, and the vaccine was

\* Corresponding author at: Inna Bleicher, Department of Obstetrics and Gynecology, Bnai -Zion Medical Center, Haifa, Israel.

E-mail address: [innableicher@gmail.com](mailto:innableicher@gmail.com) (I. Bleicher).

recommended to all pregnant women at any gestational age due to the dramatic increase in morbidity.

The objective of this study was to compare short term outcomes between vaccinated and non-vaccinated pregnant women.

## 2. Methods

This is an interim analysis of a broader prospective observational study with sequential surveillance that is continuing, that compared vaccinated and non-vaccinated pregnant women. The study was planned within few weeks after the initiation of the vaccine program. It was approved by the local Helsinki committee. We designed and performed the study in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines. We distributed online Google forms questionnaires every couple of months to assess for side effects and adverse pregnancy outcomes. The questionnaires were distributed by the primary investigator, using her private Facebook account, on social networks such as Facebook and WhatsApp. At first, we targeted medical groups only. We chose these groups because the vaccine was available only for medical workers who are pregnant at that time. Few days after sharing the 1st questionnaire in these groups, the vaccine became available to all pregnant women, regardless their occupation and thus the questionnaire was posted publicly on the wall of the primary investigator's Facebook account with a request to share the post as much as possible so it could reach as many women as possible.

In the first questionnaire, the participants were asked to provide an E-mail address and a 4 digits number (consists of 2 last digits of their personal ID number and 2 last digits of their phone number), we used this information to send the second questionnaire only to women who answered the first one. We collected the following data: maternal age, last menstrual period, presence of any risk factors for COVID-19 except being pregnant (occupational risk factors included: medical personnel, teachers, or law enforcement workers, medical risk factors included: asthma, cardiac disease, body mass index (BMI) > 30, diabetes, thyroid dysfunction), prior diagnosis of COVID-19, whether they have received the COVID vaccine and the gestational age at which they have received the vaccine, whether they were planning to be vaccinated soon, refusing vaccination or still considering it, previous pregnancy loss, and vaccination against common flu in the current and previous year. We used the e-mail addresses that were provided by the participants for sending the second questioner.

Inclusion criteria to the first questionnaire were being pregnant at enrollment and proper filling out of the data (valid e-mail address, ID number that matches the information in both questionnaires and answering all questions until the form is submitted). We excluded registries that were invalid or incompatible with the demands (for example: invalid e-mail address, wrong registration of last menstrual period that could not be correct e.c.t)

In the second questionnaire, which was sent one month following the first one, the participants were asked whether they were tested positive for COVID-19 during the last month, were they vaccinated. If yes - information was obtained regarding the amount of vaccine doses, gestational week at vaccination, as well as side effects.

For non-vaccinated women, we asked to provide the reason for choosing against vaccination. All women, regardless their vaccination status, were asked whether they were diagnosed with any of the following pregnancy complications: vaginal bleeding, pregnancy loss during first trimester (up to 13 weeks of gestation), pregnancy loss during second trimester (14–28 weeks of gestation), gestational diabetes, premature birth, premature contractions, and fetal growth restriction.

Our hypothesis was that no difference in pregnancy complications will be noted between vaccinated and non-vaccinated groups.

**Our primary outcome** was composite pregnancy complications, defined as having one or more of any of the following: vaginal bleeding at any point of gestation following the vaccination, first or second trimester pregnancy losses, fetal growth restriction, gestational diabetes or diabetes mellitus, hypertensive disease, fetal malformations observed on first or second anatomy scan (usually performed between 14 and 16 and 20–24 weeks of gestation, respectively), premature labor and premature contractions.

**Secondary outcomes** included vaccine side effects, diagnosis of COVID-19 since the first questionnaire, prevalence of vaccinated participants, and reasons for refusal to be vaccinated.

## 3. Statistical analysis

As this is the first study examining the issue of COVID-19 complications in pregnant women, no previous data was available to be based on for the calculation of sample size. Thus, a minimal sample size of 384 participants was anticipated (Gill, J., Johnson, P. & Clark, M. 2010. *Research Methods for Managers*, SAGE Publications.). Assuming incomplete response rate of about 10%, a sample of 420 respondents was sought.

Descriptive statistics were presented as means and standard deviations, medians with 25 and 75 percentiles, or as numbers with percentiles according to the types of the variables. Normal distribution of the quantitative parameters was tested by Kolmogorov Smirnov test, and parametric (*t*-test) or non-parametric (Mann Whitney test) were used for differences between the two groups (vaccinated vs. none vaccinated). Odds ratio with 95% confidence interval was used to compare primary and secondary outcomes. SPSS version 27 was used for all statistical analysis.  $P < 0.05$  was considered as significant.

## 4. Results

From January 10th to January 15th, 432 women responded to the first questionnaire. Maternal age, number of children, gestational age at enrollment and number of women in first, second and third trimester were similar between vaccinated and non-vaccinated groups according to the first questionnaire (Table 1). The second questionnaire was sent one month later and was answered by 326 women (75% response rate). In this analysis we included data only for participants who answered the first questionnaire and the second questioner for follow up. Of the 326 women who answered both, 13 patients had similar ID numbers. They were excluded from the analysis because we couldn't match the answers between the first and second questionnaire.

Full data was available for 313 women. Of them 202 (62%) women were vaccinated. (Table 2)

The information from the first questionnaire revealed that 80 women (25%) were already vaccinated. In this group, we found lower rate of previous pregnancy loss (16.3% vs 30.5%,  $p = 0.013$ ) and higher rates of flu vaccination in the current and previous years in comparison to the non-vaccinated group (Table 1).

Of the 202 (62%) women who were vaccinated according to the second questionnaire: 36 (17.8%) were vaccinated during first trimester, 110 (54.5%) during second trimester and 56 (27.7%) during third trimester (Table 2). Seventy-eight women (38.6%) received one vaccination dose, while the remaining 124 women (61.4%) received two vaccination doses. Sixty women (30%) reported no side effects, while 134 women (66%) reported local reaction at the injection site; weakness was reported by 16.8%, headache

**Table 1**  
Responders to 1st questionnaire, background comparison\*

	Vaccinated N = 80	Non- vaccinated N = 233	p-value	95% CI
Maternal age	31.7 ± 3.9	30.2 ± 5.09	P = 0.017	1.07 [1.01–1.12]
Gestational age at enrolment	21.4 ± 9.9	21.9 ± 9.4	P = 0.64	
1st trimester	19 (23.8%)	51(21.9%)	P = 0.76	
2nd trimester	38 (47.5%)	112 (48%)	P = 1.00	
3rd trimester	23 (28.7%)	70 (30.0%)	P = 0.88	
Primigravity	18 (22.5%)	70 (30.0%)	P = 0.25	
Number of children †	1 [0–2]	1 [0–2]	P = 0.21	
Previous pregnancy loss	13 (16.3%)	71 (30.5%)	<b>P = 0.013</b>	0.44 [0.23–0.85]
Flu vaccine this year	70 (78.5%)	150 (64.4%)	<b>P &lt; 0.0001</b>	3.87 [1.89–7.91]
Flu vaccine last year	60 (75.0%)	100 (43.7%)	<b>P &lt; 0.0001</b>	3.87 [2.19–6.84]
Positive for COVID so far	1 (1.3%)	12 (5.2%)	P = 0.19	
Gestational age at vaccination	20.14 ± 10.3	–		
Vaccine during 1st trimester <sup>1</sup>	24 (30%)	–		
Vaccine during 2nd trimester <sup>1</sup>	37 (46%)	–		
Vaccine during 3rd trimester <sup>2</sup>	18 (24%)	–		
Teaching staff	5 (6.3%)	14 (6.0%)	P = 1.00	
Medical employees	6 (82.5%)	83 (35.6%)	<b>P &lt; 0.0001</b>	8.52 [4.51–16.09]
No risk factors at all	10 (12.5%)	117 (50.2%)	<b>P &lt; 0.0001</b>	0.14 [0.07–0.29]
Number of comorbidities ‡				
0	70 (87.5%)	198 (85.0%)	P = 0.35	
1	7 (9%)	31 (13%)		
2+	3 (3.5%)	4 (2%)		

Data are presented as mean ± SD or n (%).

\* Missing data for 13 women who answered the first and second questionnaires but had identical ID number in the first and second questionnaire and no ability to pair the answers from the second questionnaire to the first one.

† median 25–75% Interquartile range.

‡ Comorbidities were any of the following: hypo/hyperthyroidism, chronic hypertension, BMI > 30, asthma, pre-gestational diabetes mellitus, heart disease .

<sup>1</sup> 1<sup>st</sup> trimester: from pre-conception to 13 weeks

<sup>1</sup> 2<sup>nd</sup> trimester: 14–28 weeks

<sup>2</sup> 3<sup>rd</sup> trimester: 29 weeks till birth.

**Table 2**  
second questionnaire responders: one month following the first questionnaire.

	Vaccinated N = 202	Non vaccinated N = 124	p	95% CI
Composite pregnancy complications*	32 (15.8%)	25 (20.2%)	P = 0.37	
COVID-19 positive since last questioner?	3 (1.5%)	8 (6.5%)	<b>P = 0.024</b>	<b>4.5 [1.19–17.6]</b>
Fetal growth restriction	3 (1.5%)	0 (0%)	P = 0.29	–
Pregnancy loss up to 13 gestational weeks	2 (0.9%)	1 (0.8%)	P = 1.00	–
Pregnancy loss 14–28 gestational weeks	–	–		–
Antepartum bleeding	4 (1.9%)	7 (5.6%)	P = 0.11	–
Anomaly on anatomy scan	9 (4.5%)	6 (4.8%)	P = 1.00	–
Hypertensive disorder	–	–		–
Premature contractions	4 (1.9%)	4 (3.2%)	P = 0.48	–
Preterm birth	–	–		–

Data are presented as mean ± SD or n (%).

\* composite outcome: any of the following: vaginal bleeding at any point of gestation, 1st trimester pregnancy loss (up to 13 weeks of gestation), 2nd trimester loss (14–28 weeks of gestation), fetal growth restriction, gestational and or diabetes mellitus, hypertensive disease, fetal malformations that were observed on first or second anatomy scan (usually performed between 14 and 16 and 20–24 weeks of gestation, respectively), premature labor and premature contractions.

(10.9%) and nausea (5.4%). Fever  $\geq 38^{\circ}\text{C}$  was reported by three women.

Composite pregnancy complications were similar between vaccinated and non-vaccinated groups (16% vs 20%, respectively,  $p = 0.37$ , power of 17.8). First trimester pregnancy loss (up to 13 weeks of gestation) was reported by three women: two women in the vaccinated group and one in the non-vaccinated group, a non-significant difference. Other adverse obstetric outcomes also did not differ between the two groups.

In the vaccinated group, the risk for COVID-19 was almost five times lower than in the non-vaccinated group (3 (1.5%) vs. 8 (6.5%); odds ratio 4.5, 95% CI (1.19–17.6)].

Of the 124 women in the non-vaccinated group, the main reason to avoid vaccination was lack of information regarding vaccination safety during pregnancy (76 women, 61.3%). Other reasons were fear of short- and long-term side effects (21

responses, 16.9%), being COVID-19 positive (9.6%), while 21 women stated they are planning to receive the vaccine later during pregnancy (9.6%) or shortly after birth (5.6%).

## 5. Discussion

In this analysis, we showed that short term composite pregnancy complications rate following vaccination against COVID-19 using Pfizer-BioNTech, BNT162b2 mRNA vaccine was not increased compared to the non-vaccinated group. In addition, we found that the vaccine significantly reduced the risk for COVID-19 infection (from 6.5% to 1.5%).

We chose composite outcome as the primary outcome due to expected low incidence of complications in each group. However, even when analyzing each outcome separately, we found that the rates of complications (including first trimester pregnancy loss,

vaginal bleeding during pregnancy, or major malformations) did not differ from non-vaccinated group, and from previously publications on influenza and human papilloma virus vaccine during pregnancy [10–12].

Not surprisingly, the leading reason to refuse vaccination was lack of information regarding safety during pregnancy, both short and long term. This emphasizes the importance of this and future studies.

This study has several limitations. First, it was not randomized or blinded. Second, the recruitment was based upon being part of social network, having an e-mail, and we acknowledge the mistakes in self registration and the potential bias in self-reported outcomes. Third, we should keep in mind that the incidence of complications (such as miscarriage or stillbirth) might be even higher in both groups, because events like that have psychological impact which might affect women's will to participate in a questionnaire and remember such traumatic event. Fourth, although some women were lost to follow up, the number was minimal, and thus unlikely to affect the results. Lastly, the suboptimal power for the primary outcome might undermine the validity of the conclusions. To reach a power of 80% with the yielded incidences, a 2,392 cohort would be needed. These numbers were not available in the examined period. Nevertheless, our study represents one of the first series addressing the short-term outcomes of mRNA vaccine against COVID-19 during pregnancy, the number of vaccinated women is high and is increasing as the study continues.

This study is still ongoing, and we plan to recruit more women (using same questionnaires) to reach the sample size needed for our primary outcome, moreover, most of these women should have delivered by now, and we anticipate to get more information that was not available at the time this paper was considered for publication.

Further studies addressing short- and long-term complications are crucial to provide both the physician and the patient with knowledge regarding vaccination against COVID-19 during pregnancy.

## 6. Conclusion

mRNA vaccine during pregnancy seems not to increase the rate of pregnancy complications and is effective in prevention of COVID-19 infection.

## 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.

## References

- [1] A Novel Coronavirus from Patients with Pneumonia in China, 2019 | Enhanced Reader [Internet]. [cited 2021 Feb 22]. Available from: <chrome-extension://dagcmkpagilhakfdhnbomgmjdpkdklff/enhanced-reader.html?openApp&pdf=https%3A%2F%2Fwww.nejm.org%2Fdoi%2Fpdf%2F10.1056%2FNEJMoa2001017%3FarticleTools%3Dtrue>.
- [2] WHO announces COVID-19 outbreak a pandemic. 2020 Mar 12 [cited 2021 Feb 22]; Available from: <https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic>.
- [3] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review [Internet]. Vol. 324, JAMA - Journal of the American Medical Association. American Medical Association; 2020 [cited 2021 Feb 22]. p. 782–93. Available from: <https://jamanetwork.com/>.
- [4] Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis. *BMJ* [Internet]. 2020 Sep 1 [cited 2021 Feb 22];370. Available from: <https://pmc/articles/PMC7459193/>.
- [5] Wang C-L, Liu Y-Y, Wu C-H, Wang C-Y, Wang C-H, Long C-Y. Impact of COVID-19 on Pregnancy. *Int J Med Sci* [Internet]. 2021 [cited 2021 Feb 22];2021(3):763–7. Available from: <http://www.medsci.org//creativecommons.org/licenses/by/4.0/>.
- [6] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* [Internet]. 2020 Dec 31 [cited 2021 Feb 22];383(27):2603–15. Available from: <https://pmc/articles/PMC7745181/>.
- [7] Walsh EE, Frenck RW, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *N Engl J Med* [Internet]. 2020 Dec 17 [cited 2021 Feb 22];383(25):2439–50. Available from: <https://pmc/articles/PMC7583697/>.
- [8] Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. *Nature* [Internet]. 2020 Oct 22 [cited 2021 Feb 22];586(7830):589–93. Available from: <https://doi.org/10.1038/s41586-020-2639-4>.
- [9] Cylus J, Panteli D, van Ginneken E. Who should be vaccinated first? Comparing vaccine prioritization strategies in Israel and European countries using the Covid-19 Health System Response Monitor. *Isr J Health Policy Res* [Internet]. 2021 Feb 19 [cited 2021 Feb 22];10(1):16. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/33608023>.
- [10] Dana A, Buchanan KM, Goss MA, Seminack MM, Shields KE, Korn S, et al. Pregnancy outcomes from the pregnancy registry of a human papillomavirus type6/11/16/18 vaccine. *Obstet Gynecol* [Internet]. 2009 Dec [cited 2021 Mar 6];114(6):1170–8. Available from: <https://pubmed-ncbi-nlm-nih-gov.bzion-ez.medtcp.tau.ac.il/19935016/>.
- [11] Bukowinski AT, Hall C, Chang RN, Gumbs GR, Marie A, Conlin S. Maternal and infant outcomes following exposure to quadrivalent human papillomavirus vaccine during pregnancy. [cited 2021 Mar 6]; Available from: <https://doi.org/10.1016/j.vaccine.2020.06.073>.
- [12] Chambers CD, Johnson D, Xu R, Luo Y, Louik C, Mitchell AA, et al. Risks and safety of pandemic h1n1 influenza vaccine in pregnancy: Birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants. *Vaccine* [Internet]. 2013 [cited 2021 Mar 6];31:5026–32. Available from: <http://dx.doi.org/10.1016/j.vaccine.2013.08.097>.