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Spontaneous Abortions and Policies on COVID-19 mRNA Vaccine Use During Pregnancy

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Abstract

The use of mRNA vaccines in pregnancy is now generally considered safe for protection against COVID-19 in countries such as New Zealand, USA, and Australia. However, the influential CDC-sponsored article by Shimabukuro et al. (2021) used to support this idea, on closer inspection, provides little assurance, particularly for those exposed in early pregnancy. The study presents falsely reassuring statistics related to the risk of spontaneous abortion in early pregnancy, since the majority of women in the calculation were exposed to the mRNA product after the outcome period was defined (20 weeks' gestation).

In this article, we draw attention to these errors and recalculate the risk of this outcome based on the cohort that was exposed to the vaccine before 20 weeks' gestation. Our re-analysis indicates a cumulative incidence of spontaneous abortion 7 to 8 times higher than the original authors' results ($p < 0.001$) and the typical average for pregnancy loss during this time period. In light of these findings, key policy decisions have been made using unreliable and questionable data. We conclude that the claims made using these data on the safety of exposure of women in early pregnancy to mRNA-based vaccines to prevent COVID-19 are unwarranted and recommend that those policy decisions be revisited.

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Keywords
COVID-19; Pregnancy; Adverse Events; Spontaneous Abortion

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1 Introduction

The use of mRNA vaccines in pregnancy are reported as being safe for pregnant women and their unborn child(ren) for protection against COVID-19, in countries such as New Zealand,[1] USA,[2] and Australia.[3] However, the article by Shimabukuro et al. (2021)[4] used to support this idea, on closer inspection, provides little assurance, particularly for women exposed in early pregnancy. Here, we outline these concerns and question the unrestricted use of these vaccines in pregnant women.

2 Exploration and discussion of the study used to inform current recommendations

The authors analyzed the v-safe registry data from 14 December 2020 to 28 February 2021 (an 11-week span), which included 827 pregnancies (of 3,958 enrolled) for which there was a recorded outcome. Data was collected from three U.S. vaccine safety monitoring systems: the v-safe after-vaccination health checker, the v-safe registry, and the Vaccine Adverse Event Reporting System (VAERS). The Centers for Disease Control and Prevention's (CDC) v-safe registry is a new CDC smartphone-based active surveillance system developed for the COVID-19 vaccination program, which sends text messages to participants to prompt them to complete an online survey to assess their health status and encourage reporting of adverse reactions post-vaccination until 12 months after the final dose. The authors concluded that there were no obvious safety signals precluding mRNA vaccine use in pregnancy. This was further justified with reference to a cumulative incidence of spontaneous abortion of 12.6% (104/827) that was considered similar to historic studies; however, Shimabukuro and colleagues correctly acknowledge that "the proportion of pregnant persons who reported spontaneous abortion may not reflect [the] true post-vaccination proportions because participants might have been vaccinated after the period of greatest risk in the first trimester, and very early pregnancy losses might not be recognized".[4]

However, closer inspection of the 827 women in the denominator of this calculation reveals that between 700 to 713 women were exposed to the vaccine after the timeframe for recording the outcome had elapsed (up to 20 weeks of pregnancy). Hence, a re-analysis of these figures indicates a cumulative incidence of spontaneous abortion ranging from 82% (104/127) to 91% (104/114), 7–8 times higher than the original authors' results.

Using information from the article, we derived the periods of pregnancy in which women were first exposed to the vaccine, and hence approximate counts of women who were at risk of spontaneous abortion after receiving the mRNA product: those exposed before 20 weeks' gestation. Live births occurred in 712 women (724 infants, including 12 multiples), with 700 (98.3%) first exposed to the vaccine in the third trimester, and only 12 women exposed before 26 weeks' gestation. Although many more women in the study were vaccinated before 20 weeks, the outcomes of their pregnancies were largely not available and could not have resulted in a livebirth within the study timeframe. The available results of this cohort only captured outcomes in ~8% (96/1,132) and ~0.8% (14/1,714) of women in the first and second trimesters, respectively.

Figure 1. Comparison of the exposure and outcome cohorts used by Shimabukuro et al. (2021).[4] Four cohorts of exposure were reported: periconception (30 days before last menstrual period though 14 days after), first trimester (conception to 14 weeks), second trimester (14 to 28 weeks), and third trimester (from 28 weeks until birth). Two cohorts of outcomes reported: first mRNA vaccine received before 20 weeks; and first mRNA received from 20 weeks' gestation. The infant was followed for 28 days during the perinatal period (birth–28 days).

Exposure Cohorts			
Periconception	Trimester 1 (< 14 wk)	Trimester 2 (≥ 14 and < 28 wk)	Trimester 3 (≥ 28 wk)

Outcome Cohorts		
First mRNA Exposure < 20 weeks	First mRNA Exposure ≥ 20 weeks	Infant (Birth - 28 days)

To compound the confusion, several overlapping periods of exposure and outcome were reported and used to define cohorts of women. Exposure to the vaccine was defined by trimester (periconception, first, second, and third). Outcomes were defined as women first exposed to the mRNA vaccine before 20 weeks' gestation; and first exposed from 20 weeks' gestation. The infant was followed for 28 days during the perinatal period (birth–28 days) (Figure 1).

Ranges are provided in these analyses as the total number of women whose mRNA injections occurred before, or after, 20 weeks' gestation were not specified in the article. From the information provided in the text and tables, we understand that:

1. At least 114 women were first exposed before 20 weeks (reported as pregnancy losses):
   a. Of which, 96 were in the first trimester: conception up to 14 weeks' gestation;
   b. The remaining 18 pregnant women must have been exposed in the first part of the second trimester: 14 weeks' to 20 weeks' gestation.
2. During the third trimester (from 28 weeks' gestation until birth), 700 pregnant women were reported to have been first exposed to mRNA injections.
3. The remaining 13 women exposed during the second trimester (from 14 up to 28 weeks' gestation) cannot be further classified as first exposed to mRNA before or after the 20-week cut-off for defining the type of pregnancy loss (spontaneous abortion or stillbirth), and therefore a range is reported to reflect this uncertainty.

The sweeping conclusions of safety that Shimabukuro et al. (2021)[4] make are not convincing, given their study's limitations. These include:

1. Study design issues include:
   a. No unexposed pregnancies were used;
   b. 94% of the cohort were healthcare workers;
   c. Less than 15% of pregnant women in the v-safe registry were also enrolled in the pregnancy registry.
2. For pregnancy loss in the first 20 weeks, an incorrect denominator was used in calculating the cumulative incidence. Their calculation included cohorts that were first exposed to the injection after the outcome was defined (spontaneous abortion). This point was discussed by McCullough and colleagues.[5]

3. The authors did not disclose essential descriptive statistics required to critique their recommendations, such as:
   a. Number of live births for women whose first mRNA vaccinations occurred before and after 20 weeks' gestation;
   b. The total number of pregnancies in these groups.
4. Exposure and outcomes were provided using two measures of gestation that are not interchangeable: trimester (first, second, third) and gestation (either less than 20 weeks, or 20 weeks or more) (Figure 1).
5. The timing of the first and second mRNA vaccinations was absent, with no indication of outcome. Additionally, no analysis was provided to determine if the pregnancy outcome differed by exposure to the type of product, either: Pfizer/BioNTech's BNT162b2 or Moderna's mRNA-1273.
6. The inclusion or exclusion of adverse events that occurred within 14 days of exposure was not specified.
7. A high baseline rate of 26% was used for the historical comparison of spontaneous abortion risk, an estimate that includes clinically unrecognized pregnancies and differs substantially from the definition used in this study (clinically recognized pregnancies).[5] Comparable estimates of clinically recognized pregnancies, range from 8% to 15%.[6–8] Here, we use a clinically recognized spontaneous abortion rate of 11.3% (from a study carried out in Manitoba on n = 79,978 women).[7]
8. Possible underestimation of spontaneous abortion. Spontaneous abortions were the most frequently reported pregnancy-related adverse event; however, voluntary reporting systems are notoriously delayed. The VAERS reports through to February 28, 2021 used in this article appear to be based on the date the reports were received rather than the event date and are likely to be underreported.

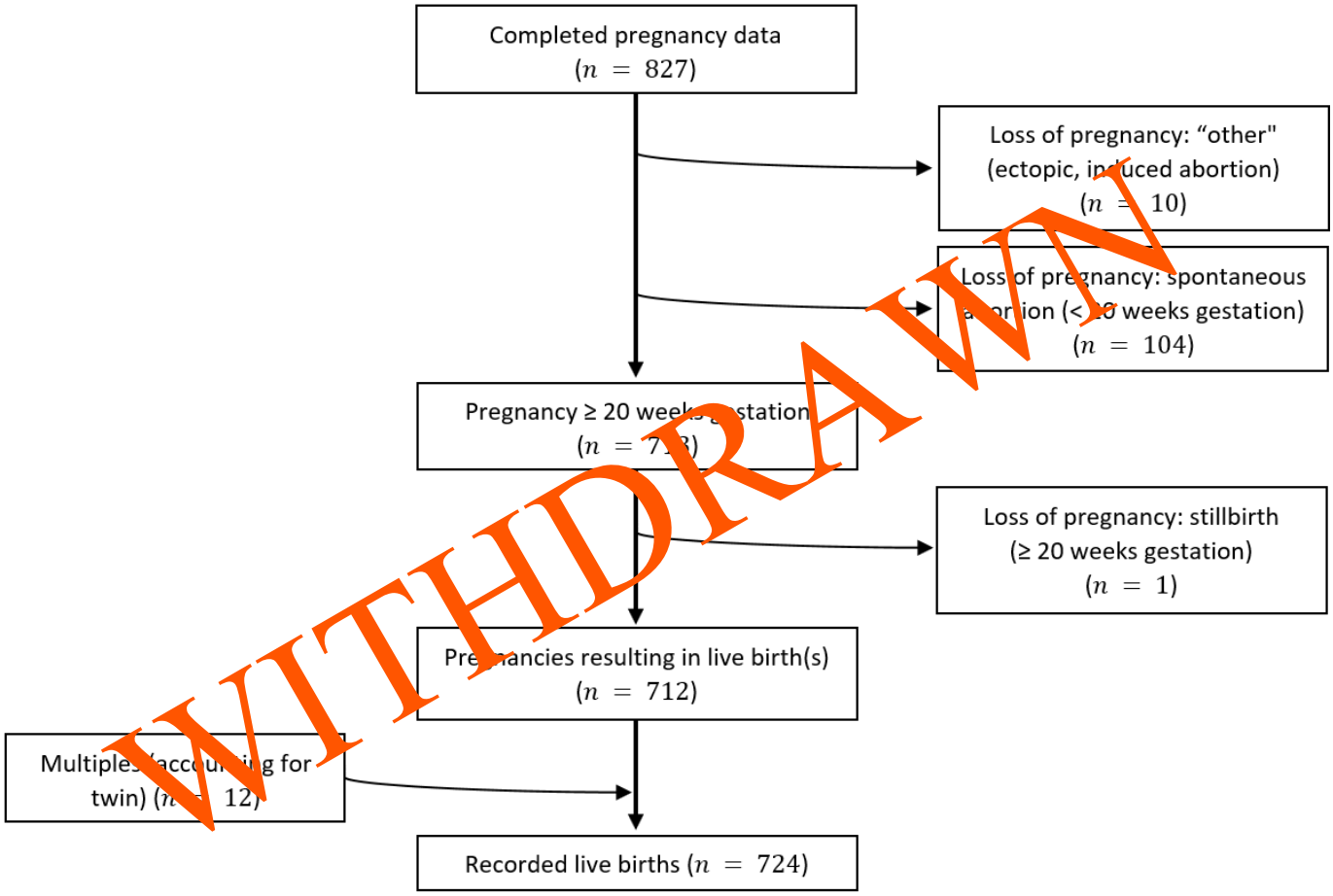
A closer look at the data

Despite the study's limitations, some information can be derived that was not presented by the authors. A flow diagram (Figure 2) illustrates the outcomes of 827 pregnant women in the study, which resulted in 714 live births (including 12 multiples). Using Figure 2, the total numbers in each exposure group can be estimated with some uncertainty (ranges provided; see Table 1). The lack of follow up in the first outcome cohort creates uncertainty in the statistics presented in the original article.[4] However, by combining Table 1 with Table 4 of the original manuscript,[4] we investigated the nature of the association between mRNA vaccine use in pregnancy and pregnancy outcome (Table 2) by cohort.

The study indicates that at least 81.9% (≥ 104/127) experienced spontaneous abortion following mRNA exposure before 20 weeks, and 92.3% (96/104) of spontaneous abortions occurred before 13 weeks' gestation (Table 4, footnotes).[4] This is a very high proportion of pregnancy loss observed in those exposed to the mRNA vaccination before 20 weeks' gestation, ranging from 81.9–91.2% (n = 114–127), which is significantly different to baseline estimates from other studies (11.3%, n = 79,978 [6]; $p < 0.001$), being 7- to 8-fold higher than expected ($p < 0.001$). The authors' interpretation of no difference in the observed incidence of pregnancy loss in those who received their first mRNA vaccine before 20 weeks' gestation compared to baseline must be questioned.

At face value, the study presented indicates that exposure to mRNA vaccination in the third trimester is safe and supported by another study exploring exposure from 29 weeks.[9] However, as highlighted by McCullough and colleagues,[5]

Figure 2. Flow diagram of the outcomes of the 827 pregnant women who received mRNA vaccines, resulting in 724 live births.



12.6% of this group reported 'Grade 3' adverse events (i.e. severe or medically significant but not immediately life-threatening)[10] and 8% reported a temperature above 38°C after the second mRNA dose (which can induce miscarriage or premature labor). The study follow-up concluded 28 days after birth, with long-term effects of prenatal exposure to infants unknown. Other studies of mRNA safety prior to the third trimester are limited by design, such as: the timeline of exposure to the mRNA vaccine was not provided;[11] and women that experienced pregnancy loss between the first and second dose were excluded.[12]

Correction to Shimabukuro et al. article

Following the submission of this article, a correction was published to the study in question.[13] The authors correctly state that "No denominator was available to calculate a risk estimate for spontaneous abortions, because at the time of this report, follow-up through 20 weeks was not yet available for 905 of the 1224 participants vaccinated within 30 days before the first day of the last menstrual period or in the first trimester. Furthermore, any risk estimate would need to account for gestational week–specific risk of spontaneous abortion." Table 4 was updated to reflect this correction. However, the article's

abstract, results and discussion continue to state and discuss the initial findings of the study, including the 12.6% spontaneous abortion rate observed in those exposed to mRNA before 20 weeks being within background ranges, rather than being updated to account for the correction. This produces a discontinuity between the corrected results table and the text. The authors continue to stand by their statement that there are no safety signals for use of the mRNA products in pregnancy.

3 Further discussion

As discussed by Shimabukuro et al., the morbidity and mortality of COVID-19 disease in pregnancy is reported to be increased and, therefore, used to justify the current international recommendations for the widespread use of mRNA vaccines in pregnancy, since pregnant women were excluded from the initial vaccine trials.[14] However, in two recent studies this increased risk was not observed;[15,16] rather, they observed that the rate of critical care unit admission and mortality in pregnancy was comparable to those rates among the general population of the same cohort;[15] and in-hospital mortality in pregnant women was lower than non-pregnant patients hospitalized with COVID-19 and viral pneumonia.[16]

The biological pathway underlying these epidemiological findings has been elucidated. Researchers have found that SARS-CoV-2 enters and fuses with the host cell via angiotensin-converting enzyme-2 (ACE-2) receptors, and the spike (S) protein S2 subunit using the heptad-repeat domains, HR1 and HR2.[13,14] Pfizer/BioNTech's BNT162b2 and Moderna's mRNA-1273 vaccines encode this spike (S) protein, which is designed to be delivered into the human cell and translated.[19] The coagulopathy induced by SARS-CoV-2 was investigated in hACE-2 competent mice by Zhang and colleagues[20] and in vitro by Grobbelaar and colleagues.[21] The binding of SARS-CoV-2 spike (S) protein to hACE-2 competent mice was identified. Administration of SARS-CoV-2 and spike (S) protein resulted in the stimulation of platelets to release coagulation factors, secretion of inflammatory factors and formation of leukocyte-platelet aggregates in hACE-2 transgenic mice.[20] In vivo, the circulation of spike (S) protein of COVID-19 patients contributes to hyper-coagulation. In the presence of the spike (S1) protein alone, findings indicate that healthy blood flow may be interfered with through major ultrastructural changes in whole blood (platelet hyperactivation noted in vitro).[21]

A pre-eclampsia-like syndrome was observed in five of 42 pregnant women infected with COVID-19, and was coupled with severe pneumonia in a prospective observational study.[22] Given the relationship between spike (S) protein encoded by mRNA vaccines and SARS-CoV-2 virus, we suggest there could be a biological mechanism for pre-eclampsia-like syndrome in vaccinated women.

Given pregnant women were excluded from the initial clinical trials, the possible impact on mRNA vaccines on the fetus and reproductive capacity of women were informed using animal studies (female rats). The Pfizer-BioNTech study of rats was reported to indicate no issues in fertility of the exposed animals or their pups. However, more careful scrutiny of the study indicates an increase (approximately 2 times) of pre-implantation loss (9.77% compared to 4.09% in the control group), but findings were reported to be within historical control data ranges (5.1–11.5%). There was additionally a low incidence of gastroschisis, mouth/jaw malformations, right-sided aortic arch and cervical vertebrae abnormalities in fetuses, once again reported to be within the range of historical control data. The study did not assess placental transfer of BNT162b2 mRNA.[23] Likewise, the Moderna studies indicated no harmful effects in pregnancy, embryo/fetal development, parturition or post-natal development in studies

carried out in rats.[24] The rodent studies and information on those who found themselves pregnant during the original clinical trials were relied on by clinicians to confer safety in pregnancy and breastfeeding, in combination with the belief that there were no biologically plausible reasons that mRNA technology would be harmful.[14]

Concerns for the effect of mRNA vaccinations in pregnancy and during breastfeeding include, but are not limited to, the following issues.

Transmission of mRNA and spike protein

The transmission of mRNA and spike protein across the placenta and through breast milk is of concern, given the unknown effect on development in utero or on a breastfeeding infant. There were no mRNA spike-encoding region amplifications detected in aqueous or liquid breast milk fractions 0–7 days post-vaccination (n=5) in a study carried out by Mattar et al. in 15 pregnant women and five breast-feeding women who received one Pfizer-BioNTech (BNT162B2) mRNA vaccination.[25] However, the presence of spike protein itself was not tested for. The authors of this study urge caution, given the small sample sizes and study duration of only one week post-exposure. In contrast to this study, voluntary reporting systems such as VAERS have received numerous reports of thrombotic thrombocytopenic purpura (TTP), gastrointestinal upset, rash, anaphylactic reaction and death (for example, VAERS ID26: 1166062; 927664; 939409; 954010; 1166062; 1224688; 1254975; 1272428; 1343886; 1395088; 1415059; 1445743; 1031318; 1113464; 1182232) following exposure to breastmilk of a recently vaccinated mother.

Inhibition of Syncytin-1

Other mechanisms which may be disrupted by the injection include syncytin-1 (syn1), a fusogenic protein of retroviral origin, essential for cell fusion and placental development.[27] Studies are required to determine if mRNA encoded spike (S) protein HR1 (or HR1a28) or HR2 has the ability to inadvertently inhibit syn1, preventing the cell fusion required for placental attachment, resulting in pregnancy loss. The rodent studies carried out by Pfizer and Moderna to determine if there could be an impact on fertility and development may need to be repeated in Old World primates, such as macaques, as they have similar syn1 and syn2 proteins to humans, whereas rats do not. The presence of autoantibodies to syn1 was investigated by Mattar et al. and although a change from baseline of autoantibodies to syn1 occurred in all 15 pregnant women exposed to the first dose of the Pfizer-BioNTech product, the change was not deemed high enough to be considered biologically significant.[25] Given the small sample size, these findings may indicate that further investigation is required. Further, an altered syn1 expression is associated with pre-eclampsia, hemolysis, elevated liver enzymes and low platelets syndrome, intrauterine growth restriction and gestational diabetes mellitus in observational studies.[29–31]

Synctyin-1 is also required for gamete fusion (syn1 and ACET2 receptors present in sperm [32] and oocytes [33]) and, additionally, found in the testes34 and ovaries.[33,35] In the Comirnaty (Pfizer/BioNTech mRNA vaccine) Package Insert submitted to the Food and Drug Administration (FDA), the manufacturers state that potential impairment of male fertility has not been evaluated (page 15).[36] A single-center prospective study was carried out on the impact of mRNA vaccination on sperm number and motility in 45 men prior to mRNA vaccination exposure (following 2–7 days abstinence), and again 70 days post-exposure to the second vaccination. No significant negative impacts on sperm parameters were reported; however, the study did not assess the fusogenic potential (syn1 is in the acrosome of the sperm head) or synctyin antibody levels in this cohort and is recommended for further research.[37]

4 Conclusion

We question the conclusions of the Shimabukuro et al.[4] study to support the use of the mRNA vaccine in early pregnancy, which has now been hastily incorporated into many international guidelines for vaccine use, including in New Zealand.[1] The assumption that exposure in the third trimester cohort is representative of the effect of exposure throughout pregnancy is questionable and ignores past experience with drugs such as thalidomide.[38] Evidence of safety of the product when used in the first and second trimesters cannot be established until these cohorts have been followed to at least the perinatal period or long-term safety determined for any of the babies born to mothers inoculated during pregnancy. Additionally, the product's manufacturer, Pfizer, contradicts these assurances, stating: "available data on Comirnaty administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy", and "it is not known whether Comirnaty is excreted in human milk" as "data are not available to assess the effects of Comirnaty on the breastfed infant" (page 14).[39]

Due to the nature of the mRNA vaccine roll-out, healthcare providers need to report any issues in pregnancy to further determine the safety of this product. Caution should be exercised in the administration of vaccines in pregnancy, as indicated by the possible association between the exposure to influenza vaccines containing H1N1pdm09 (2010–11 and 2011–12) and spontaneous abortion.[40] Considering the evidence presented here, we suggest the **immediate withdrawal of mRNA vaccine use in pregnancy (Category X)[41] and those breastfeeding, alongside the withdrawal of mRNA vaccines to children or those of child-bearing age in the general population**, until more convincing data relating to the safety and long-term impacts on fertility, pregnancy and reproduction are established in these groups.

5 Editor's notes

Editor's Note 1: This report was peer-reviewed by reviewers not affiliated with the authors. The process was single-blinded (the authors do not know who the reviewers are).

Editor's Note 2: On June 24, 2021, Dr. Shimabukuro also presented data from the Vaccine Safety Datalink to the US Advisory Committee on Immunization Practices (ACIP) and concluded that the system captured no (zero) serious adverse events or deaths that could be attributed to the COVID-19 vaccine. On June 10, 2021, Dr. Shimabukuro reported no increased risk of myocarditis using data from the VSD to the Vaccines and Related Biological Products Advisory Committee (VRBPAC). Soon after these presentations, US FDA issued an advisory on the risk of myocarditis and pericarditis from the Pfizer/Biontech Bnt162b2/Comirnaty vaccine. The information present to ACIP was critical in their decision on vaccine recommendations. I have addressed the absence of and failure of "pharmacovigilance" in a recent Editorial in this journal.

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8 Supplementary tables

Table 1. Estimating the total numbers in each group for exposure (gestation when first mRNA vaccine received) and outcome (loss of pregnancy, live birth); using information reported in the article by Shimabukuro et al. (2021).[4] Ranges for unknown values provided.

Gestation	Loss of pregnancy: Other (ectopic, induced abortion)	Loss of pregnancy: Spontaneous abortion / stillbirth	Pregnancies resulting in live birth(s)	Total
< 20 weeks	10	104	0 – 3	114 – 127
≥ 20 weeks	0	1	699 – 712	700† – 713
Total	10	105	712	827

† 700 reported in Table 4 (footnotes) from Shimabukuro et al. (2021)[4] to have received their first mRNA dose in the third trimester.

Table 2. Examining the association between the gestation (weeks) pregnant women were first exposed to mRNA vaccine and pregnancy outcome, using (i) cumulative incidence, (ii) difference in the cumulative incidence observed versus published estimates (expected), and (iii) the risk ratio of pregnancy loss in the mRNA vaccinated group, compared to historic studies of women who did not receive the mRNA vaccine (published incidence).

Gestation	Pregnancies resulting in live birth(s) (count)[a]	Published incidence of pregnancy loss (%)	Cumulative incidence of pregnancy loss[b] (%) (95% CI)	Difference in cumulative incidence (95% CI, sig.)	Risk Ratio (RR) (95% CI, sig.)
< 20 weeks	0	11.3 [c]	104/114 (91.2%) (84.1, 95.5)	0.799 (0.743, 0.856) [d]	8.07 (7.60, 8.57) [d]
	13	11.3 [c]	104/127 (81.9%) (73.9, 87.9)	0.706 (0.635, 0.777) [d]	7.25 (6.66, 7.88) [d]
≥ 20 weeks	699	< 1	1/699 (0.1%)	within range [e]	-
	712	< 1	1/712 (0.1%)	within range [e]	-

All analysis carried out in R 4.1.0, using the epiR package.

a First exposure to mRNA of 13 pregnancies vaccinated in the second trimester (from 14 up to 28 weeks gestation) were unable to be further categorized by exposure before or after 20 weeks gestation, as required for pregnancy loss definition: spontaneous abortion (< 20 weeks gestation) and stillbirth (≥ 20 weeks gestation); therefore, a range has been provided (as defined in Table 1).

b Excluding pregnancy loss as a result of other (ectopic, induced abortion; n = 10).

c Baseline of clinically recognized spontaneous abortion set to 11.3% based on a study carried out in Manitoba, Canada on n=79,978 women.[7]

d indicates a statistically significant relationship (sig. < 0.001) in the observed loss of pregnancy when mRNA was received <20 weeks gestation (observed) when compared to the published incidence (expected).

e 700 received their first mRNA dose in the third trimester, with no indication of the time to delivery post-exposure.