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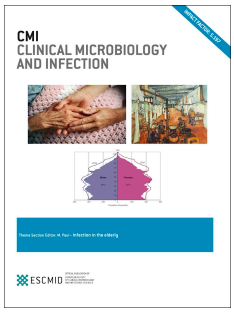

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Risk of congenital malformation following first trimester mRNA COVID-19 vaccine exposure in pregnancy: the COVI-PREG prospective cohort

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ABSTRACT:

OBJECTIVES

This study aimed to evaluate the risk of congenital malformation among pregnant women exposed to the mRNA COVID-19 vaccines during the first trimester of pregnancy, which is a developmental period where the fetus is at risk of teratogenicity.

METHODS

Pregnant women were prospectively enrolled from March 2021 to March 2022, at the time of COVID-19 vaccination. Pregnant women exposed to at least one dose of mRNA COVID-19 vaccine from conception to 11 weeks of gestations and 6 days were compared to pregnant women exposed to the vaccine from 12 weeks to the end of pregnancy. The primary outcome was a confirmed congenital malformation at birth.

RESULTS

A total of 1450 pregnant women were enrolled including 124 in the first trimester and 1326 in the second and third trimester. The overall proportion of congenital malformation was 0.81% (n=1/124; 95%CI 0.02-4.41) and 0.83% (n=11/1326; 95% CI 0.41-1.48) among pregnant exposed to the COVID-19 vaccine during the first and second/third trimester, respectively. First trimester exposure was not associated with a higher risk of congenital malformation with a relative risk (RR) of 0.89 (95%CI 0.12-6.80) with no significant changes after adjustment through exploratory analysis.

CONCLUSION

Pregnant women exposed to mRNA COVID-19 vaccine before 12 weeks of gestation did not have an increased risk of congenital malformation compared to women exposed outside the teratogenic window. As vaccination is safe and effective, emphasis must be placed on promoting vaccination during pregnancy.

KEYWORDS: COVID-19; Vaccine; Congenital anomaly; Teratogenicity; Pregnancy; Pregnant women; SARS-CoV-2

Words count:
- Abstract: 236
- Main text: 2698

Tables: 3

INTRODUCTION

COVID-19 vaccines have been accessible since December 2020.(1,2) Since SARS-CoV-2 has been responsible for millions of deaths worldwide in the general population, the development of a vaccine represented a promising approach to preventing COVID-19 severe complications.

Pregnant women who tested positive for SARS-CoV-2 are at increased risk of severe disease as well as pregnancy and neonatal adverse outcomes.(3–6) Pregnant women, however, were excluded from clinical trials evaluating the efficacy and safety of COVID-19 vaccines, and the recommendations for vaccination during pregnancy came well after the general population.(7) Swiss authorities recommended vaccination to pregnant women with comorbidities at risk of severe COVID-19 in March 2021 and extended it to all pregnant women in September 2021.(8) French authorities recommended vaccination to all pregnant women in April 2021.(9) Despite an ongoing low vaccination uptake among pregnant women, COVID-19 vaccination has been reported to be effective for severe disease and death in pregnant women.(10,11) The first safety data on COVID-19 vaccines in June 2021, did not indicate any alarming signals,(12) and more recent studies have reported no risk of adverse maternal, pregnancy, or neonatal outcomes after COVID-19 vaccine exposure.(13–16) Multiple studies have assessed neonatal outcomes after COVID-19 vaccine during pregnancy, including congenital anomalies. However, studies investigating the risk for congenital anomalies after exposure during the 1st trimester of pregnancy, which represents the exposure period with the highest risk of teratogenicity, are lacking. (12,17,18)

Ruderman et al assessed the risk of teratogenicity in pregnant women exposed to mRNA COVID-19 vaccine in the first trimester of pregnancy. No difference was reported when compared patients exposed from 30 days prior to the pregnancy to 14 weeks of gestation (weeks), to a group composed of both unvaccinated pregnant women and pregnant women vaccinated after 14 weeks.(19) Another study by Calvert et al reported a study assessing the risk of malformation in pregnant women exposed from 6 weeks before conception to 19 weeks and 6 days (19^{+6}). They found no association with congenital anomalies when comparing to unvaccinated patients.(20) Further studies are necessary to increase the level of available evidence.

We aimed to assess the risk of congenital malformations among pregnant women exposed to at least one dose of mRNA COVID-19 vaccine from conception to 11^{+6} weeks, compared to those exposed from 12 weeks to the end of pregnancy. We also aimed to describe the pregnancy outcomes in both groups.

METHODS

Study design and settings

This prospective cohort study included pregnant women registered from March 2021 to March 2022 in France and Switzerland, using the COVI-PREG registry.(21) The registry was developed to assess the impact of SARS-CoV-2 infection and COVID-19 vaccine in pregnant women. Collaborators participating in the study were hospitals or private practitioners with antenatal clinics able to enrol pregnant women at the time of or just prior to COVID-19 vaccine injection. Oral and written consents were obtained from participants. The Swiss Ethical Board (CER-VD-2020-00548) approved the study and French data was registered with the French National Data Protection Commission (CNIL - authorization 2217464).

Data collection

Pregnant women exposed to an mRNA vaccine injection during pregnancy were included at the time of vaccine injection. Local investigators of participating centres who enrolled patients completed forms at 2 time-points: i) patient's baseline characteristics, medical/obstetrical history, and vaccine exposure were collected at time of inclusion; ii) pregnancy outcomes including congenital malformations diagnosed via ultrasonography and confirmed at birth or diagnosed after birth (up to 5 days after birth) were recorded utilizing the maternal hospital discharge letters. Patient data were extracted from electronic medical records and stored using the REDCap (Research Electronic Data Capture) system.

Participants

Women who received at least one dose of mRNA COVID-19 vaccine during pregnancy were eligible for the study, regardless of whether they had previously received an injection before the current pregnancy. Only patients who reached a theoretical term of 42 weeks at the time of data extraction included. Patients without a known pregnancy outcome were excluded. Women who were under the legal age of 18 years and/or who were not able to consent were not included.

Exposure to COVID-19 vaccine and study group

Exposure group

Women who had at least one dose of an mRNA COVID-19 vaccine from conception (266 days before term date, set at 40 weeks) to 11^{+6} weeks were defined as exposed during the period at potential risk of teratogenic effect. This exposure window corresponds to the etiologically relevant period to study congenital malformations, also known as the "highly sensitive period of action of teratogens". (22)

Reference group

Participants exposed to the vaccine from 12 weeks to the end of pregnancy were considered as our reference group. Exposure outside of organogenesis is not considered as an etiologically relevant period to study congenital malformations.

The gestational age (GA) was calculated differently in Switzerland and in France and based either on the last menstrual period (LMP) or embryo's crown-rump-length (CRL) at the first trimester ultrasound. In Switzerland, it is recommended to perform a first trimester ultrasound examination between 11 weeks and 0 day and 13^{+6} weeks. If the theoretical CRL corresponding to the patient reported LMP differed of more than five days compared to the measured CRL by ultrasound, the GA was set based on the CRL measured by ultrasound. If the difference was less than five days, GA was based on patient reported LMP. In France, it is recommended to perform a first trimester ultrasound examination during the same gestational weeks and the CRL measured by ultrasound was systematically used to set the estimated due date based directly on the crown-rump length.

Exposure information was collected including the type of COVID-19 vaccine (i.e., BNT162b2 or mRNA-1273) and vaccination pattern (i.e., number of doses of vaccine). In the case of multiple injections during the pregnancy, the GA at first injection during pregnancy was used to designate the exposure group for each participant.

Primary outcome – Congenital malformations

Congenital malformation was defined as at least one birth defect either diagnosed at birth, or diagnosed prenatally via ultrasound and confirmed at birth. Observed malformations were classified as either genetic, major or minor in accordance with EUROCAT definitions.(23) Malformation of genetic origin was defined as a separate group according to the EUROCAT classification. Two independent experts (MCA & DB) classified birth defects as major, minor, or genetic using the same EUROCAT guidelines. In cases of discordant classification, consensus was achieved through discussion. International Classification of Disease 10^{th} version (ICD-10) codes were used to describe individual congenital malformations.(24)

Secondary outcomes

Pregnancy outcomes

Pregnancy outcomes were defined as a livebirth (≥24 weeks), stillbirth (fetal demise ≥20 weeks), late spontaneous abortion (delivery from 14 to 23^{+6} weeks), early spontaneous abortion (<14 weeks), and termination of pregnancy (TOP), including TOP for fetal anomaly (TOPFA).

Covariates

Patient baseline characteristics were collected: maternal age (categorized into ≤ 25 years (y), 26-30 y, 31-35y, 36-40 y, and > 40 y), country of residence, medical history, addiction during pregnancy and obstetrical history including congenital malformation in a previous pregnancy. Obstetrical outcomes for the current pregnancy were also captured: pregnancy infections, obstetric complications, mode of delivery, and GA at delivery.

Statistical analysis

Descriptive statistics were performed to assess the baseline characteristics, exposures, and the outcomes of interest. Proportions were reported with their 95%CI. To evaluate the association between first trimester exposure and congenital malformation, we performed a univariate generalized linear regression model to estimate Risk Ratios (RR) with 95%CI. Giving the number of co-variates that could be imbalanced between groups and the small number of events expected in each group, a multivariate generalized linear regression analysis was performed, as an exploratory analysis. The model was then adjusted for all unbalanced baseline characteristics, defined as a standardized difference of more than 10% between groups. The univariate and multivariate models were formed to compare the proportions of infants/fetuses with any major or minor malformation; those with genetic anomalies were excluded. Statistical analyses were performed using Stata (StataCorp. 2015. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

RESULTS

A total of 1452 pregnant women were eligible to the study and two patients vaccinated after the first trimester of pregnancy were excluded due to unknown pregnancy outcome status. Among the 1450 remaining patients, 124 were exposed to a mRNA vaccine during the first trimester of pregnancy and 1326 during the second and third trimesters of pregnancy (reference group). Baseline characteristics are presented in Table 1. The groups were unbalanced for maternal drug use, multiparity, history of pulmonary disease, pre-existing diabetes, renal and a history of fetal malformation (Table 1)

Congenital malformations

The proportion of any major or minor congenital malformation overall was 0.81% (n=1/124; 95%CI 0.02-4.41) among the offspring of pregnant women exposed to the COVID-19 vaccine during the first trimester, and 0.83% (n=11/1326; 95%CI 0.41-1.48) among the offspring of pregnant women exposed to the COVID-19 vaccine during the second and third trimesters. First trimester exposure was not associated with a higher risk of congenital malformation with a RR of 0.89 (95%CI 0.12-6.80).

Considering our exploratory analysis, the multivariate model adjusted for all potential confounders imbalanced between groups resulted in an adjusted RR of 1.01 (95%CI 0.13-7.73) (Table 2).

Classification of major, minor congenital malformations, and genetic malformations are presented in Table 2. The list of major and minor malformations is reported in Table 3.

Pregnancy outcomes

Pregnancies resulted in livebirths for 97.58% (95%CI 93.09-99.50; n=121/124) of patients exposed in the first trimester, and 99.77% (95%CI 99.34-99.95; n=1323/1326) in patients exposed in the second and third trimester of pregnancy.

Among women exposed during the first trimester, two (1.61%; 95%CI 0.20-5.70; n=2/124) early spontaneous abortions were reported at 8 weeks after a first dose of vaccine during the first and second week following conception, respectively. In the same exposure group, one participant (0.81%; 95%CI 0.02-4.41; n=1/124)), who was vaccinated in the week following conception, had a late spontaneous abortion that occurred at 16 weeks in a context of chorioamnionitis.

Among women exposed from 12 weeks of pregnancy, two (0.15%; 95%CI 0.02-0.54; n=2/1326) had a late spontaneous abortion at 14 and 16 weeks following vaccination at 12 and 13 weeks respectively with no reported cause for the first and in the context of chorioamnionitis for the second. One (0.08%; 95%CI 0.00-0.42; n=1/1326) woman vaccinated at 14 weeks, reported a stillbirth at term.

DISCUSSION

This study reports no increased risk of congenital malformation among pregnant women vaccinated with at least one injection of mRNA COVID-19 vaccine from conception to 11^{+6} weeks compared to pregnant women vaccinated from 12 weeks and 0 days of gestation to the end of pregnancy. The reported proportion of congenital malformation remained low with 0.81% (95%CI 0.02-4.41; n=1/124) and 0.83% (95%CI 0.41-1.48; n=11/1326) in the first trimester exposure and reference group respectively.

Our results align with current literature. Based on patients exposed from 30 days before conception to 14 weeks, Ruderman *et al*. reported no increased risk of congenital anomaly compared to unvaccinated and vaccinated women in the second and third trimester (adjusted OR = 1.05; 95%CI, 0.72-1.54). Results were similar when they restricted the period of exposure to 2 to 10 weeks (crude OR=0.92; 95%CI 062-1.36). This study, however, contained several limitations. Spontaneous abortions were not included in the study. Fetal structural anomalies were defined as anomalies identifiable at the anatomy ultrasound. Non-chromosomal anomalies has been reported to be up to 27.6% in a recent study on

more than 100.000 ultrasounds performed at 11-13 weeks.(25) Cases detected prior to anatomical screening at may have led to a medically indicated TOP, which were not considered in their study. Additionally, cases identified during third trimester ultrasonography or at birth may also have been inadvertently excluded.(25) The study from Calvert et al. in Scotland reported no association of vaccination with congenital malformations (aOR = 1.01, 95%CI 0.83-1.24) when comparing vaccinated pregnant women from 6 weeks prior to conception to 19^{+6} weeks to women not vaccinated during this period. Despite the strength of the nationwide design, results are limited by the lack of details regarding patient characteristics and the type of malformations reported. The vaccine exposure window is longer which could lead to an underestimation of a potential teratogenic effect occurring during the high-risk time period (conception to 11^{+6} weeks).

The main strength of our study is the prospective recruitment of women at the time of vaccine injection. This enabled us to collect information on pregnant women vaccinated in the first trimester before they experienced an abortion or TOPFA. As first trimester ultrasound examination is recommended for all pregnant women between 11 and 13^{+6} weeks for both Switzerland and France, the exposure window was accurately identified.

Several limitations, however, need to be considered. First, very few women were exposed in the first trimester of pregnancy. This is likely secondary to the recommendation from the authorities to preferentially consider vaccination after 12 weeks. (8,9,26) The small number of first trimester participants and events resulted in imprecise risk estimates with wide confidence limits. Therefore, even with reassuring data, this must be interpreted carefully and need to be confirmed in further studies. Second, the proportion of congenital malformations for both groups was low, probably because congenital malformation data were based on maternal hospital discharge letters and thus malformations diagnosed in the neonatal period or beyond has not been reported. The proportion of major malformations reported in our study remain lower than those reported in the literature ranging from 2% to 4% after early pregnancy vaccine exposure.(19,20) Similarly, the proportion of malformation in our study was lower than the proportion reported in the canton of Vaud in Switzerland based on the EUROCAT registry, representing 2.9% of pregnancies, including 0.7% accounting for TOPFA.(27) The EUROCAT registry includes patients with congenital anomalies diagnosed up to 12 months and more after birth compared to a maximum of 5 days after birth in our study. This difference impacts the proportion of congenital malformation as many congenital anomalies are diagnosed after 7 days after birth.(28) It is, however, not expected that the underreporting of malformations has been imbalanced between the exposure and the reference groups as all malformations were identified using the same methodology. Similarly, the reported proportion of early spontaneous abortion in the first

trimester exposure group was unexpectedly low, suggesting a possible selection bias of patients at low risk of spontaneous abortion. In addition, patients that had an early spontaneous abortion were not excluded, underestimating the proportion of malformation, however likely marginal due to the very small number of events in the exposure group. Third, our reference group was recruited at the time of vaccination and thus did not include those that experienced early or late abortion, TOPFA, or stillbirth occurring before the 2nd/3rd trimester vaccination. This may have led to unreported malformations leading to fetal death prior to inclusion. Fourth, our reference group consisted of women that were vaccinated during the 2nd/3rd trimesters therefore representing an exposed population. It is unlikely, however, that exposure to a COVID-19 vaccine could induce a malformation, as major malformation observed in this group were related to deficits of organogenesis (Table 3). Finally, in our cohort, we did not have any information about the use of assisted reproductive technology, which has been reported to represent a risk factor for congenital malformations.(29)

The mRNA COVID-19 vaccines have been reported to be safe and effective against COVID-19 infection and severity.(11,13,16) As vaccine uptake during pregnancy remains low, vaccination should be promoted for pregnant women anytime during pregnancy.(30) Women should be correctly informed about the safety and efficacy profile of the vaccine.
Our study did not assess for potential neurodevelopmental disorders through a longer-term follow-up and this should be addressed in future studies.

In conclusion, our study suggests that pregnant women exposed to an mRNA COVID-19 vaccine before 12 weeks did not have an increased risk of congenital malformation compared to women exposed during the 2nd/ 3rd trimester of pregnancy, in the limits of small sample size, leading to imprecise risk estimates. Whilst these data are reassuring, additional studies are required to confirm our findings. Pregnant women who tested positive for COVID-19 are at higher risk of maternal, pregnancy, and neonatal adverse outcomes. COVID-19 vaccines have been reported to be safe and effective. As willingness for vaccination remains low among pregnant women, emphasis must be placed on promoting vaccination during pregnancy.

Authors' contribution

GF, EM, DB, and AP conceived and designed the study. GF, EM, and AP analysed and interpreted the data. GF drafted the manuscript. EM, DB, and AP critically revised the manuscript. DB and AP provided supervision and mentorship. All authors (GF, EM, LP, CD, CM, BMT, TQ, MTB, LS, CB, AP, SS, DK, CG, APR, MCR, JM, RCB, KL, EG, MCA, UW, DB and AP) contributed to data collection. All authors made a

significant contribution in reviewing the manuscript drafting or revision and accepts accountability for the overall work. All authors approved the final version of the report.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. Alice Panchaud received grants from the Swiss Federal Office of Public Health and the CHUV Foundation; she also received grants from Vifor, the European Medicine Agency (EMA/2017/09/PE and EMA/2017/09/PE/11), the Fonds Paritaire RBP IV and a H2020 grant (ConcePTION WP 3-4), outside the submitted work. Begoña Martinez de Tejada reported receiving financial support from the General Health Division in Geneva, Switzerland, and being a medical advisor for Effik consulting fees and lectures) and Pierre Fabre (consulting fees), outside the submitted work; she also reported having a research agreement for clinical devices with Pregnolia and having been paid as a legal expert in several malpractice cases, outside the submitted work. Loïc Senthiles has been a consultant for Dilafor and Ferring Pharmaceuticals and has received payment in the past for presentations and educational events from Bayer, GlaxoSmithKline, Ferring Pharmaceuticals, and Sigvaris. All other authors declare no conflicts of interest.

Data availability statement

Data are available through joint research agreements from the corresponding authors.

Acknowledgments

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Ethics statement

This research project was reviewed and approved the Swiss Ethical Board (CER-VD-2020-00548) and French data was registered with the French National Data Protection Commission (CNIL - authorization 2217464).

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What is already known on this topic

- Pregnant women are at increased risk of severe COVID-19.
- mRNA COVID-19 vaccines seem to be safe in terms of maternal and pregnancy outcomes.
- Data evaluating the risk of congenital malformation after exposure to mRNA COVID-19 vaccines during the 1st trimester are scarce.

What this study adds

- Pregnant women exposed to an mRNA COVID-19 vaccine during the high teratogenic risk period (from conception to 11 weeks and 6 days of gestation) did not have an increased risk of congenital malformation.
- mRNA COVID-19 vaccines should be promoted to all pregnant women at any stage of pregnancy.

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Table 1: Baseline characteristics and exposure information among pregnant women who received at least one dose of mRNA vaccine during pregnancy.

	1st trimester exposure* n= 124		2nd/3rd trimester exposure** n= 1326		
	n	%	n	%	Std. Diff.
PATIENTS BASELINE CHARACTERISTICS					
Maternal age (years) at first dose - n %					
≤25	**2**	**1.6%**	**35**	**2.6%**	-7.1
26-30	**21**	**16.9%**	**234**	**17.6%**	-1.9
31-35	**55**	**44.4%**	**617**	**46.5%**	-4.4
36-40	**37**	**29.8%**	**374**	**28.2%**	3.6
>40	**8**	**6.5%**	**53**	**4.0%**	11.0
Missing	**1**	**0.8%**	**13**	**1.0%**	-1.8
Country of residence - n %					
France	**27**	**21.8%**	**49**	**3.7%**	56.3
Switzerland	**97**	**78.2%**	**1277**	**96.3%**	-56.3
Maternal addiction					
Any	**4**	**3.2%**	**20**	**1.5%**	11.3
Drug	**1**	**0.8%**	**1**	**0.1%**	11.1
Tobacco	**3**	**2.4%**	**19**	**1.4%**	7.2
Alcohol	**1**	**0.8%**	**2**	**0.2%**	9.5
Obstetrical history					
Multiparous	**70**	**56.5%**	**648**	**48.9%**	15.2
Nulliparous	**54**	**43.5%**	**678**	**51.1%**	-15.2
Medical history					
Total	**33**	**26.6%**	**388**	**29.3%**	-6.0
Pulmonary	**1**	**0.8%**	**43**	**3.2%**	-17.4
Cardiac	**2**	**1.6%**	**30**	**2.3%**	-4.7
Hypertensive	**2**	**1.6%**	**16**	**1.2%**	3.4
Diabetes	**0**	**0.0%**	**9**	**0.7%**	-11.7
Immunosuppression	**0**	**0.0%**	**6**	**0.5%**	-9.5
Neurological	**0**	**0.0%**	**6**	**0.5%**	-9.5
Digestive	**2**	**1.6%**	**8**	**0.6%**	9.7
Renal	**0**	**0.0%**	**8**	**0.6%**	-11.0
Urological	**0**	**0.0%**	**4**	**0.3%**	-7.8
Oncological	**1**	**0.8%**	**3**	**0.2%**	8.1
Thyroid imbalance	**8**	**6.5%**	**85**	**6.4%**	0.2
Other	**17**	**13.7%**	**170**	**12.8%**	2.6
Previous pregnancy complications					
Preeclampsia	**3**	**2.4%**	**15**	**1.1%**	9.8
Intrauterine growth restriction	**3**	**2.4%**	**19**	**1.4%**	7.2
Fetal Malformation	**0**	**0.0%**	**7**	**0.5%**	-10.3
Preterm birth	**3**	**2.4%**	**28**	**2.1%**	2.1
Postpartum haemorrhage	**3**	**2.4%**	**33**	**2.5%**	-0.4
Stillbirth	**0**	**0.0%**	**4**	**0.3%**	-7.8
Other	**6**	**4.8%**	**51**	**3.8%**	4.9
EXPOSURE to COVID-19 vaccine					
Type of mRNA vaccine					
Pfizer BioNTech -BNT162b2	**51**	**41.1%**	**482**	**36.3%**	24.9
Moderna - mRNA-1273	**68**	**54.8%**	**815**	**61.5%**	6.8
Unknown	**4**	**3.2%**	**29**	**2.2%**	9.5
Vaccination pattern during the study period					
Single vaccine injection	**104**	**83.9%**	**280**	**23.3%**	-
Two vaccine injections	**20**	**16.1%**	**1046**	**86.9%**	-
GA at first injection (weeks) median; [IQR] (min-max)	**3**	**[2-5] (2-11)**	**23**	**[17-28] (12-40)**	-
GA at second injection (weeks) median; [IQR] (min-max)	**8**	**[7-9] (5-11)**	**27**	**[22-32] (14-40)**	-

* first trimester exposure: exposure to the vaccine from conception to 11 weeks of gestation and 6 days

** second and third trimester exposure: exposure to the vaccine from 12 weeks of gestation to the end of pregnancy

PPROM: preterm premature rupture of membranes

GA: gestational age

Table 2: Major, minor, and genetic congenital malformations among pregnant women exposed to an mRNA COVID-19 vaccine in the first trimester compared to pregnant women exposed in the second and third trimesters of pregnancy.

	1st trimester exposure n= 124			2nd/3rd trimester exposure n= 1326							
	n	**%**	**95%CI**	**n**	**%**	**95%CI**	RR	**95%CI**	adj. RR**	**95%CI**	
Congenital malformation*	**1**	**0.81%**	0.02 - 4.41	**11**	**0.83%**	0.41 - 1.48	0.89	0.12 - 6.80	1.01	0.13 - 7.73	
MAJOR	**1**	**0.81%**	0.02 - 4.41	**6**	**0.45%**	0.17 - 0.98	-				
Minor	**0**	-		**5**	**0.38%**	0.12 - 0.88	-				
Genetic malformation	**0**	-		**2**	**015%**	0.02 - 0.54	-				

RR: risk ratio
adj. RR: adjusted risk ratio
** Congenital malformation classification (major + minor) according to the EUROCAT classification*
*** adjusted analysis on unbalanced potential confounders: maternal age >40 years, drug use, nulliparity, medical history (pulmonary, diabetes and renal disease), and obstetrical history (previous pregnancy fetal malformation)*

Table 3: list of congenital malformations according to the period of mRNA COVID-19 vaccine exposure.

1st trimester exposure n=1/124			2nd/3rd trimester exposure n=11/1326		
MAJOR					
ICD-10-BPA code	**Description**	**GA at 1st injection**	**ICD-10-BPA code**	**Description**	**GA at 1st injection**
Q700	Syndactyly on the right hand	5 weeks	**Q620**	Congenital hydronephrosis >10mm	18 weeks
			Q660	Right club foot	26 weeks
			Q254	Congenital heart defect (right aortic arch + patent ductus arteriosus + perimembranous ventricular septal defect)	12 weeks
			Q54	Hypospadias	14 weeks
			D180	Haemangioma (on the right cheek)	15 weeks
			Q278	Isolated aberrant right subclavian artery	18 weeks
Minor					
ICD-10-BPA code	**Description**	**GA at 1st injection**	**ICD-10-BPA code**	**Description**	**GA at 1st injection**
-			**Q189**	Dysmorphic face (no genetic anomaly identified)	20 weeks
			Q179	Right ear hypoplasia	20 weeks
			Q179	Bilateral ear fistulas	15 weeks
			P835	Bilateral hydrocele of testis	14 weeks
			Q669	Left foot malposition (abduction, dorsal extension, and valgus)	27 weeks

ICD-10-BPA: international classification of disease version 10 - British paediatric association
GA: gestational age