Year : 2023

The COVI-PREG registry: SARS-COV-2 among pregnant women, from natural history to maternal, fetal, pregnancy and neonatal outcomes

Favre Guillaume

Favre Guillaume, 2023, The COVI-PREG registry: SARS-COV-2 among pregnant women, from natural history to maternal, fetal, pregnancy and neonatal outcomes

Originally published at : Thesis, University of Lausanne

Posted at the University of Lausanne Open Archive http://serval.unil.ch
Document URN : urn:nbn:ch:serval-BIB_0D2EF9DBB8BB3

UNIL | Université de Lausanne
Faculté de biologie et de médecine

Materno-fetal and Obstetrics Research Unit,
Service d'obstétrique,
Département Femme Mère Enfant, CHUV

The COVI-PREG registry: SARS-COV-2 among pregnant women, from natural history to maternal, fetal, pregnancy and neonatal outcomes

Thèse de doctorat ès sciences de la vie (PhD)

présentée à la

Faculté de biologie et de médecine
de l'Université de Lausanne

par

Guillaume FAVRE

Médecin spécialiste en gynécologie obstétrique et diplômé d'une thèse de doctorat en médecine de l'université de Lausanne.

Jury

Prof. Carole CLAIR, Présidente
Prof. David BAUD, Directeur de thèse
Dre Ursula WINTERFELD, Co-directrice de thèse
Prof. Karine NIELSEN SAINES, Experte
Prof. Gilbert GREUB, Expert

Lausanne
(2023)

UNIL | Université de Lausanne
Faculté de biologie et de médecine

Ecole Doctorale
Doctorat ès sciences de la vie

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Président·e	Madame	Prof.	Carole	**Clair**
Directeur·trice de thèse	Monsieur	Prof.	David	**Baud**
Co-directeur·trice	Madame	Dre	Ursula	**Winterfeld**
Expert·e·s	Madame	Prof.	Karin	**Nielsen-Saines**
	Monsieur	Prof.	Gilbert	**Greub**

le Conseil de Faculté autorise l'impression de la thèse de

Guillaume Favre

Master - Diplôme de deuxième cycle des études médicales DCEM, Université Claude Bernard / Lyon I, France

intitulée

The COVI-PREG registry: SARS-CoV-2 among pregnant women, from natural history to maternal, fetal, pregnancy and neonatal outcomes

Lausanne, le 13 septembre 2023

pour le Doyen
de la Faculté de biologie et de médecine

Prof. Carole Clair

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

Completing this thesis writing, I would like to acknowledge and give my warmest thanks to several people that made this step of my life possible.

To Lamia, my love, who supported and still supports me every day and encouraged me in these special years and to whom I dedicate this work.

To my friend and mentor Prof. Léo Pomar, who was the trigger of this thesis, after this famous night drinking one of these finest old rums, discussing about ski touring and talking about this new virus from China.

To my friend Céline Pomar, who taught me how to deliver a woman during my first steps in the labor ward and who took care of me at home too when I was the family's roommate.

To my thesis director Prof. David Baud who accepted to supervise my PhD project, and who gave me the strength to register my first IRONMAN triathlon. Thank you for accepting the second place behind me in our IRONMAN races private ranking.

To my thesis co-director, Dre Ursula Winterfeld for her support all along the thesis, always available, who instilled me the importance of clinical pharmacology assessment in pregnancy. I will never forget the bike ride to Bergamo!

To Prof. Alice Panchaud, who taught me to approach epidemiology with rigor and precision.

To my parents, who supported me during all these years and gave me the opportunity to live my dreams. To my mom who has always been the person behind the scenes without whom I could not be where I am. To my dad who sparked my enthusiasm for research.

To my brother, who allowed me to cultivate my curiosity and taught me so much. I will not forget that *"with two "O" you can make glasses".*

To my Med-School friends and their partners Alex & Audrey, Antoine & Camille, Arnaud, & Sophie, Marion & Max, and Stan & Manon, who keep supporting and with whom I enjoy every year summer since the first year of university.

To my residency friends, Martin & Vivi with whom skiing is not just a hobby but a way of life, and Morbier is not just a cheese.

To my former obstetrics chief and friend, Dre Bénédicte Breton who introduce me to obstetrics from the beginning, and Jean-Baptiste Guilbert, who made the Obs & Gyn journey possible and taught me how to practice surgery.

To my friend Maud, with whom we have stood our ground during professional storms in the canton of Neuchâtel. To my friend Adri and his "petit pote", who motivated me to run almost every single day during 12 weeks prior to the Roma marathon.

To my "lab" friends: Charlotte, Eva, Emeline, Karine, and Françoise for all these shared moments inside that creepy office and the extra-work events.

To the Goyaves Roses, Arthur, Eléonore and Malo who made that Raid in France dream possible.

And to my hospital colleagues and friends.

ABSTRACT

In December 2019, a new virus called SARS-CoV-2, responsible for COVID-19, emerged in Wuhan, China. It rapidly spread globally and was declared a public health emergency of international concern by the World Health Organization in January 2020. Pregnant women have not been spared from this pandemic and were deemed particularly vulnerable due to the high risk of adverse outcomes reported in the past outbreaks caused by viruses from the coronavirus family (SARS-CoV-1 and MERS-CoV). To assess the impact of SARS-CoV-2 on pregnant women and the safety of COVID-19 vaccines during pregnancy, we created the COVI-PREG project, which gathered international data on SARS-CoV-2 and pregnancy through an online registry.

Based on an international cohort of pregnant women included in the registry, we were able to report that COVID-19 represented a high risk for pregnant women, risks to maternal health, risk to the pregnancy, and risk to the infant, who could experience adverse neonatal outcomes. Pulmonary disease, chronic hypertension, and pre-gestational diabetes have been identified as independent risk factors for severe disease. The Delta variant of the virus has been associated with a significantly higher risk of severe disease and the Omicron variant with a lower risk than the Pre-Delta variant in our French and Swiss sub-population. More than one third of pregnant women experienced mental health disorders during the pandemic including anxiety and/or depressive symptoms. The mRNA COVID-19 vaccine exposure among pregnant women in Switzerland was safe and no signal was reported considering maternal, pregnancy, and neonatal outcomes. Focusing on first trimester COVID-19 vaccine exposure in France and Switzerland, no increased risk of congenital malformation has been identified. Pregnant women who tested positive for SARS-CoV-2 have been reported to be exposed to medicines that were not assessed in terms of safety and efficacy, highlighting that pregnancy pharmacovigilance needs to be improved for future considerations. Our latest research findings reported that public and private stakeholders collecting data on multiple sclerosis drug exposure during pregnancy matched 96% of their data collection variables to a framework of core data elements items which can serve as a reference to the field, a first step towards pregnancy pharmacovigilance harmonization in the future.

In conclusion, the COVI-PREG project has allowed us to rapidly and extensively study the impact of SARS-CoV-2 on pregnant women and has shown that they are at risk of adverse maternal, pregnancy and neonatal outcomes. The registry also provided evidence on the safety of COVID-19 vaccine during pregnancy. Interestingly, the project has highlighted that pregnant women represent a neglected population, especially regarding medication safety assessment, emphasizing the need to improve pregnancy pharmacovigilance systems. COVI-PREG represents a sustainable and reliable tool to improve participation of pregnant women in research, especially in the field of infectious diseases and drug safety.

RÉSUMÉ

En décembre 2019, un nouveau virus nommé SARS-CoV-2, responsable du COVID-19, est apparu à Wuhan, en Chine. Il s'est rapidement propagé dans le monde et fut déclaré « urgence de santé publique de portée internationale » par l'organisation mondiale de la santé en janvier 2020. Les femmes enceintes ont rapidement été considérées comme potentiellement à risque par les experts du domaine, compte tenu des complications rapportées après exposition aux précédents membres de la famille des coronavirus (SARS-CoV-1 et MERS-CoV). Nous avons créé le projet COVI-PREG, qui a permis de rassembler des données internationales sur le SARS-CoV-2 et la grossesse par le biais d'un registre en ligne visant à évaluer initialement l'impact du SARS-CoV-2 chez les femmes enceintes, puis la sécurité du vaccin contre le COVID-19 pendant la grossesse.

A travers notre cohorte de femmes enceintes, nous avons constaté que l'infection par le COVID-19 représentait une menace pendant la grossesse, et était associé à un risque non négligeable de complication pour la mère, la grossesse et le nouveau-né. Les maladies pulmonaires, l'hypertension et le diabète ont été identifiés comme des facteurs de risque de maladie grave. Le variant Delta du virus était associé à un risque plus élevé de maladie grave et le variant Omicron à un risque plus faible comparé au variant Pré-Delta dans notre sous-population franco-suisse. Plus d'un tiers des femmes enceintes ont présenté des troubles de santé mentale, notamment des symptômes d'anxiété et/ou de dépression pendant la période de pandémie. L'exposition des femmes enceintes au vaccin contre COVID-19 était sûre et aucun signal n'a été observé concernant la mère, la grossesse et le nouveau-né. En ce qui concerne l'exposition au vaccin contre le COVID-19 au premier trimestre de grossesse en France et en Suisse, aucun risque accru de malformation congénitale n'a été constaté. Les femmes enceintes qui ont été testées positives au SARS-CoV-2 ont été exposé à des médicaments qui n'ont pas été évalués en termes de sécurité et d'efficacité, soulignant que l'étude de pharmacovigilance durant la grossesse doit être améliorée. Nos dernières recherches ont montré que les institutions publiques et privées qui recueillent des données sur l'exposition aux médicaments de la sclérose en plaques pendant la grossesse, faisaient correspondre 96% de leurs variables de collecte de données à un ensemble d'éléments de référence ce qui est très encourageant dans l'évaluation des pratiques actuelles.

En conclusion, le projet COVI-PREG nous a permis d'étudier rapidement et de manière approfondie l'impact du SARS-CoV-2 chez les femmes enceintes et a montré qu'elles étaient à risque de maladie sévère ainsi que d'issues défavorable concernant la grossesse et le nouveau-né. Le registre a également permis d'apporter des preuves de l'innocuité du vaccin COVID-19 pendant la grossesse. Nous avons constaté que les femmes enceintes sont une population négligée, notamment sur l'évaluation de la sécurité des médicaments, soulignant la nécessité d'améliorer les systèmes de pharmacovigilance pendant la grossesse. COVI-PREG est un outil durable et fiable pour améliorer l'implication des femmes enceintes dans la recherche, notamment en ce qui concerne les maladies infectieuses et la sécurité des médicaments.

I - INTRODUCTION & STATE OF THE ART

1 - A historical review of SARS-CoV-2 emergence

On December 31st 2019, the municipal health commission of Wuhan, China, reported a cluster of pneumonias cases.[1] The information was soon relayed publicly by the World Health Organization (WHO) on January 5th 2020. In Mid-January 2020, Chinese scientists revealed the sequence of the suspected virus, called novel coronavirus 2019 (2019-nCoV).[2] This new virus from the family of *Coronaviridae* (Figure 1) is a ribonucleic acid (RNA) virus (Figure 2). These viruses are called "coronavirus" because of the crow-like ring of spikes at the surface of the viral envelope. The 2019-nCoV, later called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is responsible for coronavirus infectious disease 2019 (COVID-19), which can lead to a severe clinical form characterized by an acute respiratory distress syndrome.

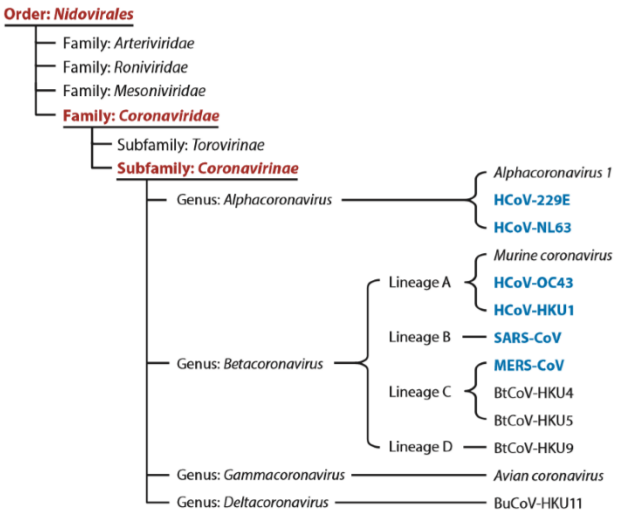


Figure 1: Classification scheme of coronaviruses. *From: Yan et al. International Journal of Environmental Research and Public Health, 2020.*[3]

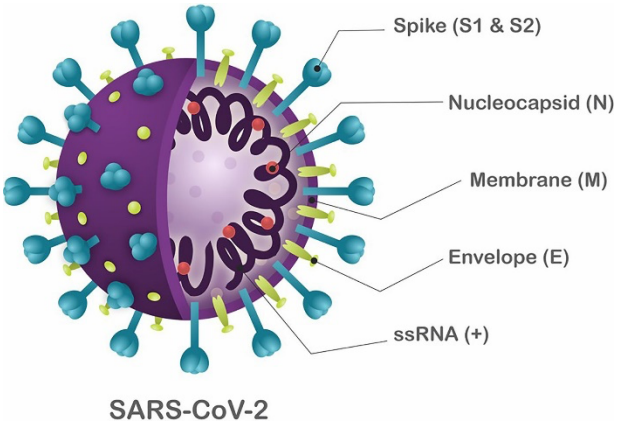


Figure 2: Schematic structure of SARS-CoV-2. The viral structure is primarily formed by the structural proteins such as spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The S, M, and E proteins are all embedded in the viral envelope, a lipid bilayer derived from the host cell membrane. The N protein interacts with the viral RNA into the core of the virion. *From: Santos IA et al. Front Microbiol. 2020.*[4]

The Coronavirus family of viruses includes several known viruses that can infect humans, such as human coronavirus 229E (HCoV-229E) or human coronavirus OC43 (HCoV-OC43) causing benign flu-like symptoms. However, other viruses in the same family, such as SARS-CoV-1 and Middle East respiratory syndrome CoV (MERS-CoV), are responsible for severe and critical disease, and have a very high fatality rate.

A very early clinical report based on 99 patients who tested positive for SARS-CoV-2 in Wuhan, was published at the end of January 2021. A total of 90% of patients reported flu-like symptoms including fever in 83%, cough in 81% and shortness of breath in 31% of patients. Patients required intensive care unit (ICU) admission in 23% of cases. An acute respiratory distress syndrome (ARDS) was confirmed in 17% of patients and 11% died.[5]

The first case of confirmed COVID-19 outside China was reported on January 13, 2020 in Thailand and in Europe on January 24, 2020, in France. One week later, the WHO declared that the outbreak constituted a public health emergency of international concern (PHEIC).[6] The spread of the virus rapidly became a global pandemic.

The origin of the transmission of this virus to the human is unclear but circumstantial evidence suggests that this disease is a zoonosis and that the epicenter of the outbreak was the seafood market of Wuhan, China.[7] The principal mode by which individuals are infected with SARS-CoV-2 is through exposure to respiratory fluids containing the virus. Exposure can occur by inhalation of very fine respiratory droplets and aerosol particles, deposition of respiratory droplets and particles on exposed mucous membranes (mouth, nose, or eye) or touching mucous membranes with hands that have been soiled.[8]

2 - SARS-CoV-2: What about pregnancies?

At the beginning of the pandemic, no information was available regarding the risk of the disease among pregnant women.

However, two members of the coronavirus family, SARS-CoV-1 and MERS-CoV were known to be responsible for severe complications during pregnancy. Based on a case series of 12 pregnant women infected with SARS-CoV-1, four (n = 4/7; 57%) out of seven women infected during the first trimester of pregnancy had an early miscarriage. Among the five other pregnant women infected during the second and third trimesters of pregnancy, two (n = 2/5; 40%) had fetal growth restriction and four (n = 4/5; 80%) delivered prematurely. Overall, three (n = 3 /12; 25%) women died during pregnancy. Among 11 pregnant women infected with MERS-CoV, 10 (n = 10/11; 91%) developed an adverse outcome, including two (n = 2/11; 18%) newborns who did not survive after birth, one (n = 1/11; 9%) stillbirth, and three (n = 3/11; 27%) maternal deaths.[9–11] At this stage of the public health crisis, considering that SARS-CoV-2 came from the same virus family, concerns were raised about the risk of severe COVID-19 to pregnant women.

In pregnancy, various physiological alterations, notably whithin the immune system, result in an adaptive immunological response in expectant mothers. The precise nature of these changes is still not well understood, but they contribute to increased susceptibility to infections among pregnant women compared to their non-pregnant counterparts.[12] In addition, the respiratory system undergoes anatomic changes, in part due to the hormonal state of pregnancy and increased intra-abdominal pressure, which result in decreased functional residual capacity and total lung capacity.[13] Women also have a 20% increased oxygen consumption during pregnancy.[14] All these changes place pregnant women at increased susceptibility to infection, especially respiratory tract infections, with an increased risk of serious complications.

Women who are infected with seasonal influenza or H1N1 influenza during pregnancy are reported to be at greater risk of hospitalization and severe disease requiring intensive care unit admission, especially in the third trimester of pregnancy. Influenza infection is also associated with an increased risk of adverse pregnancy and neonatal outcomes, including preterm birth, neonatal intensive care unit admission (NICU) and fetal death.[15] The flu vaccine, an inactivated vaccine which is safe during pregnancy, is recommended to all pregnant women at any stage during pregnancy.[16,17]

3 - The COVI-PREG project

In March 2020, we established an international registry following pregnant women suspected of SARS-CoV-2 infection, called COVI-PREG.[18] We developed a structured data collection tool accessible online by any institutions with antenatal clinics and/or labor wards intending to participate worldwide (Figure 3). The primary objective of the registry was to collect global

data on women exposed to SARS-CoV-2 during pregnancy, in order to rapidly assess the impact of the virus in this specific population.

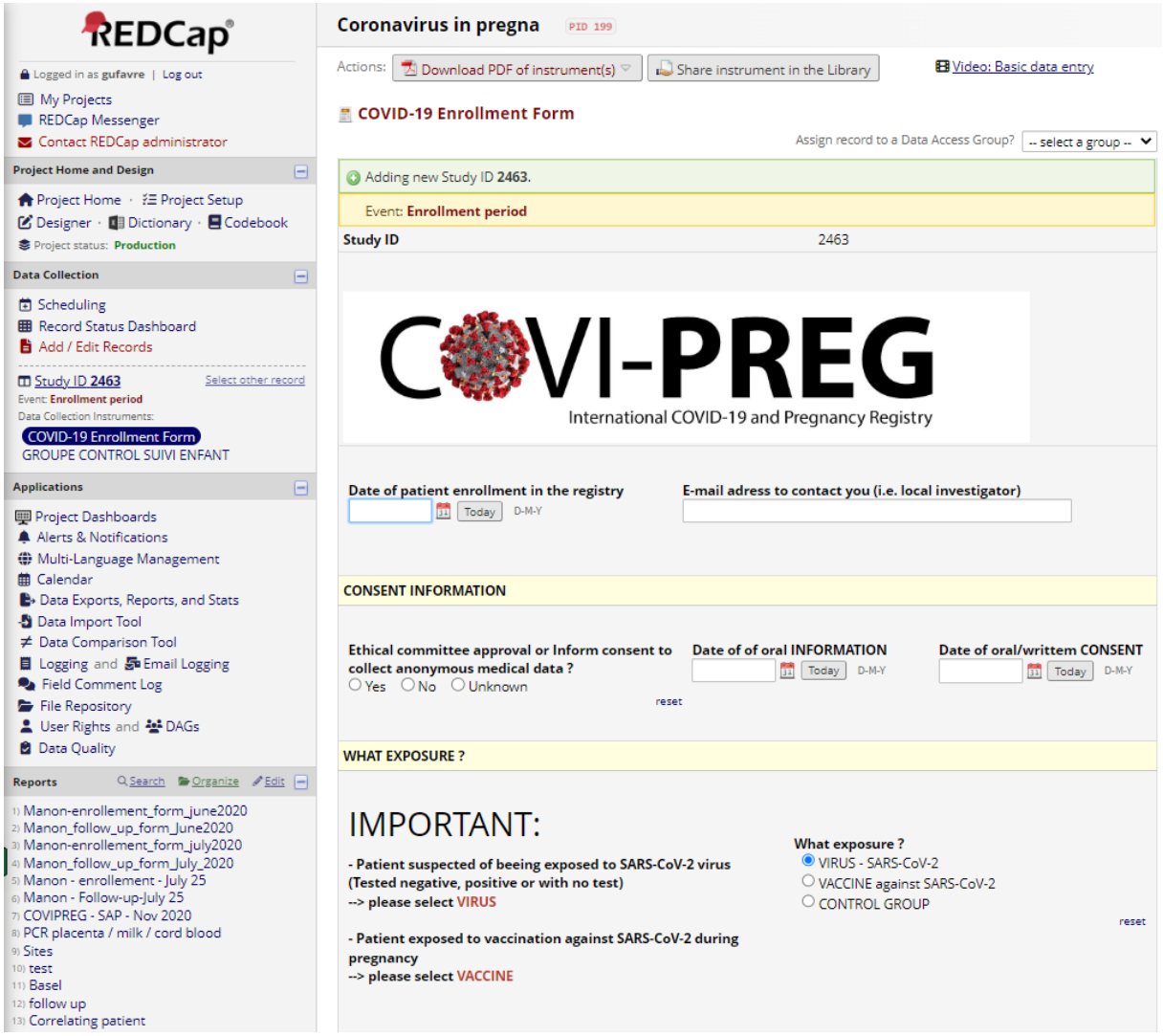


Figure 3: Screenshot of the COVI-PREG online interface

The first studies published in the literature reported a similar risk of severe COVID-19 disease among pregnant women who tested positive for SARS-CoV-2 compared to the general population.[19,20] However, these studies compared pregnant women with non-pregnant adults, who were overwhelmingly represented by older individuals, which biased the

interpretation of the data. When evaluating the data in further detail, pregnant women had the same risk of developing a severe form of COVID-19 than a patient aged 50 to 60 years.[21]

During the development of the COVID-19 vaccines, pregnant women were excluded from clinical trials, although it was necessary to gather safety data for this subpopulation.[22] As a result, we made changes to our registry to monitor and track women who were administered COVID-19 vaccines while pregnant.

The emergence of new medications to prevent and treat a new disease can lead to safety concerns for pregnant women. COVID-19 has highlighted the issue of pregnant women being overlooked in drug safety considerations, further exacerbating their existing vulnerabilities.

4 - Building a pregnancy pharmacovigilance model for the future

As pregnant women are excluded from most clinical trials assessing the safety and efficacy of medications, information on risk/benefit ratio of medication use during pregnancy are rarely available. Current approaches to fill the evidence gap include observational studies based on primary source data collection methods, where data is collected directly from health care providers and/or pregnant women. When it comes to comparing and/or combining studies to strengthen the evidence base, a major challenge is the lack of homogeneity of definitions and key elements. In that respect, the ConcePTION project aims to improve the way drug use during pregnancy is studied by building and testing a trustworthy European ecosystem for generating, monitoring, and providing robust and rapid evidence on medication safety in pregnancy and breastfeeding. Through this ConcePTION research project, our work package aimed to develop a new pharmacovigilance model in pregnancy for the future by identifying

current model issues, addressing these issues and providing recommendations from a group of experts in the field.

II - AIMS

The COVI-PREG project aimed to assess the impact of SARS-CoV-2 infection and COVID-19 vaccine exposure during pregnancy, on maternal, fetal, pregnancy and neonatal outcomes. Specific goals were set for the project:

- To identify risk factors of severe COVID-19 and assess the impact on maternal, pregnancy, and neonatal outcomes in pregnant women testing positive for SARS-CoV-2

- To assess the safety and risks associated with mRNA COVID-19 vaccine injection among women exposed during pregnancy

- To assess the risk of congenital malformation after COVID-19 vaccine exposure during the first trimester of pregnancy

- To identify risk factors for mental health impairment among pregnant women during the COVID-19 pandemic

- To evaluate the impact of infection with pre-Delta, Delta and Omicron SARS CoV-2 variants of concern among unvaccinated pregnant women, who were tested positive for SARS-CoV-2

- To describe COVID-19 related medication use in pregnant women who tested positive for SARS-CoV-2

Due to the challenges in gathering data on medication use during pregnancy, as well as the exclusion of pregnant women from clinical trials, we have expanded our focus to include the study of pharmacovigilance during pregnancy. As part of the ConcePTION project, our efforts have been directed towards assessing pregnancy pharmacovigilance, with a particular

emphasis on the standardization of data collection elements in pregnancy reports assessing drug safety, from both public and private partners.

III - SUMMARY OF RESULTS

1 - Risk factors of severe COVID-19 and maternal, pregnancy, and neonatal outcomes in pregnant women tested positive to SARS-CoV-2

Maternal outcomes and risk factors for COVID-19 severity among pregnant women

Scientific Reports, 2021 - https://doi.org/10.1038/s41598-021-92357-y

Manon Vouga*, **Guillaume Favre*,** Oscar Martinez-Perez*, Leo Pomar*, David Baud & Alice Panchaud for the COVI-PREG group

*Joint first authors

Brief summary of results

The aim of this study was to identify risk factors of severe COVID-19 in pregnant women who tested positive for SARS-CoV-2 and describe the maternal pregnancy and neonatal outcomes. Patients were recruited at the time of infection using the international COVI-PREG registry. Severe COVID-19 was defined as advanced oxygen support requirement (high flow oxygen to mechanical ventilation), intensive care unit admission or maternal death. The primary outcome consisted of the identification of risk factors of severe COVID-19, using a nested case control analysis comparing severe to non-severe pregnant women. Logistic regression was performed to identify risk factors. Secondary outcomes focused on the description of maternal pregnancy and neonatal outcomes between the two groups. A total of 926 pregnant women tested positive for SARS-CoV-2, including 92 severe COVID-19 and 834 non-severe. Risk factors associated with severe COVID-19 were pulmonary comorbidities [crude OR 3.9,

95% CI 1.6–8.9], hypertensive disorders (crude OR 3.5, 95% CI 1.2–9.1), diabetes (crude OR 2.6, 95% CI 1.2–5.3) and BMI > 30 (crude OR 1.7, 95% CI 1.1–2.9). In a multivariate analysis adjusting for significant risk factors, pulmonary comorbidities (aOR 4.3, 95% CI 1.9–9.5), hypertensive disorders (aOR 2.7, 95% CI 1.0–7.0) and diabetes (2.2, 95% CI 1.1–4.5) remained significantly associated with severe disease, while BMI > 30 did not (aOR 1.3, 95% CI 0.8–2.2). Obstetrical outcomes were poorer in the severe women group with an increased risk of caesarean section (absolute caesarean sections rate 70.7%; n = 53/75, compared to 30.9%; n = 203/656), and preterm delivery (absolute risk 62.7%; n = 32/51, compared to 36.3%; n = 78/215). Neonates in the severe group were more frequently admitted to the NICU (absolute risk 41.3%; n = 31/75, compared to 11.6%; n = 76/656). In conclusion, risk factors for severe COVID-19 in pregnant women were pulmonary disease, hypertensive disorders, and diabetes. Women with severe disease had poorer obstetrical and neonatal outcomes.

Author contribution

Guillaume Favre participated in the conception and the design of the COVI-PREG registry. He played a crucial role in the development of the COVI-PREG data report form and the online platform. He also participated in the conception and design of the study and contributed to patient recruitment and collection of data for one of the participating centers (Lausanne University Hospital). He participated in the interpretation of the results and co-wrote the first draft of the manuscript with Manon Vouga. He reviewed, revised, and approved the final version of the manuscript.

2 - Safety of mRNA COVID-19 vaccine among women exposed during pregnancy

COVID-19 mRNA vaccine in pregnancy: Results of the Swiss COVI-PREG registry, an observational prospective cohort study

The Lancet Regional Health - Europe, 2022 - https://doi.org/10.1016/j.lanepe.2022.100410

Guillaume Favre, Emeline Maisonneuve, Léo Pomar, Ursula Winterfeld, Charlotte Daire, Begoña Martinez de Tejada, Dominique Delecraz, Sonia Campelo, Mirjam Moser, Monya Todesco-Bernasconi, Stefanie Sturm, Irene Hösli, Cécile Monod, Brigitte Frey Tirri, Stylianos Kalimeris, Carolin Blume, Jérôme Mathis, Roland Zimmerman, Anda Petronela Radan, Daniel Surbek, David Baud & Alice Panchaud

Brief summary of results

In this prospective cohort study, we aimed to describe the adverse events following mRNA COVID-19 vaccine from one week before the last menstrual period to the end of pregnancy and assess the impact on pregnancy and neonatal outcomes. Pregnant women were included at the time of the injection of the first dose of the vaccine. Early adverse events (EAE) were defined as any event occurring within 1 month following vaccination injection, divided into local, systemic, and severe EAE. Secondary outcomes were pregnancy outcomes and neonatal outcomes. Among 1012 women included, 894 had 2 injections of mRNA COVID-19 vaccine injection just before or during pregnancy including 271 with the BNT162b2 (Pfizer/BioNTech) vaccine and 623 with the mRNA-1273 (Moderna). A total of 727 (81.3%) and 720 (80.5%) of patients had a local adverse event after the first and second dose, respectively. At least one systemic adverse event was reported in 316 (35.4%) and 602 (67.3%), respectively for the first and second dose. Local EAE were similar between vaccines and doses, mainly represented by pain at the site of injection. Systemic EAE, however, were more frequent for the second dose (78.3%; n = 488) of mRNA-1273 (Moderna), compared to the first dose of the same vaccine

(37.6%; n = 234) and the first (30.3%; n = 82) and second (42.1%; n = 114) dose of the BNT162b2 (Pfizer/BioNTech). The more frequent reported systemic EAE were fatigue, headache, and muscle pain. Out of 1012 women that had at least one injection just before or during pregnancy, four (0.4%; n = 4) severe EAE were reported including deep vein thrombosis associated with pulmonary embolism (21 weeks), preterm premature rupture of membranes and placental abruption leading to emergency delivery (31 weeks); thoracic herpes zoster (17 weeks); and hospitalization for surveillance of fever (32 weeks). Early spontaneous abortion after vaccine exposure before 14 weeks occurred in one patient (0.9%; n = 1/107). Late spontaneous abortion after vaccine exposure before 20 weeks occurred in one patient (0.4%; n = 1/228). Among the 513 patients who were exposed before 37 weeks and delivered after 24 weeks, and whose pregnancy outcome was known, 33 individuals experienced a preterm birth (6.4%; n = 33/513). Among the 530 women who were exposed after 20 weeks and delivered after 24 weeks, and whose pregnancy outcome was known, all (n = 530/530) had a livebirth, including 5 twin pregnancies. Neonatal intensive care unit admission occurred in 4.7% (n = 25/535) and no neonatal death was recorded. Although frequent local and systemic effects have been reported following exposure to mRNA COVID-19 vaccines during pregnancy, severe adverse events have been uncommon. Furthermore, women who received the vaccine during pregnancy did not experience higher rates of adverse pregnancy or neonatal outcomes when compared to historical data on the background risks in the obstetric population.

Author contribution

Guillaume Favre conceived and designed the study, participated in the funding acquisition and project administration. He participated in the data collection and analyzed the data. He drafted the manuscript, reviewed, revised, and approved the final version of the manuscript.

3 – Risk of congenital malformation after COVID-19 vaccine exposure during the first trimester of pregnancy

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

Clinical Microbiology and Infection, 2023 – https://doi.org/10.1016/j.lanepe.2022.100410

Guillaume Favre, Emeline Maisonneuve, Léo Pomar, Charlotte Daire, Cécile Monod, Begoña Martinez de Tejada, Thibaud Quibel, Monya Todesco Bernasconi, Loïc Sentilhes, Caroline Blume, Andrea Papadia, Stephanie Sturm, Dirk Bassler, Claudia Grawe, Anda Petronela Radan, Marie-Claude Rossier, Jérôme Mathis, Romina Capoccia Brugger, Karine Lepigeon, Eva Gerbier, Marie Claude Addor, Ursula Winterfeld, David Baud & Alice Panchaud, on behalf of the COVI-PREG group

Brief summary of results

This study aimed to evaluate the risk of congenital malformation in pregnant women exposed to mRNA COVID-19 vaccines during the first trimester of pregnancy, which is a developmental period where the fetus is at risk of teratogenicity. Pregnant women exposed to the mRNA COVID-19 during pregnancy were included at the time of injection. Data collection was performed using the COVI-PREG registry. Women who received at least one dose of mRNA COVID-19 vaccine during pregnancy were eligible for the study. Women who had at least one dose of an mRNA COVID-19 vaccine from conception (266 days before term date, set at 40 weeks of gestation) to 11 weeks of gestation and 6 days were allocated to the exposure group. Women exposed to the vaccine from 12 weeks of gestation to the end of pregnancy were allocated to the reference group. Congenital malformation was defined as at least one birth defect categorized as a major or minor malformation according to the EUROCAT criteria. Birth defects were classified by two experts into major, minor and genetic malformations. To investigate a potential association between COVID-19 vaccine exposure in the first trimester

and the risk of malformation, we utilized a generalized linear regression model to calculate risk ratios through both univariate and multivariate analyses. A total of 1450 pregnant women were included, with 124 exposed during the first trimester and 1326 after that period. The proportion of congenital malformation was 0.81% (n = 1/124; 95% CI 0.02-4.41) among participants exposed during the first trimester and 0.83% (n = 11/1326; 95% CI 0.41-1.48) among pregnant women exposed after that period. The 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) and an adjusted RR of 1.01 (95% CI 0.13-7.73). The proportion of major malformation was 0.81% (n = 1/124; 95% CI 0.02-4.41) and 0.45% (n = 6/1326; 95% CI 0.17-0.98) in the first trimester and second-third trimester exposure group, respectively. The proportion of minor congenital malformation was 0.00% (n = 0/124) and 0.38% (n = 5/1326; 95% CI 0.12-0.88) in the first trimester and second-third trimester exposure group, respectively. Two (n = 2/1326; 0.15%, 95% CI 0.02-0.054) genetic malformations were reported in the second and third trimester exposure group (2 cases with confirmed trisomy 21) and none in the first trimester exposure group. In conclusion, pregnant women exposed to an mRNA COVID-19 vaccine before 12 weeks of gestation did not have an increased risk of congenital malformation compared to women exposed in the second and third trimester.

Author contribution

Guillaume Favre conceived and designed the study, participated in the administration of the project. After participating to data collection, he extracted, analyzed, and interpreted the data. He drafted the manuscript, reviewed, revised, and approved the final version of the manuscript.

4 - Impact of COVID-19 pandemic on pregnant women mental health

Mental health in pregnant individuals during the COVID-19 pandemic based on a Swiss online survey

Scientific Reports, 2022 - https://doi.org/10.1038/s41598-022-21881-2

Guillaume Favre, Cléa Kunz, Simone Schwank, Ho-Fung Chung, Anda Petronela Radan, Luigi Raio, Mihaela Fluri, Ursula Winterfeld, David Baud & Léo Pomar

Brief summary of results

This study aimed to evaluate the mental health of pregnant women during the early COVID-19 pandemic period and the risk factors associated with impaired mental health status. The study was conducted from October 2020 to February 2021 and women who were pregnant at the time of the survey were eligible. An online questionnaire was composed of three mental health evaluation scales: the Edinburgh Postnatal Depression Scale (EPDS), the Generalized Anxiety Disorder 7 questions (GAD-7), and the Impact Event Scale–Revised (IES-R). An EPDS score of ≥ 13/30 was considered representative of major depressive symptoms. GAD-7 scores were classified into minimal (0–4), mild (5–9), moderate (10–14), and severe anxiety (15–21). IES-R scores were categorized into mild (0–39), moderate (40–55), and severe (56–88) symptoms. A secondary outcome was mental health impairment, a composite outcome defined as at least one of the following conditions: (i) GAD-7 score ≥ 10 (ii) EPDS score ≥ 13 or (iii) IES-R score ≥ 40. A case control analysis was performed comparing patients with mental health impairment and patients without, to identify risk factors. A total of 736 patients were included. Anxiety disorder was evaluated by the GAD-7 as mild in 38.3% (n = 282), moderate in 9.6% (n = 71), severe in 2.0% (n = 15). Depressive symptoms were evaluated by the EPDS as

minimal in 45.7% (n = 336), moderate in 21.5% (n = 158), and severe in 32.9% (n = 242). The IES-R score that assessed distress caused by traumatic events was reported as mild in 85.7% (n = 631), moderate in 10.3% (n = 76), severe in 3.9% (n = 29), and missing in 14.3% (n = 105). A total of 272 (37.0%) participants were identified to have a mental health impairment. The association between the risk of mental health impairment and foreign nationality was significant with an OR of 1.48 (95% CI [1.06–2.05]; p = 0.021) as well as fetal and pregnancy worries because of coronavirus with a crude OR of 1.46 (95% CI [1.08–1.98]; p = 0.014) and 1.65 (95% CI [1.22–2.24]; p = 0.001). Adjusted ORs were only significant for foreign nationality (aOR 1.51; 95% CI [1.07–2.13]; p = 0.020) and pregnancy worries because of coronavirus (aOR 1.62; 95% CI [1.10–2.40]; p = 0.016). Our results suggest that pregnant women had a high risk of mental health impairment during the pandemic and should therefore be better informed about the impacts of the pandemic on pregnancy. Emphasis should be placed on vulnerable populations such as foreign nationals regardless of socio-economic or educational status.

Author contribution

Guillaume Favre participated in data collection and performed the statistical analysis. He extracted, analyzed, and interpreted the data. He took the lead in drafting the manuscript, reviewed, revised, and approved the final version of the manuscript.

5 - Impact of pre-Delta, Delta and Omicron SARS-CoV-2 variants infection among unvaccinated pregnant women tested positive for SARS-CoV-2

Maternal and perinatal outcomes following pre-Delta, Delta, and Omicron SARS-CoV-2 variants infection among unvaccinated pregnant women in France and Switzerland: a prospective cohort study using the COVI-PREG registry

The Lancet Regional Health - Europe, 2022 - https://doi.org/10.1016/j.lanepe.2022.100569

Guillaume Favre, Emeline Maisonneuve , Léo Pomar , Charlotte Daire, Christophe Poncelet, Thibaud Quibel, Cécile Monod, Begoña Martinez de Tejada, Leonhard Schäffer, Andrea Papadia, Anda Petronela Radan, Monya Todesco-Bernasconi, Yves Ville, Cora Alexandra Voekt, Béatrice Eggel-Hort, Romina Capoccia-Brugger, Silke Johann, Claudia Grawe, Sophie Defert, Nicolas Mottet, Christian R Kahlert, Charles Garabedian, Loïc Sentilhes, Brigitte Weber, Steffi Leu, Dirk Bassler, Karine Lepigeon, Ursula Winterfeld, Alice Panchaud & David Baud for the French and Swiss COVI-PREG group

Brief summary of results

This study aimed to evaluate the impact of pre-Delta, Delta, and Omicron SARS-CoV-2 variants on maternal and perinatal outcomes. We recruited pregnant women at the time of a positive SARS-CoV-2 test. Patients were allocated to periods of variants predominance based on national relative variant frequencies: Pre-Delta period (Delta variant <20% of national samples), Delta period (Delta variant >80%) and Omicron period (Omicron variant >80%). Primary outcome was maternal adverse outcome defined as a composite outcome with either ICU admission, acute respiratory distress syndrome, high-flow oxygen, non-invasive ventilation, or mechanical ventilation requirement. Secondary outcomes were preterm birth (<37 weeks of gestations), and pregnancy/neonatal outcomes. Overall, 2055 patients were included with 1402 patients during the pre-Delta period, 262 patients during the Delta period, and 391 patients during the Omicron period. A severe maternal adverse outcome occurred in 3.4% (n = 47/1402; 95% CI 2.5–4.5), 6.5% (n = 17/262; 95% CI 3.8–10.2), and 1.0% (n = 4/391;

95% CI 0.3–2.6) of patients during the pre-Delta, Delta, and Omicron period, respectively. The Delta period was associated with more severe outcomes compared to the pre-Delta period (adjusted risk ratio [aRR] of 1.8; 95% CI 1.1–3.2). Hospitalization for COVID-19 occurred in 12.6% (n = 176/1402; 95% CI 10.9-14.4) of patients during the pre-Delta period, 17.2% (n = 45/262; 95% CI 12.8-22.3) during the Delta period, and 12.5% (n = 49/391; 95% CI 9.4–16.2) during the Omicron period. The Omicron period was associated with fewer severe maternal adverse outcomes compared to the pre-Delta period (aRR = 0.3; 95% CI, 0.1–0.8). Out of 1544 pregnant women with a pregnancy resulting in a livebirth after 23 weeks and exposed to SARS-CoV-2 before 37 weeks, preterm birth occurred in 9.3% (n = 92/993; 95% CI 7.5–11.2) of patients, 13.7% (n = 23/168; 95% CI 8.9–20.5), and 11.0% (n = 27/245; 95% CI 7.4–15.6) during the pre-Delta, Delta, and Omicron period, respectively. Out of 1964 pregnant women who tested positive for SARS-CoV-2 and had a known pregnancy outcome after 20 weeks, stillbirths were reported in 0.5% (n = 6/1159 ;95% CI0.2–1.1), 2.8% (n = 6 /210 ;95% CI 1.0–6.0), and 0.9% (n = 2/213 ;95% CI 0.1–3.4) of patients during the pre-Delta, Delta, and Omicron periods, respectively. In conclusion, pregnant women who tested positive for SARS-CoV-2 during the Delta period were at a higher risk of severe maternal adverse outcome, compared to the pre-Delta and Omicron periods. Omicron was associated with less severe maternal adverse outcomes, but the rate of hospitalizations remained high.

Author contribution

Guillaume Favre conceived and designed the study. After participating to data collection, he extracted, analyzed, and interpreted the data. He drafted the manuscript, reviewed, revised, and approved the final version of the manuscript.

6 - COVID-19 related medicine use in pregnant women positive for SARS-CoV-2

COVID-19-related medicine utilization study in pregnancy: The COVI-PREG cohort

British Journal of Clinical Pharmacology, 2022 - *https://doi.org/10.1111/bcp.15611*

Guillaume Favre, Eva Gerbier , Emeline Maisonneuve , Léo Pomar , Ursula Winterfeld, Karine Lepigeon, Kitty WM Bloemenkamp, Odette de Bruin , Hurley Eimir, Hedvig Nordeng, Satu J Siiskonen, Miriam CJM Sturkenboom, David Baud & Alice Panchaud for the COVI-PREG and CONSIGN group

Brief summary of results

This study aimed to describe the use of COVID-19-related medicines during pregnancy and their evolution between the early/late periods of the pandemic. Pregnant women who tested positive for SARS-CoV-2 were included at the time of the test. The exposure to COVID-19 related medicines were defined as any medicine reported to treat a COVID-19 event including the following categories: antibiotics, antivirals, hydroxy-chloroquine (HCQ), corticosteroids (for maternal indication), anti-interleukin 6 (anti-IL6) and immunoglobulins. The pandemic period was divided into the early period (March to June 2020) and the late period (July 2020 to July 2021). July 2020 coincides with a key change in the clinical guidelines against the use of HCQ and the recommendation for the use of dexamethasone for patients requiring oxygen support. A total of 1964 pregnant women who tested positive for SARS-CoV-2 were included. Overall, 10.4% (n = 205/1964) of pregnant women received at least one COVID-19-related medicine. Antibiotics were used in 8.6% (n = 169), corticosteroids in 3.2% (n = 62), antivirals in 2.0% (n = 39), HCQ in 1.4% (n = 27), and anti-IL6 (tocilizumab) in 0.3% (n = 5). The usage of COVID-19-related medicines varied among patient groups: 3.1% (12/381) in asymptomatic patients, 4.2% (52/1233) in non-hospitalized patients, 19.7% (46/233) in patients hospitalized

without oxygen, 72.1% (44/61) in patients requiring oxygen support, 95.7% (22/23) in patients requiring high flow oxygen or non-invasive ventilation patients, 96.2% (25/26) in patients requiring mechanical ventilation, and 57.1% (4/7) among patients who died. The proportion of patients who received at least one medicine to treat COVID-19 during the early period was higher (16.7%, n = 99/592; 95% CI 13.8–20.0) compared to the late period (7.7%, n = 104/1358; 95% CI 6.3–9.2). Antibiotics, antivirals and HCQ use for COVID-19 decreased between early and late periods of the pandemic. There was a trend towards higher use of corticosteroids for COVID-19 in the late period compared to the early period, with usage rates of 3.5% (n = 48/1358; 95% CI 2.6-4.7) and 2.4% (n = 14/592; 95% CI 1.3-3.9), respectively. To conclude, COVID-19 related medicine use in pregnant women was low but increased with the severity of symptoms. The tendency for an increased use of corticosteroids seemed to be aligned with the evolution of guidelines.

Author contribution

Guillaume Favre conceived and designed the study. After participating to data collection, he extracted, analyzed, and interpreted the data. He drafted the manuscript, reviewed, revised, and approved the final version of the manuscript.

7 - Standardization of data collection elements in pregnancy reports assessing drug safety, from public and private partners

Improving data collection as part of pregnancy safety studies: Towards standardization of data elements in pregnancy reports from public and private partners, a contribution from the ConcePTION project.

Drug Safety, 2023 – In review

Guillaume Favre, Jonathan L. Richardson, Alan Moore, Yvonne Geissbühler, Valentine Jehl, Alison Oliver, Svetlana Shechtman, Orna Diav-Citrin, Maya Berlin, Tal De-Haan, Alice Panchaud, David Baud, Anil Mor, Meritxell Sabidó, Christina Chambers, Yrea R.J. van Rijt-Weetink, Eugène P. van Puijenbroek, Laura M. Yates, Michael Stellfeld & Ursula Winterfeld

Brief summary of results

The aim of the study was to assess the possibility of alignment of data collected by different stakeholders of pregnancy pharmacovigilance (public and private) to a set of already published core data elements (CDE), defined by experts in the field as a reference framework for studies assessing drug safety in pregnancy. A total of seven data access providers (DAPs) involved in the pharmacovigilance of drugs used for the treatment of multiple sclerosis during pregnancy were participating in this study. These DAPs were categorized into three groups: pregnancy registries, enhanced pharmacovigilance programs and teratogen information services. DAPs were asked to answer a set of questions to describe the degree of alignment of their primary data collection variables to the 51 CDE items considering their strict definitions. For each CDE item, possibility of alignment was categorized as directly taken, derived, divergent or missing. Most of the DAPs variables conformed to the CDE items and definitions (85%, n = 305/357 directly taken from existing fields and 12%, n = 42/357 derived by combining different variables).

Few of the DAPs variables were not aligned with CDE items, either because the definitions were different from the CDE definition (1%, n = 3/357 divergent definition), or because the variables were missing (2%, n = 7/357). DAPs variables that had a divergent definition were maternal date of birth, mother's age at last menstrual period, and maternal pre-pregnancy BMI. The missing CDE items were maternal pre-pregnancy BMI, medication route of exposure, medication frequency of use, maternal death outcome, molar pregnancy or blighted ovum pregnancy outcome and infant head circumference at birth. To conclude, DAPs were able to match a very high proportion of the CDE items, showing that alignment of dataset content and clinical definitions by diverse stakeholders is feasible, an important prerequisite for harmonization and exchange of data analysis.

Author contribution

Guillaume Favre took part in the conception of the study. After participating in the data collection, he extracted, analyzed, and interpreted the data. He drafted the manuscript with Ursula Winterfeld and Michael Stellfeld, reviewed, revised, and approved the final version of the manuscript.

IV - DISCUSSION

The COVI-PREG project allowed us to provide essential and comprehensive data regarding the impact of this COVID-19 pandemic on pregnant women, especially regarding the impact of SARS-CoV-2 infection, COVID-19 vaccine, and specific inherent managements.

This research tool was rapidly implemented at the very beginning of the pandemic. It was widely shared worldwide, thanks to our strong maternal fetal medicine (MFM) network, to follow as quickly and as accurately as possible the impact of SARS-CoV-2 among pregnant women. Based on his little sister the Zika virus pregnancy registry, we adapted its variables and its structure to be able to follow a new unknown virus in pregnant women. This step forced us to anticipate any complications that could occur after an exposure to a new virus. Similarly, we had to anticipate the use of medications potentially proposed to pregnant women, as well as the impact and possible side-effects of the vaccine. This resulted in the design of a generic tool capable of monitoring and assessing any infectious disease during pregnancy. COVI-PREG has been conceived as a web-based survey composed of multiple linked “bricks” that could be added, modified, or deleted depending on the situation and the level of details required. Alongside the spread of SARS-CoV-2 and the publication of thousands of studies describing the course of the disease, we adapted the registry in real time to collect all the information that could help monitor the impact of such a disease in pregnant women. The best examples of the adaptability of the registry were the addition of follow-up data regarding new drugs to treat COVID-19 and implementation of COVID-19 vaccines. As soon as a new COVID-19 related drug was available on the market, or a repurposed drug was susceptible to be used in pregnant women, we added them to the registry and updated the variables to be collected in a matter of hours. At the time COVID-19 vaccines became available for the general population, the registry had already been prepared to collect information on

exposure during pregnancy, including all safety information related to a new product administered to pregnant women, such as potential adverse effects on the mother, the pregnancy/fetus, and her neonate. In other words, COVI-PREG was a living registry, adapted instantly to its pandemic environment.

Thanks to this ingenious tool, we have provided a way for collaborators worldwide to collect data on COVID-19 in pregnant women, using a user-friendly and straightforward online platform. The COVI-PREG registry gave us the opportunity to be among the first research groups to share essential information on COVID-19 and pregnant women, with several major publications in the field. Even in an extremely tense situation of a global pandemic with hospital overload and reduced health resources caused by the outbreak, this tool allowed us to monitor this disease among this vulnerable population. In mid-2021 we have been mandated by the Swiss Federal Office of Public Health to provide an evaluation on the topic of pregnant women and COVID-19, leading to a report on the COVI-PREG project and its scientific results.[23] Since COVI-PREG demonstrated its valuable effectiveness during the COVID-19 pandemic, we already adapted the registry to new emergent pathogens such as monkeypox virus.[24]

Additionally, this project brought together research teams at the international level, in Europe, but also in America, Africa, and Asia. This collaborative network has been effective for COVID-19 and has created a solid and sustainable relationship for future projects. The most significant example is represented by the Swiss collaboration between obstetric units that has always been challenging before the project. Through a collaborative effort, we have united most Swiss maternity units towards a common goal. All Swiss regions were represented in the COVI-PREG project and strong relationships were established between professionals, giving a perspective for future common clinical and research projects. A new research project called

"CMV-PREG", is already running and was based on the COVI-PREG system. The participants of this new project are members of the recently formed Swiss collaboration. The aim of this project is to assess the effect of cytomegalovirus (CMV) exposure during pregnancy, as well as its treatments and impact of the infection on the fetus.[25]

Unfortunately, this project also illustrates that pregnant women are still neglected, although known to be potentially vulnerable especially to infections, due to the various physiological changes that occur during pregnancy. Very few clinical trials have included pregnant women, either in studies assessing the course of COVID-19 or the safety and efficacy of associated treatments. Similarly, they were excluded from studies evaluating the safety and efficacy of COVID-19 vaccines. The ConcePTION project on pharmacovigilance in pregnancy has highlighted that the challenge of collecting robust and accurate data regarding drug safety during pregnancy is not a recent issue limited to the COVID-19 pandemic. These findings underscore the need to address the underrepresentation of pregnant patients in research. Paradoxically, pregnant women are neglected in research, although they combine several characteristics that should place them in a privileged situation to be included in research, as they are young, at risk for infections and other complications and there is not one, but two patients involved.

The COVI-PREG registry had several limitations. It limits the scientific assessment to observational studies and is dependent on data collection methodology. Strict criteria must be established for patient's inclusion and data collection to avoid selection bias and requires rigor in its management. Data collection can be time-consuming depending on the situation as inclusion in performed patient by patient and can be difficult in situations where a high number of patients need to be included. This can require a significant number of resources. This limitation explains the lack of a control group in COVI-PREG, where inclusion was

impossible given the high number of patients tested positive for COVID-19 who needed inclusion. The governance of a project of this magnitude is also very challenging, and requires a dedicated team, to run it properly, update it in time and provide support for collaborators. Compared to national registries (e.g., Nordic registry databases), that collect exhaustive data from electronic health records, COVI-PREG has included a relatively low number of patients, but this is the price of obtaining accurate and clinically relevant data. Both methods are useful and complementary as they assess different aspects of a disease.

Given that infectious diseases are becoming more and more important, as is climate change that potentiates the previous issue, and that pregnant women are underrepresented in research until now, the COVI-PREG tool represents a sustainable and reliable resource for considering pregnant women in future monitoring perspectives.

To conclude, the COVI-PREG project allowed us to rapidly and widely study the impact of SARS-CoV-2 among pregnant women, reporting that pregnant women were at risk of maternal, pregnancy and neonatal adverse outcomes during this worldwide public health crisis. Additionally, the registry was able to evolve along with the emergence of COVID-19 vaccine and provided evidence on its safety during pregnancy. Finally, it highlighted that pregnant women represent a neglected population, especially regarding medication safety assessment, thus providing insight into future perspectives to assess and improve pregnancy pharmacovigilance systems. COVI-PREG represents a sustainable and reliable tool to improve the participation of pregnant women in research, especially in infectious diseases and drug safety studies and also in other research studies pertaining to pregnancy-related complications.

V - REFERENCES

1. Pneumonia of unknown cause – China [Internet]. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2020-DON229

2. Archived: WHO Timeline - COVID-19 [Internet]. Available from: https://www.who.int/news/item/27-04-2020-who-timeline---covid-19

3. Yan Y, Shin WI, Pang YX, et al. The First 75 Days of Novel Coronavirus (SARS-CoV-2) Outbreak: Recent Advances, Prevention, and Treatment. International Journal of Environmental Research and Public Health 2020;17(7):2323.

4. Santos I de A, Grosche VR, Bergamini FRG, Sabino-Silva R, Jardim ACG. Antivirals Against Coronaviruses: Candidate Drugs for SARS-CoV-2 Treatment? Front Microbiol 2020;11:1818.

5. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet 2020;395(10223):507–13.

6. COVID-19 Public Health Emergency of International Concern (PHEIC) Global research and innovation forum [Internet]. Available from: https://www.who.int/publications/m/item/covid-19-public-health-emergency-of-international-concern-(pheic)-global-research-and-innovation-forum

7. Worobey M, Levy JI, Malpica Serrano L, et al. The Huanan Seafood Wholesale Market in Wuhan was the early epicenter of the COVID-19 pandemic. Science 2022;377(6609):951–9.

8. CDC. Scientific Brief: SARS-CoV-2 Transmission [Internet]. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html

9. Favre G, Pomar L, Musso D, Baud D. 2019-nCoV epidemic: what about pregnancies? Lancet 2020;395(10224):e40.

10. Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol 2004;191(1):292–7.

11. Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection during pregnancy: Report of two cases & review of the literature. J Microbiol Immunol Infect 2019;52(3):501–3.

12. Abu-Raya B, Michalski C, Sadarangani M, Lavoie PM. Maternal Immunological Adaptation During Normal Pregnancy. Front Immunol 2020;11:575197.

13. Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. Front Pharmacol 2014;5:65.

14. Stone S, Nelson-Piercy C. Respiratory disease in pregnancy. Obstet Gynaecol Reprod Med 2007;17(5):140–6.

15. Meijer WJ, van Noortwijk AGA, Bruinse HW, Wensing AMJ. Influenza virus infection in pregnancy: a review. Acta Obstetricia et Gynecologica Scandinavica 2015;94(8):797–819.

16. ACOG Committee Opinion No. 732: Influenza Vaccination During Pregnancy. Obstet Gynecol 2018;131(4):e109–14.

17. Grohskopf LA, Blanton LH, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2022-23 Influenza Season. MMWR Recomm Rep 2022;71(1):1–28.

18. Panchaud A, Favre G, Pomar L, et al. An international registry for emergent pathogens and pregnancy. Lancet 2020;395(10235):1483–4.

19. Chen L, Li Q, Zheng D, et al. Clinical Characteristics of Pregnant Women with Covid-19 in Wuhan, China. N Engl J Med 2020;382(25):e100.

20. Breslin N, Baptiste C, Gyamfi-Bannerman C, et al. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. Am J Obstet Gynecol MFM 2020;2(2):100118.

21. Favre G, Pomar L, Baud D. Coronavirus disease 2019 during pregnancy: do not underestimate the risk of maternal adverse outcomes. Am J Obstet Gynecol MFM 2020;2(3):100160.

22. Dashraath P, Nielsen-Saines K, Madhi SA, Baud D. COVID-19 vaccines and neglected pregnancy. The Lancet 2020;396(10252):e22.

23. OFSP O fédéral de la santé publique. Coronavirus: recherche et science [Internet]. Available from: https://www.bag.admin.ch/bag/fr/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/situation-schweiz-und-international/forschung-wissenschaft.html

24. Pomar L, Favre G, Baud D. Monkeypox infection during pregnancy: European registry to quantify maternal and fetal risks. Ultrasound Obstet Gynecol 2022;60(3):431.

25. CMV-preg [Internet]. HESAV. Available from: https://hesav.ch/cmv-preg/

VI - ARTICLES

Article 1: Maternal outcomes and risk factors for COVID-19 severity among pregnant women

Article 2: COVID-19 mRNA vaccine in pregnancy: Results of the Swiss COVI-PREG registry, an observational prospective cohort study

Article 3: Risk of congenital malformation following first trimester mRNA COVID-19 vaccine exposure in pregnancy: the COVI-PREG prospective cohort

Article 4: Mental health in pregnant individuals during the COVID-19 pandemic based on a Swiss online survey

Article 5: Maternal and perinatal outcomes following pre-Delta, Delta, and Omicron SARS-CoV-2 variants infection among unvaccinated pregnant women in France and Switzerland: a prospective cohort study using the COVI-PREG registry

Article 6: COVID-19-related medicine utilization study in pregnancy: The COVI-PREG cohort

Article 7: Improving data collection as part of pregnancy safety studies: Towards standardization of data elements in pregnancy reports from public and private partners, a contribution from the ConcePTION project.

scientific reports

Check for updates

OPEN

Maternal outcomes and risk factors for COVID-19 severity among pregnant women

Manon Vouga[1,82], Guillaume Favre[1,82], Oscar Martinez-Perez[2,82], Leo Pomar[1,82], Laura Forcen Acebal[3], Alejandra Abascal-Saiz[4], Maria Rosa Vila Hernandez[5], Najeh Hcini[6], Véronique Lambert[6], Gabriel Carles[6], Joanna Sichitiu[1,7], Laurent Salomon[7], Julien Stirnemann[7], Yves Ville[7], Begoña Martinez de Tejada[8], Anna Goncé[9], Ameth Hawkins-Villarreal[9], Karen Castillo[9], Eduard Gratacos Solsona[9], Lucas Trigo[10], Brian Cleary[11], Michael Geary[12], Helena Bartels[12], Feras Al-Kharouf[12], Fergal Malone[12], Mary Higgins[13], Niamh Keating[14], Susan Knowles[15], Christophe Poncelet[16], Carolina Carvalho Ribeiro-do-Valle[17], Fernanda Surita[17], Amanda Dantas-Silva[17], Carolina Borrelli[17], Adriana Gomes Luz[17], Javiera Fuenzalida[18], Jorge Carvajal[18], Manuel Guerra Canales[19], Olivia Hernandez[20], Olga Grechukhina[21], Albert I. Ko[22], Uma Reddy[22], Rita Figueiredo[23], Marina Moucho[23], Pedro Viana Pinto[23], Carmen De Luca[24], Marco De Santis[24], Diogo Ayres de Campos[25], Inês Martins[25], Charles Garabedian[26], Damien Subtil[26], Betania Bohrer[27], Maria Lucia Da Rocha Oppermann[28], Maria Celeste Osorio Wender[28], Lavinia Schuler-Faccini[29], Maria Teresa Vieira Sanseverino[29], Camila Giugliani[30], Luciana Friedrich[27], Mariana Horn Scherer[29], Nicolas Mottet[31], Guillaume Ducarme[32], Helene Pelerin[33], Chloe Moreau[33], Bénédicte Breton[34], Thibaud Quibel[35], Patrick Rozenberg[35], Eric Giannoni[1], Cristina Granado[36], Cécile Monod[36], Doris Mueller[36], Irene Hoesli[36], Dirk Bassler[37], Sandra Heldstab[38], Nicole Ochsenbein Kölble[39], Loïc Sentilhes[40], Melissa Charvet[40], Jan Deprest[41], Jute Richter[41], Lennart Van der Veeken[42], Béatrice Eggel-Hort[43], Gaetan Plantefeve[44], Mohamed Derouich[45], Albaro José Nieto Calvache[46], Maria Camila Lopez-Giron[46], Juan Manuel Burgos-Luna[46], Maria Fernanda Escobar-Vidarte[46], Kurt Hecher[47], Ann-Christin Tallarek[47], Eran Hadar[48], Karina Krajden Haratz[49], Uri Amikam[50], Gustavo Malinger[50], Ron Maymon[51], Yariv Yogev[49], Leonhard Schäffer[52], Arnaud Toussaint[53], Marie-Claude Rossier[54], Renato Augusto Moreira De Sa[55], Claudia Grawe[56], Karoline Aebi-Popp[57], Anda-Petronela Radan[58], Luigi Raio[58], Daniel Surbek[58], Paul Böckenhoff[59], Brigitte Strizek[59], Martin Kaufmann[60], Andrea Bloch[61], Michel Boulvain[62], Silke Johann[63], Sandra Andrea Heldstab[64], Monya Todesco Bernasconi[64], Gaston Grant[65], Anis Feki[65], Anne-Claude Muller Brochut[66], Marylene Giral[67], Lucie Sedille[67], Andrea Papadia[68], Romina Capoccia Brugger[69], Brigitte Weber[70], Tina Fischer[71], Christian Kahlert[72], Karin Nielsen Saines[73], Mary Cambou[74], Panagiotis Kanellos[75], Xiang Chen[76], Mingzhu Yin[77], Annina Haessig[78], Sandrine Ackermann[1], David Baud[1,81,82]✉ & Alice Panchaud[79,80,82]

Pregnant women may be at higher risk of severe complications associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which may lead to obstetrical complications. We performed a case control study comparing pregnant women with severe coronavirus disease 19 (cases) to pregnant women with a milder form (controls) enrolled in the COVI-Preg international registry cohort between March 24 and July 26, 2020. Risk factors for severity, obstetrical and

[1]Materno-fetal and Obstetrics Research Unit, Department "Femme-Mère-Enfant", University Hospital, Lausanne, Switzerland. [2]Obstetricia y Ginecologia, Puerta de Hierro University Hospital, Madrid, Spain. [3]Obstetrics and Gynaecology Department, 12 de Octubre University Hospital, Madrid, Spain. [4]La Paz Universitary Hospital, Madrid, Spain. [5]Hospital Santa Caterina, Gerona, Spain. [6]Department of Obstetrics and Gynaecology, CHOG,

Saint-Laurent du Maroni, France. [7]Obstétrique et de Médecine fœtale, Hopital Necker-Enfants Malades, Paris, France. [8]Obstetrics Division, Department of Pediatrics Gynecology and Obstetrics, University Hospitals of Geneva, Geneva, Switzerland. [9]BCNatal Maternal-Fetal Medicine Service, Hospital Clínic, University of Barcelona, Barcelona, Spain. [10]Fetal Medicine Research Center, Hospital Clínic and Hospital Sant Joan de Déu, Barcelona, Spain. [11]Service of Pharmacy, The Rotunda Hospital, Dublin, Ireland. [12]Maternal-fetal Medicine, The Rotunda Hospital, Dublin, Ireland. [13]UCD Perinatal Research Centre, National Maternity Hospital, Dublin, Ireland. [14]Maternal Medicine, National Maternity Hospital, Dublin, Ireland. [15]Microbiology, National Maternity Hospital, Dublin, Ireland. [16]Obstetric and Gynecology Unit, Centre Hospitalier René Dubos, Cergy-Pontoise, France. [17]Department of Obstetrics & Gynecology, University of Campinas, Campinas, Brazil. [18]Maternal-Fetal Medicine, Department of Obstetrics, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile. [19]Medicina Materno Fetal, Hospital San José, Santiago, Chile. [20]Hospital Felix Bulnes Cerda, Santiago, Chile. [21]Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, New Haven, CT, USA. [22]Department of Epidemiology of Microbial Diseases, Yale of School of Public Health, New Haven, CT, USA. [23]Serviço ginecologia e obstetrícia, Centro Hospitalar e Universitário São João, Porto, Portugal. [24]Teratology Information Service, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy. [25]Medical School, Santa Maria University Hospital, Lisbon, Portugal. [26]Department of Obstetrics, Jeanne de Flandre University Hospital, Lille, France. [27]Pediatra e Neonatologista, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. [28]Maternity Ward, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. [29]Departamento de Genética, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. [30]Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. [31]Department of Obstetrics and Gynecology, Université de Franche Comté, Besançon, France. [32]Department of Obstetrics and Gynecology, Centre Hospitalier Departemental de Vendée, La Roche sur Yon, France. [33]Clinical Research Department, Centre Hospitalier Départemental de Vendée, La Roche sur Yon, France. [34]Department of Obstetrics and Gynecology, Annecy Genevois Hospital, Annecy, France. [35]Department of Gynecology and Obstetrics, Intercommunal Hospital Centre of Poissy-Saint-Germain-en-Laye, Poissy, France. [36]Department of Obstetrics and Antenatal Care, University Hospital Basel, Basel, Switzerland. [37]Department of Neonatology, UniversitätsSpital Zürich, Zurich, Switzerland. [38]Department of Anthropology, University of Zurich, Zurich, Switzerland. [39]Clinic of Obstetrics, UniversitätsSpital Zürich, Zurich, Switzerland. [40]Department of Obstetrics and Gynecology, Bordeaux University Hospital, Bordeaux, France. [41]Department of Obstetrics and Gynecology, University Hospitals Leuven, Leuven, Belgium. [42]Department of Regeneration and Development, Katholieke Universiteit Leuven, Leuven, Belgium. [43]Obstetric and Gynecology Unit, Sion Hospital, Sion, Switzerland. [44]Service de Réanimation polyvalente et USC, Victor Dupouy Hospital, Argenteuil, France. [45]Obstetrics Unit, Victor Dupouy Hospital, Argenteuil, France. [46]Obstetrics and Gynecology Department, Fundacion Clinica Valle de Lili, Universitary Hospital, Cali, Colombia. [47]Department of Obstetrics and Fetal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [48]Maternal-Fetal Medicine Unit, Rabin Medical Center, Tel-Aviv University, Tel Aviv, Israel. [49]Division of Ultrasound in Obstetrics and Gynecology, Lis Maternity Hospital, Tel Aviv, Israel. [50]Division of Ultrasound in ObGy, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel. [51]Israeli Society of Obstetrics and Gynecology, Hasaf Harofe Medical Center, Tel Aviv University, Tel Aviv, Israel. [52]Obstetrics Cantonal Hospital of Baden, Affiliated Hospital of the University of Zurich, Baden, Switzerland. [53]Department of Gynecology and Obstetrics, Intercantonal Hospital of Broye, Payerne, Switzerland. [54]Obstetrics and Gynecology, Hospital Riviera Chablais, Rennaz, Switzerland. [55]Maternal-Fetal Unit, Federal Fluminense University, Rio de Janeiro, Brazil. [56]Department of Obstetrics, Gynecology Stadtspital Triemli Zürich, Zurich, Switzerland. [57]Department of Infectious Diseases, University Hospital Bern, Bern, Switzerland. [58]Department of Obstetrics and Gynecology, Inselspital, Bern, Switzerland. [59]Department of Obstetrics and Prenatal Medicine, University Hospital Bonn, Bonn, Germany. [60]Obstetric and Gynecology Unit, Spital Bülach, Bülach, Switzerland. [61]Obstetric and Gynecology Unit, Hopital du Jura, Delémont, Switzerland. [62]Pôle Department of Gynecology and Obstetrics, GHOL Hôpital de Nyon, Nyon, Switzerland. [63]Department of Obstetrics and Gynecology Spitalzentrum OBerwallis, Standort Visp, Visp, Switzerland. [64]Frauenklinik, Kantonsspital Aarau, Aarau, Switzerland. [65]Department of Obstetrics and Gynecology, HFR Fribourg Hospital, Fribourg, Switzerland. [66]GynEcho Medical Practice, Fribourg, Switzerland. [67]Department of Obstetrics and Gynecology, La Rochelle Hospital, La Rochelle, France. [68]Department of Obstetrics and Gynecology, Ente Ospedaliero Cantonale of Lugano, Lugano, Switzerland. [69]Department of Obstetrics and Gynecology Réseau Hospitalier Neuchâtelois, Neuchâtel, Switzerland. [70]Department of Obstetrics and Gynecology, Kantonsspital Obwalden (KSOW), Sarnen, Switzerland. [71]Frauenklinik, Kantonsspital Saint Gall, Saint Gall, Switzerland. [72]Infectious Diseases and Hospital Epidemiology, Kantonsspital Saint Gall, Saint Gall, Switzerland. [73]Division of Infectious Diseases, Department of Pediatrics, David Geffen UCLA School of Medicine, Los Angeles, CA, USA. [74]Cardiac Surgery Department, David Geffen UCLA School of Medicine, Los Angeles, CA, USA. [75]Department of Obstetrics and Gynecology, Kantonsspital Uri, Altdorf, Switzerland. [76]Dermatology Unit, Xiangya Hospital, Changsha, China. [77]Hunan Engineering Research Center of Gynecology and Obstetrics Disease, Xiangya Hospital, Changsha, China. [78]Department of Obstetrics and Gynecology, Zuger Kantonsspital, Zug, Switzerland. [79]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland. [80]Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. [81]Materno-Fetal & Obstetrics Research Unit, Department of Obstetrics and Gynecology, Centre Hospitalier Universitaire Vaudois (CHUV), 1011 Lausanne, Switzerland. [82]These authors contributed equally: Manon Vouga, Guillaume Favre, Oscar Martinez-Perez, Leo Pomar, David Baud and Alice Panchaud. ✉email: david.baud@chuv.ch

immediate neonatal outcomes were assessed. A total of 926 pregnant women with a positive test for SARS-CoV-2 were included, among which 92 (9.9%) presented with severe COVID-19 disease. Risk factors for severe maternal outcomes were pulmonary comorbidities [aOR 4.3, 95% CI 1.9–9.5], hypertensive disorders [aOR 2.7, 95% CI 1.0–7.0] and diabetes [aOR2.2, 95% CI 1.1–4.5]. Pregnant women with severe maternal outcomes were at higher risk of caesarean section [70.7% (n = 53/75)], preterm delivery [62.7% (n = 32/51)] and newborns requiring admission to the neonatal intensive care unit [41.3% (n = 31/75)]. In this study, several risk factors for developing severe complications of SARS-CoV-2 infection among pregnant women were identified including pulmonary comorbidities, hypertensive disorders and diabetes. Obstetrical and neonatal outcomes appear to be influenced by the severity of maternal disease.

Altered immunity, reduced respiratory capacity, vascular and hemodynamic changes put pregnant women at higher risk of complications, while specific harm to the exposed fetus/newborn may be observed. Although, early reports from the SARS-CoV-2 epidemic[1] suggested that the clinical course for infected pregnant women was similar to the general population, more recent data suggest a higher risk of severe outcomes in pregnant women compared to the general population at an equivalent age, with severe outcomes observed in 8 to 11%[2–6]. In the general population, preexisting health conditions, namely pulmonary pathologies, hypertension and diabetes have been associated with severe outcomes[7,8]. Information on the impact of these determinants on the maternal disease evolution and other risk factors specific to pregnancy is still fragmented, although evidence suggest that they might contribute to the severity of the disease[6,9]. Furthermore, fetal/newborn risks still need to be better assessed as vertical transmission of the virus and placental infection appears to be possible with newborns potentially demonstrating related symptoms[10–13], while a significantly higher rate of preterm deliveries (25–30%) among women with Coronavirus disease 19 (COVID-19) has been reported[3,4].

Information on specific risks among pregnant women are urgently needed to provide evidence-based guidelines for the management of this vulnerable population. To accomplish this, we developed an international web registry[14] in March 2020, to promote a structured collection of data regarding pregnant women and their fetuses exposed to SARS-CoV-2. Using this dataset, we performed a case–control study to assess the risk of severe maternal outcomes and associated risk factors as well as a description of pregnancy/neonatal outcomes stratified for the severity of the disease among pregnant women with a confirmed SARS-CoV-2 infection.

Materials and methods

Study setting and population. The patients enrolled in this study are part of the COVI-Preg international registry investigating the consequences of SARS-Cov-2 infection during pregnancy[14]. All pregnant women tested for SARS-CoV-2 infection at any stage of gestation were eligible for inclusion in this multicenter study except those < 18 years of age as well as individuals declining to consent or not able to consent for themselves. Informed oral or written consent was obtained for all participants. Deidentified data were prospectively recorded by each center (Table S1) using the REDCap (Research Electronic Data Capture) electronic data capture tool[15,16]. Quality checks were performed as described in the Supplementary Materials. Using this dataset, we performed a case control study among pregnant women with a confirmed SARS-CoV-2 infection.

The study was approved by both the Swiss Ethical Board (CER-VD-2020-00548) and the local ethics boards at each participating center. The study was conducted from March 24th to July 26th, 2020. All methods were carried out in accordance with relevant guidelines and regulations in the manuscript.

Inclusion criteria and SARS-CoV-2 status. Pregnant women were tested for SARS-CoV-2 either because of a suspected infection due to ongoing symptoms compatible with COVID-19 or an history of potential exposure or through routine systematic screening instituted during the pandemic in some hospitals depending on local capacities and guidelines. Maternal testing was performed using a nasopharyngeal RT-PCR for SARS-CoV-2 swab test. Pregnant women with a positive RT- PCR test result at any stage during pregnancy irrespective of clinical signs and symptoms were considered as having a confirmed infection and included in the present study. Pregnant women with a SARS-CoV-2 negative test and no other positive test result during the entire follow-up period were excluded.

Case and control definition. Pregnant women with severe adverse outcomes, defined as any of the following: (1) the need for advanced oxygen support (i.e. high flow cannula, non-invasive ventilation through CPAP or mechanical ventilation), (2) admission to the intensive care unit (ICU) and (3) maternal death, were classified as cases. The control group included pregnant women with either mild adverse outcomes, defined as maternal hospitalization requiring oxygen supplementation, or no adverse outcomes, defined as outpatient management or hospitalization not requiring oxygen supplementation.

Identification of risk factors for severe adverse maternal outcome. Pregnant women with severe adverse outcomes (cases) were compared to pregnant women with mild or no adverse outcomes (controls). The effect of maternal characteristics known to be risk factors[7,8,17] for SARS-CoV-2 severe adverse outcomes in the general population were tested (i.e. maternal age > 35 years old, obesity defined as a BMI > 30, hypertensive disorders, pre-and gestational diabetes, preexisting pulmonary, cardiovascular, renal, or oncologic disease and immunosuppression), as well as pregnancy related risk factors such as nulliparity (dichotomized as yes/no), eth-

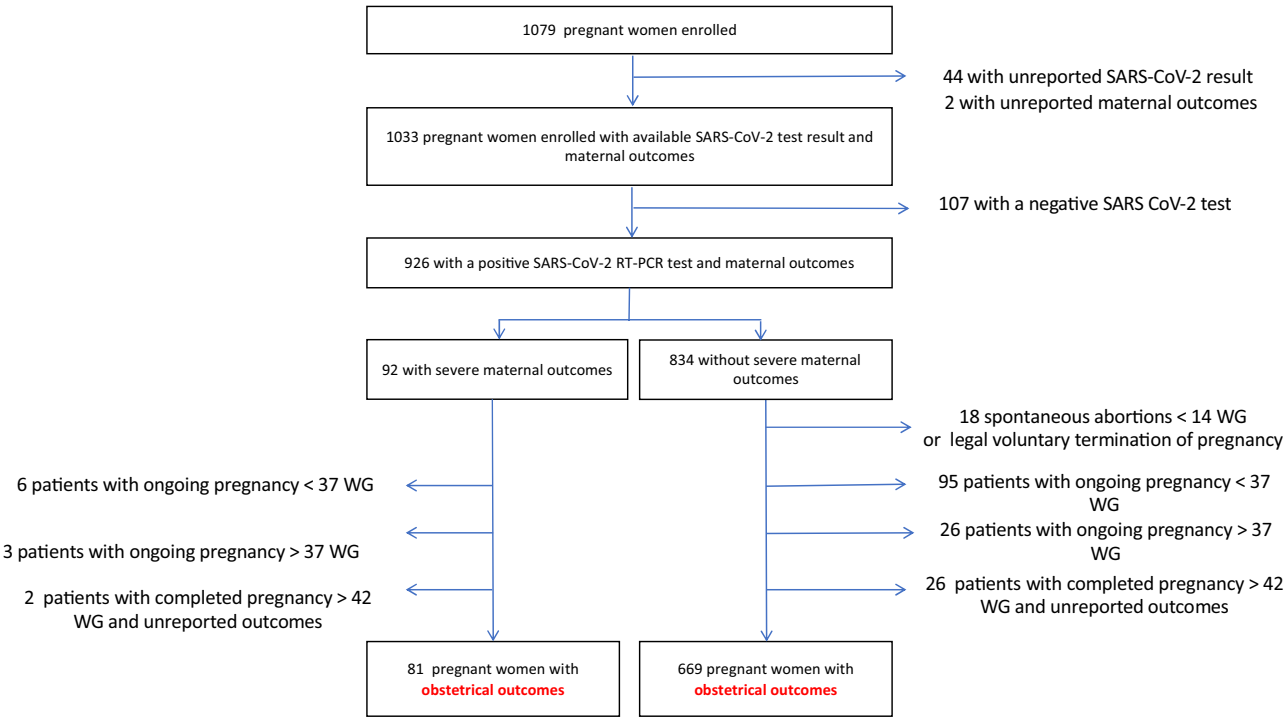


Figure 1. Flow chart. The COVI-Preg international registry was launched in March 2020. To date, 120 centers from 16 countries have contributed patients (supplementary Table 1). All pregnant women tested for SARS-CoV-2 infection at any stage of gestation were eligible for inclusion in this multicenter study except those < 18 years of age as well as individuals declining to consent or not able to consent for themselves. Deidentified data were prospectively recorded by each center using the REDCap (Research Electronic Data Capture) electronic data capture tool[15,16]. At inclusion (i.e. at the time of SARS-CoV-2 screening), the following data were recorded: socio-demographic characteristics, obstetrical history and information on SARS-CoV-2 exposure. Pregnancies were monitored as clinically indicated according to local protocols. After inclusion, the following data were collected: results of maternal testing (SARS-CoV-2 and/or other infectious pathogens), COVID-19 history, maternal, pregnancy and neonatal outcomes. Data were analyzed using Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2WG, weeks ‘gestation.

nicity (defined as Caucasian yes/no), multiple pregnancy, gestational age at infection (dichotomized as < or > 20 WG)[9].

Secondary outcomes: absolute risk (%) of obstetrical outcomes and neonatal outcomes. For completed pregnancies (i.e. pregnancy ending in either fetal loss > 14 WG or livebirth, obstetrical outcomes (pregnancy outcome, GA at delivery, mode of delivery) and neonatal outcomes (neonatal death, neonatal admission to the ICU (NICU), birthweight and rates of suspected perinatal SARS-CoV-2) were assessed. For multiple gestations (n = 26), the analysis considered the whole pregnancy. Fetal loss was defined as a spontaneous antepartum fetal death > 14 WG (i.e. late miscarriage (14–24 WG) and stillbirth (fetal demise > 24 WG). Suspected perinatal SARS-CoV-2 transmission was defined as a positive RT-PCR result performed at birth.

Statistical analysis. We performed a multivariate analysis to estimate odds ratios (OR) with 95% CIs adjusting for risk factors of COVID-19 severity (i.e. maternal age, BMI, pre- and gestational hypertensive disorders (including pre-eclampsia), pre-and gestational diabetes, pre-existent pulmonary comorbidities, other pre-gestational comorbidities (cardiovascular, renal, oncological diseases and immunosuppression), and gestational risk factors of severe maternal outcomes (ethnicity, parity, pregnancy conditions (threatened preterm labor, placenta previa, placental malfunction and PPROM) and exposure after 20WG) and accounting for missing values as described in the supplementary material.

Statistical analyses were performed using Stata 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). A *P* value less than 0.05 was considered as statistically significant.

Results

Between March 24 and July 26, 2020, 1079 pregnant women tested for SARS-CoV-2 were enrolled in the registry among which 926 had a confirmed SARS-CoV-2 infection (Fig. 1). Socio-demographic characteristics are presented in Table 1. A third of the women were asymptomatic (31.9% n = 295/926), while cough (40.4%, n = 374/926), fever (32.4%, n = 300/926) and anosmia/ageusia (17.8%, n = 165/926) were the most reported

Socio-demographic factors	Pregnant women with a confirmed SARS-CoV-2 infection (n = 926)
Maternal age	
Median—y.o. (IQR)	32 (28–36)
Age > 35 y.o.– no (%)	272 (29.4)
Unknown	5 (0.5)
Ethnicity—no (%)	
Caucasian	494 (53.4)
Hispanic or Latin-American	217 (23.4)
Afro-American	117 (12.6)
Asian or Pacific Islands	30 (3.2)
Other	44 (4.8)
Unknown	24 (2.6)
Region of residence—no (%)	
North America	27 (2.9)
South and Central America	249 (26.9)
Europe	490 (52.9)
Middle East	17 (1.8)
Central Asia	3 (0.3)
South East Asia	6 (0.6)
Africa	26 (2.8)
Unknown	108 (11.6)
Previous pregnancies—no (%)	
Nulliparous	346 (37.4)
Multiparous	568 (61.3)
Multiparous ≥ 3	102 (11.0)
Previous cesarean sections > 1	135 (14.6)
Unknown	12 (1.3)
Previous adverse pregnancy outcomes—no (%)	
Stillbirths	18 (1.9)
Unknown	163 (17.6)
Maternal comorbidities	
Any maternal comorbidities—no (%)	170 (18.4)
Pulmonary comorbidities	35 (3.8)
Cardiac comorbidities	14 (1.5)
Hypertension	19 (2.1)
Pregestational diabetes	12 (1.3)
Immunosuppression	4 (0.4)
Thyroid dysfunction	34 (3.7)
Oncologic comorbidities	9 (1.0)
Hematologic comorbidities	17 (1.8)
Auto-immune diseases	4 (0.4)
Other (neurological, urological, digestive, orthopedic)	85 (9.2)
Unknown	4 (0.4)
Maternal BMI	
Median (IQR)	26 (23–30)
BMI > 30—no (%)	208 (22.5)
BMI > 35—no (%)	81 (8.8)
Unknown—no (%)	122 (13.2)
Any drugs	63 (6.8)
Cigarettes	61 (6.6)
Alcohol	5 (0.5)
Unknown	17 (1.8)
Current pregnancy—no (%)	
Multiple pregnancy	24 (2.6)
Ongoing pregnancy conditions	
Any	114 (12.3)
Pre-eclampsia	10 (1.1)
Continued	

Socio-demographic factors	Pregnant women with a confirmed SARS-CoV-2 infection (n = 926)
Gestational diabetes	45 (4.9)
IUGR	7 (0.8)
Abnormal fetal doppler	1 (0.1)
Macrosomia	6 (0.7)
Threatening preterm labor	5 (0.5)
Placenta previa	2 (0.2)
PPROM	5 (0.5)
Other	46 (5.0)
Unknown	33 (3.6)
Fetal malformation	18 (1.9)
Risk of DS	
High risk > 1/1000	24 (2.6)
Unknown	341 (36.8)

Table 1. Description of the population (sociodemographic characteristics). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; y.o., years old; IQR, interquartile range; BMI, body mass index; PPROM, preterm premature rupture of the membranes; IUGR, intrauterine growth restriction; DS, Down syndrome; WG, weeks' gestation.

COVID-19 history	Pregnant women with a confirmed SARS-CoV-2 infection (n = 926)
Timing of exposure—no (%)	
< 20 WG	89 (9.6)
Median GA at exposure WG (IQR)	12 (9–16)
> 20 WG	826 (89.2)
Median GA at exposure WG (IQR)	38 (34–40)
Unknown	11 (1.2)
Clinical manifestation—no (%)	
Asymptomatic	295 (31.9)
Fever	300 (32.4)
Cough	374 (40.4)
Dyspnea	146 (15.8)
Sore throat	83 (9.0)
Myalgia	148 (16.0)
Fatigue	191 (20.6)
Headache	121 (13.1)
Nausea/vomiting	48 (5.2)
Anosmia/ageusia	165 (17.8)
Other	81 (8.8)
Maternal outcomes—no (%)	
No adverse outcomes	828 (89.4)
Mild adverse outcomes	6 (0.6)
Severe adverse outcomes	92 (9.9)
Maternal deaths	6 (0.6)
Admission to ICU	37 (4.0)
Advanced oxygen support	68 (7.3)

Table 2. Description of the population (COVID-19 history). First trimester was defined from 1 to 13 6/7 weeks' gestation (WG), second trimester from 14 0/7 to 27 6/7 WG and third trimester from 28 WG. For symptomatic patients, trimester of exposure was defined as the gestational age (GA) at onset of symptoms. For asymptomatic patients, the trimester of exposure was defined as the GA at SARS-CoV-2 testing. For symptomatic patients, the trimester of exposure was defined as the gestational age (GA) at onset of symptoms. For asymptomatic patients, the trimester of exposure was defined as the GA at SARS-CoV-2 testing. IQR, interquartile range; ICU, Intensive Care Unit; WG, weeks' gestation.

Maternal outcomes	Pregnant women with a POSITIVE test result for SARS-CoV-2												
	Severe adverse maternal outcomes n = 92		No/mild adverse maternal outcomes n = 834										
	n (%)	95% CI	n (%)	95% CI	OR[a]	95%CI	p value	aOR[b]	95%CI	p value	aOR[c]	95%CI	p value
Maternal age													
Age > 35 y.o	28 (30.4)	21.3–40.9	244 (29.3)	26.2–32.5	1.0	0.6–1.7	0.9042	1.1	0.7–1.8	0.708	1.1	0.7–1.7	0.755
Unknown	0 (0.0)	n.a.	5 (0.6)	0.2–1.4									
Ethnicity													
Caucasian	41 (44.6)	34.2–55.3	453 (54.3)	50.9–57.7	0.7	0.4–1.1	0.0926	0.7	0.5–1.2	0.214			
Unknown	3 (3.3)	0.7–9.2	21 (2.5)	1.6–3.8									
Previous pregnancies													
Nulliparous—no (%)	29 (31.5)	22.2–42.0	317 (38.0)	34.7–41-4	0.8	0.5–1.2	0.2564	0.8	0.5–1.3	0.412			
Unknown	1 (1.1)	0.0–5.9	11 (1.3)	0.7–2.3									
Maternal comorbidities gestational/pre-gestational													
Pre-gestational comorbidities	19 (20.7)	12.9–35.7	123 (14.8)	12.4–17.3									
Pulmonary comorbidities	10 (10.9)	5.3–19.1	25 (3.0)	1.9–4.4	**3.9**	**1.6–8.9**	**0.0013**	**4.3**	**1.9–9.5**	**0.000**	**4.0**	**1.8–8.9**	**0.001**
Any other	6 (6.5)	2.6–13.7	40 (4.8)	0.7–6.5	1.4	0.5–3.4	0.4473	0.9	0.3–2.4	0.841	0.9	0.4–2.4	0.891
Cardiac comorbidities	3 (3.3)	0.7–9.2	11 (1.3)	0.7–2.3									
Renal diseases	2 (2.2)	0.3–7.6	4 (0.5)	0.1–1.2									
Immunosuppression	1 (1.1)	0.0–5.9	3 (0.4)	0.1–1.0									
Oncologic comorbidities	1 (1.1)	0.0–5.9	8 (1.0)	0.4–1.9									
Hematologic comorbidities	2 (2.2)	0.2–7.6	15 (1.8)	1.0–2.9									
Auto-immune diseases	1 (1.1)	0.0–5.9	3 (0.4)	0.1–1.0									
Gestational comorbidities	9 (9.8)	4.6–17.8	71 (8.5)	6.7–10.6	1.2	0.5–2.5	0.6949	1.2	0.6–2.6	0.592			
Multiple pregnancy	2 (2.2)	0.2–7.6	22 (2.6)	1.7–4.0									
Other	8 (8.7)	3.8–16.4	54 (6.5)	4.9–8.4									
Hypertensive disorders	7 (7.6)	3.1–15.1	19 (2.3)	1.4–3.5	**3.5**	**1.2–9.1**	**0.0103**	**2.7**	**1.0–7.0**	**0.044**	**2.7**	**1.0–7.1**	**0.042**
Pre-gestational	4 (4.3)	1.2–10.8	15 (1.8)	1.0–2.9									
Gestational /Pre-eclampsia	4 (4.3)	1.2–10.8	6 (0.7)	0.3–1.6									
Diabetes	12 (13.0)	6.9–21.7	45 (5.4)	4.0–7.2	**2.6**	**1.2–5.3**	**0.0094**	**2.2**	**1.1–4.5**	**0.036**	**2.2**	**1.1–4.5**	**0.034**
Pregestational	4 (4.3)	1.2–10.8	8 (1.0)	0.4–1.9									
Gestational	8 (8.7)	3.8–16.4	37 (4.4)	3.1–6.1									
Unknown	0 (0.0)	n.a.	2 (0.2)	0.0–0.9									
Maternal BMI													
BMI > 30	28 (30.4)	21.3–40.9	180 (21.6)	18.8–24.5	**1.7**	**1.1–2.9**	**0.0220**	1.3	0.8–2.2	0.351	1.4	0.8–2.4	0.201
BMI > 35	15 (16.3)	9.4–25.5	66 (7.9)	6.2–10.0									
Unknown	12 (13.0)	6.9–21.7	110 (13.2)	11.0–15.7									
COVID-19 exposure													
Timing of exposure													
> 20 weeks gestation	84 (91.3)	83.6–96.2	742 (89.0)	86.6–91.0	1.1	0.5–2.8	0.8538	1.4	0.7–3.2	0.356			
Unknown	0 (0.0)	n.a.	11 (1.3)	0.7–2.3									

Table 3. Risk factors for severe adverse maternal outcomes among pregnant women with a positive SARS-CoV-2 test. The effect of maternal characteristics known to be risk factors[7,8,17] were tested (i.e. maternal age > 35 year old, obesity defined as a BMI > 30, hypertensive disorders (including pre-eclampsia), pre-and gestational diabetes, pre-existent pulmonary, cardiovascular, renal, oncologic diseases and immunosuppression), as well as pregnancy related risk factors such as pregnancy conditions (threatened preterm labor, placenta previa, placental malfunction and preterm premature rupture of the membrane (PPROM) (dichotomized as yes/no))), nulliparity (dichotomized as yes/no), ethnicity (defined as Caucasian yes/no), multiple pregnancy, age of pregnancy at infection (dichotomized as < or > 20 WG)[9]. In bold are presented significant results. SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; OR, odds ratio; aOR, adjuster odds ratio; y.o.; years old; BMI, Body Mass Index; n.a., non-applicable. [a]ORs were calculated without missing values. [b]Adjusted for specific COVID-19 risk factors (maternal age, pulmonary comorbidities, hypertensive disorders, diabetes mellitus, maternal BMI and other maternal comorbidities with a low prevalence in the cohort), specific pregnancy risk factors (ethnicity, parity, other pregnancy conditions (placenta previa, preterm premature rupture of the membrane , preterm labor, IUGR) and timing of exposure. [c]Adjusted for specific COVID-19 risk factors only (maternal age, pulmonary comorbidities, hypertensive disorders, diabetes mellitus, maternal BMI and other maternal comorbidities with a low prevalence in the cohort).

symptoms. 9.9% (n = 92/926) experienced severe maternal outcomes, including 7.3% (n = 68/926) requiring advanced oxygen support and 4.0% (n = 37/926) requiring ICU admission; 6 maternal deaths were recorded (0.6%) (Table 2).

Risk factors for severe maternal outcomes among positive pregnant women. In a univariate analysis pulmonary comorbidities [crude OR 3.9, 95% CI 1.6–8.9], hypertensive disorders [crude OR 3.5, 95% CI 1.2–9.1], diabetes [crude OR 2.6, 95% CI 1.2–5.3] and BMI > 30 [crude OR 1.7, 95% CI 1.1–2.9] were significantly associated with an increased risk of severe maternal outcomes (Table 3). In a multivariate analysis adjusting for risk factors of COVID-19 severity, gestational risk factors of severe maternal outcomes, and accounting for missing values through multiple imputation, pulmonary comorbidities [aOR 4.3, 95% CI 1.9–9.5], hypertensive disorders [aOR 2.7, 95% CI 1.0–7.0] and diabetes [2.2, 95% CI 1.1–4.5] remained significantly associated, while BMI > 30 did not retain significance [aOR 1.3, 95% CI 0.8–2.2]. When adjusting for COVID-19 risk factors only, similar results were obtained (Table 3). Common pregnancy related risk factors were not associated with severe maternal outcomes (i.e. nulliparity, ethnicity, multiple pregnancy, gestational age at infection).

Secondary outcomes. *Absolute risk of pregnancy, obstetrical and neonatal outcomes.* No differences were observed in terms of livebirth rate among positive women with severe adverse outcomes (i.e. cases) compared to women with no or mild adverse outcomes (i.e. controls) [absolute rate 92.6% (n = 75/81) compared to 98.1% (n = 656/669)] (Table 4), although a trend toward poorer obstetrical outcomes was observed among women with severe adverse outcomes [absolute rate of fetal loss > 14 WG 7.4% (n = 6/81) compared to 1.9% (n = 13/669)]. An increased risk of caesarean section was observed among patients with severe adverse outcomes [absolute caesarean sections rate 70.7% (n = 53/75) compared to 30.9% (n = 203/656)]. Similarly, women with severe maternal outcomes were at increased risk of preterm delivery < 37WG [absolute risk 62.7% (n = 32/51) compared to 36.3% (78/215)] and < 34 WG [absolute risk 51.9% (n = 14/27) compared to 20.5% (24/117)], most of which were iatrogenic [81.3% (n = 26/32) and 85.7% (n = 12/14), respectively]. Newborns born to mothers with severe adverse pregnancy outcomes were more frequently admitted to NICU [absolute risk 41.3% (n = 31/75) compared to 11.6% (n = 76/656)]. The most frequent reasons for admission were prematurity [71.0% (n = 22/31)] and respiratory distress [48.5% (n = 15/31)] (Table 4). A positive SARS-CoV-2 test at birth was observed in 2.9% of neonates (n = 11/384).) The rates of suspected perinatal transmission and reduced birthweight were similar between newborns born to mothers with severe outcomes compared to those with no or mild outcomes.

Discussion

In this study, we present the largest cohort of pregnant women tested for SARS-Cov-2 worldwide and the first analysis of primary data stratified by the severity of maternal disease, allowing us to identify specific risk factors associated with adverse maternal outcomes.

Severe adverse outcomes, defined by maternal death, admission to ICU and/or advanced oxygen support were observed in 9.9% of cases. Pulmonary comorbidities, hypertensive disorders and diabetes mellitus were significantly associated with an increased risk of severe maternal outcomes, while usual pregnancy related risk factors were not. No difference in the livebirth rate was observed between pregnant women with severe adverse outcomes and patients with an uncomplicated course. Nevertheless, a significant increased risk of caesarean section, preterm birth and neonatal admission to the intensive care unit was observed, highlighting that obstetrical and neonatal outcomes are influenced by the severity of maternal disease.

The rate of severe disease observed here is similar to what has been previously reported in other large cohorts[3–5] and summarized in a recent meta-analysis[6],where the risk of severe disease among pregnant women with COVID-19 was estimated to be 13% (95%CI 6–21%). Importantly, this risk of severe maternal complications appears significantly higher when compared to a non-pregnant population at an equivalent age, with an increased odds of ICU admission or mechanical ventilation up to 1.6 (95%CI 1.3–2.0) and 1.9 (95%CI 1.4–2.6) respectively[6].

Risk factors for severe maternal disease appear to be similar to what has been previously described in the general population, namely pulmonary pathologies, hypertension and diabetes[7,8]. Congruently, in their meta-analysis, Allotey et al. observed an increased risk of severe disease among pregnant women > 35 y.o., those with chronic hypertension, pre-existing diabetes, or body mass index > 30[6]. Interestingly, in our study, after adjustment, obesity was not independently associated with an increased risk of severe adverse outcomes. This could be explained by the fact that overweight patients often suffer from hypertension and diabetes (metabolic syndrome), which could act as the predominant causal factors. Both are associated with macro- and micro-vascular complications, and endothelial dysfunction has been suggested as a major pathophysiological mechanism associated with COVID-19 severity[18,19]. In pregnancy, endothelial change is a well-known mechanism of obstetrical complications, such as gestational hypertension, HELLP (Hemolysis, elevated liver enzymes, low platelets) and pre-eclampsia[20], and may contribute to the increased risk of COVID-19 complications. In our study, we did not observe any association with maternal age. This could be explained by the low number of patients > 35 y.o. included. Similarly, ethnicity (non-Caucasian versus Caucasian) was not associated with poorer outcomes, unlike previously described[21].

We observed a 2.9% rate of positive test among newborns born to mothers with a positive SARS-CoV-2 test. The clinical relevance of this finding remains unclear, as, at the time of the study, we were lacking comprehensive data regarding COVID-related symptoms or COVID-suspected symptoms among newborns, repeated testing and long-term follow-up. Perinatal transmission of SARS-CoV-2 has been reported by others, both in case of vaginal and cesarean sections, and was associated in some cases with neonatal symptoms[1,4,22]. In all reported cases, the possibility of postnatal infection through contacts with parents or medical personal remains difficult

Obstetrical/neonatal outcomes	Pregnant women with a positive test result for SARS-CoV-2			
	Severe adverse maternal outcomes n = 81		No/mild adverse maternal outcomes n = 669	
	n (%)	95% CI	n (%)	95% CI
Pregnancy outcomes > 14 WG				
Livebirth	75 (92.6)	84.6–97.2	656 (98.1)	96.7–99.0
Fetal loss > 14 WG	6 (7.4)	2.8–15.4	13 (1.9)	1.0–3.3
Termination of pregnancy	1 (1.2)	0.0–6.7	2 (0.3)	0.0–1.1
Obstetrical outcomes among livebirth	75		656	
GA at delivery (Weeks gestation)				
Median GA (IQR)	37 (34–38)		39 (38–40)	
Unknown GA at delivery	0 (0.0)	n.a.	2 (25.8)	15.1–41.0
Obstetrical management				
All vaginal deliveries	22 (29.3)	19.4–41.0	447 (68.1)	64.4–71.7
Vaginal delivery after spontaneous onset of labour	10 (45.5)	24.4–67.8	280 (62.6)	58.0–67.1
Vaginal delivery after induction of labour	12 (54.5)	32.2–75.6	167 (37.4)	32.9–42.0
Caesarean sections—no (%)	53 (70.7)	59.0–80.6	203 (30.9)	27.4–34.6
Elective caesarean sections—no (%)	21 (39.6)	26.5–54.0	85 (41.9)	35.0–49.0
Emergency pre-labor caesarean sections—no (%)	12 (22.6)	12.3–36.2	16 (7.9)	4.6–12.5
In labour caesarean sections after induction	12 (22.6)	12.3–36.2	52 (25.6)	19.8–32.2
In labour caesarean sections after spontaneous	8 (15.1)	6.7–27.6	50 (24.6)	18.9–31.2
Unknown	0 (0.0)	n.a.	6 (0.9)	0.3–2.0
Preterm birth among pregnancy with exposure < 37 WG	51		215	
All preterm birth < 37 WG—no (%)	32 (62.7)	48.1–75.9	78 (36.3)	29.8–43.1
Latrogenic birth among preterm birth—no (%)	26 (81.3)	63.6–92.8	49 (62.8)	51.1–73.5
Unknown—no (%)	0 (0.0)	n.a.	1 (1.3)	0.0–6.9
Unknown GA at delivery	0 (0.0)	n.a.	1 (0.5)	0.1–2.6
Preterm birth among pregnancy with exposure < 34WG	27		117	
All preterm birth < 34 WG—no (%)	14 (51.9)	31.9–71.3	24 (20.5)	13.6–29.0
Latrogenic birth among preterm birth—no (%)	12 (85.7)	57.2–98.2	14 (58.3)	36.6–77.9
Unknown—no (%)	0 (0.0)	n.a.	0 (0.0)	n.a.
Unknown GA at delivery	0 (0.0)	n.a.	1 (0.9)	0.0–4.7
Neonatal outcomes among livebirths	75		656	
Neonatal death	0 (0.0)	n.a.	1 (0.2)	0.0–0.8
NICU admission—no (%)				
All NICU admission	31 (41.3)	30.1–53.4	76 (11.6)	9.2–14.3
Prematurity	22 (71.0)	52.0–85.8	32 (42.1)	30.9–54.0
Respiratory distress	15 (48.4)	30.2–66.9	18 (23.7)	14.7–34.8
Sepsis	0 (0.0)	n.a.	5 (6.6)	2.2–14.7
Cardiovascular complications	0 (0.0)	n.a.	0 (0.0)	n.a.
Hypoglycemia	0 (0.0)	n.a.	10 (13.2)	6.5–22.9
Hyperbilirubinemia	1 (3.2)	0.1–16.7	9 (11.8)	5.6–21.3
Coagulopathy	0 (0.0)	n.a.	0 (0.0)	n.a.
Neurologic complications	0 (0.0)	n.a.	2 (2.6)	0.3–9.2
Other	3 (9.7)	2.0–25.8	19 (25.0)	15.7–36.3
Unknown	5 (6.7)	2.2–14.9	47 (7.2)	5.3–9.4
SARS-CoV-2 perinatal transmission rates				
Total of SARS-CoV-2 test at birth—no (%)	44 (58.7)	46.7–69.9	340 (51.8)	47.8–55.7
Suspected SARS CoV-2 perinatal transmission (positive RT-PCR at birth)—no (%)	2 (4.5)	0.6–15.5	9 (2.6)	1.2–5.0
Birthweight				
Birthweight < P10—no (%)	1 (1.3)	0.0–7.2	39 (5.9)	4.3–8.0
Unknown	5 (6.7)	2.2–14.9	12 (1.8)	0.9–3.2

Table 4. Obstetrical and neonatal outcomes depending on maternal severity among women with a positive SARS-CoV-2 test. Obstetrical and neonatal outcomes among positive women were assessed based on the severity of maternal disease through a case control study comparing positive women with severe adverse maternal outcomes (cases) to positive women with no or mild adverse maternal outcomes (control). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CI, confidence interval; WG, weeks 'gestation; GA, gestational age; NICU, Neonatal Intensive Care Unit; n.a., non-applicable.

to exclude[1,4]. Alternatively, transplacental transmission has been suspected in few cases, where specific IgM were detected among newborns[23,24]. Nevertheless, perinatal/vertical transmission appear to be rare and mainly associated with good neonatal outcomes[1,4,23,24].

Our study has several limitations. First, we present here the outcomes among pregnant women with a confirmed SARS-CoV-2 infection and therefore only observational conclusions can be drawn regarding the absolute risks of severe disease and adverse obstetrical/neonatal outcomes, as a control group of negative patients was not included. Nevertheless, this was beyond the scope of the present study, whose first aim was to identify specific risk factors.

Second heterogeneities exist between participating centers in the testing of pregnant women. While some centers performed routine systematic screening of presenting women independently of compatible symptoms, other only tested symptomatic pregnant women. This could have led to a selections bias of more severe symptomatic COVID-19 cases. If a symptomatic SARS-CoV-2 infection is associated with poorer maternal, obstetrical and neonatal outcomes, this selection bias may have resulted in an overestimation of the absolute risk of adverse outcomes. However, the rate of asymptomatic infections among included positive women of 31.9% (n = 295/926) is quite similar to the rate of asymptomatic infection described in the general population, estimated to range around 40–45%[25,26] and suggests a low impact of this potential bias. Similarly, patients admitted with severe disease were very likely systematically tested for SARS-CoV-2, which may have led to a possible overestimation of the actual rate of severe adverse outcome among positive patients. Follow-up analysis, including patients with ongoing pregnancies with an uncomplicated course based on systematic screening will help assess the exact risk in a more general population of pregnant women.

Third, most patients were included during the 3rd trimester of gestation, with the majority included close to delivery, while 130 pregnancies were still ongoing at the time of analysis. Although, we did not observe any impact of the gestational age (i.e. > 20 WG) on the severity of maternal disease, this could be related to a lack of statistical power. Pregnancy-related vascular complications only occur after 20 WG, which would suggest an increased risk of maternal complications in cases of maternal infection at a later stage of the pregnancy, as observed by others[9]. In our cohort, severe maternal outcomes were also observed in women exposed at < 20 WG, with an overall similar risk (n = 8/89, 9.0%) to what was described in the whole cohort. Therefore, caution should also be taken with pregnant women infected in early pregnancy.

Although our data regarding obstetrical outcomes are reassuring, definite conclusions cannot be drawn. Infections occurring at an earlier stage of gestation may be associated with poorer obstetrical outcomes. Viral particles have been detected within the placentas of women infected earlier during pregnancy[10,12,13,27]. Although placental infection seems rare, it has been associated with evidence of malperfusion[28–30], which is known to be associated with reduced fetal growth and intra-uterine fetal death. Of note, Khalil et al. have shown an increase in the number of stillbirths during the epidemic peak, without being able to determine whether this is a direct effect of the virus[31]. At the time of analysis, pregnancies < 37WG that were exposed during the 1st and 2nd-trimesters were still ongoing (Fig. 1), suggesting an uncomplicated course. Subsequent analysis, including those patients, are needed to better define obstetrical and neonatal outcomes.

In conclusion, pregnant women, particularly those with associated comorbidities, seem to be at higher risk of severe complications of SARS-CoV-2 infection. Obstetrical and neonatal outcomes appear to be influenced by the severity of maternal disease; complications include caesarean sections, neonatal prematurity and neonatal admission to the intensive care unit. Further studies are needed to assess maternal and neonatal outcomes for cases of earlier exposure.

Received: 5 January 2021; Accepted: 8 June 2021
Published online: 06 July 2021

References

1. Yu, N. *et al.* Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: A retrospective, single-centre, descriptive study. *Lancet Infect. Dis.* **20**(5), 559–564 (2020).
2. Collin, J., Byström, E., Carnahan, A. & Ahrne, M. Public Health Agency of Sweden's Brief Report: Pregnant and postpartum women with severe acute respiratory syndrome coronavirus 2 infection in intensive care in Sweden. *Acta Obstet. Gynecol. Scand.* **99**, 819–822 (2020).
3. Knight, M. *et al.* Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: National population based cohort study. *BMJ* **369**, m2107 (2020).
4. Martínez-Perez, O. *et al.* Association between mode of delivery among pregnant women with COVID-19 and maternal and neonatal outcomes in Spain. *JAMA* https://doi.org/10.1001/jama.2020.10125 (2020).
5. Vivanti, A. J. *et al.* Retrospective description of pregnant women infected with severe acute respiratory syndrome coronavirus 2, France. *Emerg. Infect. Dis.* **26**, 2069 (2020).
6. Allotey, J. *et al.* Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis. *BMJ* **370**, m3320 (2020).
7. Zhou, F. *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* **395**, 1054–1062 (2020).
8. Petrilli, C. M. *et al.* Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. *BMJ* **369**, m1966 (2020).
9. Badr, D. A. *et al.* Are clinical outcomes worse for pregnant women ≥ 20 weeks' gestation infected with COVID-19? A multicenter case-control study with propensity score matching. *Am. J. Obstet. Gynecol.* https://doi.org/10.1016/j.ajog.2020.07.045 (2020).
10. Sisman, J. *et al.* Intrauterine transmission of SARS-COV-2 infection in a preterm infant. *Pediatr. Infect. Dis. J.* https://doi.org/10.1097/INF.0000000000002815 (2020).
11. Zeng, L. *et al.* Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. *JAMA Pediatr.* https://doi.org/10.1001/jamapediatrics.2020.0878 (2020).

12. Baud, D. *et al.* Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. *JAMA* https://doi.org/10.1001/jama.2020.7233 (2020).
13. Algarroba, G. N. *et al.* Visualization of severe acute respiratory syndrome coronavirus 2 invading the human placenta using electron microscopy. *Am. J. Obstet. Gynecol.* **223**, 275–278 (2020).
14. Panchaud, A. *et al.* An international registry for emergent pathogens and pregnancy. *Lancet* **395**, 1483–1484 (2020).
15. Harris, P. A. *et al.* Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J. Biomed. Inform.* **42**, 377–381 (2009).
16. Harris, P. A. *et al.* The REDCap consortium: Building an international community of software platform partners. *J. Biomed. Inform.* **95**, 103208 (2019).
17. CDC COVID-19 Response Team. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019—United States, February 12-March 28, 2020. *MMWR Morb. Mortal. Wkly. Rep.* **69**, 382–386 (2020).
18. Monteil, V. *et al.* Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell* **181**, 905-913.e7 (2020).
19. Varga, Z. *et al.* Endothelial cell infection and endotheliitis in COVID-19. *Lancet* **395**, 1417–1418 (2020).
20. Roberts, J. M. *et al.* Preeclampsia: An endothelial cell disorder. *Int. J. Gynecol. Obstet.* **32**, 299–299 (1990).
21. Sze, S. *et al.* Ethnicity and clinical outcomes in COVID-19: A systematic review and meta-analysis. *EClinicalMedicine* **29**, 100630 (2020).
22. Wang, S. *et al.* A case report of neonatal COVID-19 infection in China. *Clin. Infect. Dis.* https://doi.org/10.1093/cid/ciaa225 (2020).
23. Dong, L. *et al.* Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. *JAMA* https://doi.org/10.1001/jama.2020.4621 (2020).
24. Zeng, H. *et al.* Antibodies in infants born to mothers with COVID-19 pneumonia. *JAMA* https://doi.org/10.1001/jama.2020.4861 (2020).
25. Oran, D. P. & Topol, E. J. Prevalence of asymptomatic SARS-CoV-2 infection: A narrative review. *Ann. Intern. Med.* https://doi.org/10.7326/M20-3012 (2020).
26. Lavezzo, E. *et al.* Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'. *Nature* https://doi.org/10.1038/s41586-020-2488-1 (2020).
27. Penfield, C. A. *et al.* Detection of SARS-COV-2 in placental and fetal membrane samples. *Am. J. Obstet. Gynecol. MFM* **100133**, 438. https://doi.org/10.1016/j.ajogmf.2020.100133 (2020).
28. Prabhu, M. *et al.* Pregnancy and postpartum outcomes in a universally tested population for SARS-CoV-2 in New York City: A prospective cohort study. *BJOG* https://doi.org/10.1111/1471-0528.16403 (2020).
29. Shanes, E. D. *et al.* Placental pathology in COVID-19. *Am. J. Clin. Pathol.* **154**, 23–32 (2020).
30. Hosier, H. *et al.* SARS-CoV-2 infection of the placenta. *J. Clin. Investig.* https://doi.org/10.1172/JCI139569 (2020).
31. Khalil, A. *et al.* Change in the incidence of stillbirth and preterm delivery during the COVID-19 pandemic. *JAMA* https://doi.org/10.1001/jama.2020.12746 (2020).

Acknowledgements

We thank all patients, midwives and nurses involved in this project for their contribution and for providing crucial help in data management, data entry and ethical procedures, especially Mrs Karine Lepigeon and Caroline Lombard (Lausanne University Hospital), Véronique Othenin-Girard, Marika Santagata and Monia Moreau (Geneva University Hospital).

Author contributions

M.V., G.F., O.M.P., L.P., D.B. and A.P. conceived and designed COVI-Preg. All authors (n = 129) provided cases in COVI-Preg. M.V. and A.P. performed the statistical analysis. M.V., G.F., L.P., D.B. and A.P. interpreted the results, did the literature review and wrote the first draft. All authors provided critical inputs to the paper, reviewed and approved the final version.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-021-92357-y.

Correspondence and requests for materials should be addressed to D.B.

COVID-19 mRNA vaccine in pregnancy: Results of the Swiss COVI-PREG registry, an observational prospective cohort study

Guillaume Favre,[a,1] Emeline Maisonneuve,[b,1] Léo Pomar,[a,c] Ursula Winterfeld,[d] Charlotte Daire,[a] Begoña Martinez de Tejada,[e,f] Dominique Delecraz,[g] Sonia Campelo,[g] Mirjam Moser,[h] Monya Todesco-Bernasconi,[h] Stefanie Sturm,[i] Irene Hösli,[j] Cécile Monod,[j] Brigitte Frey Tirri,[k] Stylianos Kalimeris,[l] Carolin Blume,[l] Jérôme Mathis,[m,n] Roland Zimmerman,[o] Anda Petronela Radan,[n] Daniel Surbek,[n] David Baud,[a,1]* and Alice Panchaud[a,b,p,1]

[a]Materno-fetal and Obstetrics Research Unit, Department "Femme-Mère-Enfant", University Hospital, Lausanne, Switzerland
[b]Institute of Primary Health Care (BIHAM), University of Bern, Switzerland
[c]School of Health Sciences (HESAV), University of Applied Sciences and Arts Western Switzerland, Lausanne, Switzerland
[d]Swiss Teratogen Information Service, Clinical pharmacology unit, Lausanne University Hospital and University of Lausanne, Switzerland
[e]Obstetrics Division, Department of Pediatrics, Gynecology, and Obstetrics Geneva University Hospitals, Geneva, Switzerland
[f]Faculty of Medicine, University of Geneva, Switzerland
[g]Research Platform, Department of Pediatrics, Gynecology, and Obstetrics, Faculty of Medicine, University of Geneva, Switzerland
[h]Department of Obstetrics and Gynecology, Cantonal Hospital Aarau, Aarau, Switzerland.
[i]Frauenpraxis, Schaffhausen, Switzerland
[j]Department of Obstetrics and Gynecology, University Hospital Basel, Basel, Switzerland.
[k]Department of Gynecology and Obstetrics, Cantonal Hospital Baselland, Liestal, Switzerland.
[l]Department of Obstetrics and Gynecology, Cantonal Hospital Graubünden, Chur, Switzerland.
[m]Obstetrics and Gynecology Unit, Biel Hospital, Biel, Switzerland
[n]Department of Obstetrics and Feto-maternal Medicine, University Hospital of Bern, Switzerland.
[o]Department of Obstetrics, University Hospital of Zurich, Zurich, Switzerland.
[p]Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Switzerland

Summary

Background Pregnant individuals with coronavirus disease 2019 (COVID-19) are at increased risk of severe disease, prematurity, and stillbirth. In March 2021, vaccination for at risk pregnant women was recommended in Switzerland, expanding this to all pregnant women in May 2021. Our aim was to assess the safety of mRNA COVID-19 vaccines in pregnancy.

Methods This multicentre prospective cohort study describes early adverse events and perinatal outcomes in pregnant women who received at least one dose of mRNA vaccine between March 1st and December 27th, 2021 in Switzerland, using the COVI-PREG registry. Early adverse events were collected at least one month following vaccine administration. Pregnancy and neonatal outcomes were extracted from medical records using the maternity discharge letters providing follow-up information up to 5 days after birth.

Findings Of 1012 vaccinated women, 894 (88·3%) received both injections during pregnancy, with BNT162b2 (n = 271) or mRNA-1273 (n = 623) vaccines. Local events (mainly local pain) were reported in 81·3% and 80·5% after the first and second doses. Rates of systemic reactions (mainly fatigue and headache) were similar after the first dose and most frequent after the second dose of mRNA-1273. Of the 1012 women, four (0·4%; 95%CI [0·1-1·0]) severe early adverse events occurred: pulmonary embolism, preterm premature rupture of membranes, isolated fever with hospitalisation, and herpes zoster. Of 107 patients vaccinated before 14 weeks, one (0·9%; 95%CI [0·0-5·1]) early spontaneous abortions was reported (8 weeks). Of 228 vaccinated before 20 weeks one (0·4%; 95%CI [0·0-2·4]) late spontaneous abortion was reported (16 weeks). Of 513 women exposed before 37 weeks, 33 (6·4%; 95%CI [4·5-8·9]) delivered preterm. Among 530 patients exposed in pregnancy, no stillbirth was reported and 25 (4·7%; 95%CI [3·0-6·8]) neonates were admitted to intensive care unit.

The Lancet Regional Health - Europe 2022;18: 100410
Published online 29 May 2022
https://doi.org/10.1016/j.lanepe.2022.100410

*Corresponding author at: Materno-fetal & Obstetrics Research Unit, Department of Obstetrics and Gynecology, Centre Hospitalier Universitaire Vaudois (CHUV), 1011 Lausanne Switzerland.
E-mail address: David.baud@chuv.ch (D. Baud).

[1] Contributed equally to the work.

Interpretation Frequent local and systemic effects were described after exposure to mRNA COVID-19 vaccines during pregnancy but severe events were rare. Women vaccinated during pregnancy did not experience higher adverse pregnancy or neonatal outcomes when compared to historical data on background risks in the obstetric population.

Funding This research was funded by a grant from the Swiss Federal Office of Public Health and the CHUV Foundation.

Keywords: SARS-CoV-2; COVID-19; Vaccine; Safety; mRNA; Pregnant women; Pregnancy

Research in context

Evidence before this study

Pregnant women are at higher risk of severe form of COVID-19, however, have been excluded from COVID-19 mRNA vaccine clinical trials. We searched on PubMed and pre-print platforms for safety observational studies including pregnant women exposed to mRNA COVID-19 vaccines as of March 28th, 2022. Several studies have reported reassuring safety data in pregnant women exposed to COVID-19 vaccination. These studies, however, were either retrospective, or had only a small number of patients with pregnancy outcomes, or focused on a single outcome (e.g., spontaneous abortion), or specific period of exposure (e.g. third trimester exposure). A single prospective study from the United States surveillance system (v-safe pregnancy registry) reported no obvious safety signals among 827 pregnant women exposed to COVID-19 vaccine throughout all pregnancy, including more than 600 pregnant women exposed before 37 weeks of gestation. The study reported a low level of detail on population baseline characteristics and patients were mostly vaccinated in the third trimester, without describing severe early adverse events following vaccination.

Added value of this study

Our study is the first European study that reports Swiss nationwide safety results from more than 1000 pregnant women exposed to mRNA COVID-19 vaccine with high quality details including more than 500 patients with a pregnancy outcome available. We observed that most pregnant women experienced mild local and systemic early adverse events after injection, and more frequently after the second dose of mRNA-1273 (Moderna) vaccine. We reported similar rates of early and late spontaneous abortions after vaccine exposure during pregnancy when compared to historical data on background risks in the obstetric population. We found that pregnant women exposed to mRNA COVID-19 vaccine had low rates of preterm births, small neonates for gestational age, neonatal intensive care unit admission, and no stillbirth were reported. The mRNA COVID-19 vaccine exposure in pregnant women seemed safe.

Implications of all the available evidence

Our study shows that mRNA COVID-9 vaccines seem safe throughout all pregnancy, in terms of early adverse events, pregnancy, and neonatal outcomes. Pregnant women and health care professionals should be aware of this information as vaccination remains an effective solution against COVID-19 in this population at risk. Further studies are needed to assess long term outcomes such as infant developmental outcomes. Efforts must be made to continue to monitor the safety and efficacy of these already marketed mRNA COVID-19 vaccines in a larger sample of pregnant women and appropriate control groups to provide risk estimates, with a particular focus on first trimester exposure, rare adverse events and long-term outcomes (e.g. infant developmental outcomes).

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is of particular concern during pregnancy as pregnant women have a higher susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with a severe form of the disease reported in 8 to 10%.[1–3] Pregnant patients that test positive for COVID-19 also have an increased risk of adverse pregnancy and neonatal outcomes, with higher rates of preterm birth, neonatal intensive care unit admission, and stillbirth.[2–4] As of December 2020, this viral infection became preventable through the rollout of COVID-19 vaccinations. A two-dose regimen of messenger RNA (mRNA) vaccination reported 94·1-95·0% efficacy against COVID-19 illness in adults[5,6] and a third vaccine dose (booster) sustained the efficacy at 91-93% while the Delta variant was predominant.[7,8] With the emergence of the Omicron variant, even with a substantially lower vaccine efficacy for COVID-19 symptoms,[7,9] the efficacy against hospitalization remains at 70%.[10] As pregnant women, however, were excluded from COVID-19 vaccine trials, efficacy and safety data were initially lacking for this population.[11] In April 2021, the V-safe

surveillance system did not identify any obvious safety concerns following vaccination in 35,691 pregnant patients who received mRNA COVID-19 vaccines in the United States (US). In the 827 completed pregnancies stemming from the V-safe pregnancy registry, the distribution of perinatal outcomes was similar to pregnant patients not exposed to the vaccine.[12] The risk of spontaneous abortion following mRNA COVID-19 vaccination either before conception or during the first trimester of pregnancy was also similar to historical data on background risks in the obstetric population.[13] Despite a still low COVID-19 vaccination rate among pregnant women, available studies show that COVID-19 vaccination in pregnancy is effective against SARS-CoV-2 infection and severe disease.[14–16] Pregnant women exposed to the COVID-19 vaccine experienced similar early adverse events than non-pregnant women and no trends was reported regarding adverse perinatal outcomes, in the still limited available literature.[17–22] As of March 2021, the Swiss Society of Gynaecologists and Obstetricians (SGGG) and the Federal Office of Public Health recommended vaccination for pregnant women with additional risk factors for severe COVID-19 disease, and this recommendation was extended to all pregnant women in May 2021.[23] Despite the growing evidence for efficacy and safety of COVID-19 vaccines in pregnancy and the risk-benefit balance in favour of COVID-19 vaccination in pregnancy, many pregnant women remain reluctant to receive the COVID-19 vaccine in Europe.[24] The core element to address vaccine hesitancy is to provide consistent and fair information to health care providers giving them the tools to best advise pregnant women.

The aim of our study was to augment the current safety information on early adverse events in pregnant women, as well as on perinatal outcomes after exposure to COVID-19 vaccine any time during pregnancy through the COVI-PREG registry in Switzerland.[25]

Methods

Data source, information, and study time points

Participants were enrolled between March 1, 2021 and December 27, 2021, in the COVI-PREG vaccine registry, a prospective cohort study that aimed to assess the safety of mRNA vaccines against COVID-19 in pregnant women. Informed consent was obtained for all participants. The study was promoted through the SGGG (www.sggg.ch) to all Swiss private practice gynaecologists and public hospitals. A questionnaire regarding vaccine adverse events was distributed at the vaccination visit before or at the time of injection (Figure S1 - supplementary materials). These questionnaires were collected at least one month after injection by primary care gynaecologists who participated in the study by returning the de-identified questionnaires to their reference centre. The updated final questionnaire was returned at the end of the pregnancy. De-identified information about medical history, pregnancy, and neonatal outcomes were collected from the maternity discharge letters sent by primary care gynaecologists to their reference centre providing follow up information up to 5 days after birth. De-identified data were then recorded by the reference centres using the REDCap (Research Electronic Data Capture) secure web application in accordance with the approval of the Swiss Ethical Board (CER-VD-2020-00548) (Figure S2 - supplementary materials). The STROBE guidelines were used to ensure the reporting quality of this observational study.[26]

Study population

Pregnant women who received at least one injection of a mRNA vaccine against COVID-19 between one week before their last menstrual period (LMP) and the end of pregnancy were included in the study. Patients who were under 18 years of age or not able to consent were not included. Women with no information on the date of injection, the occurrence of early adverse events and their description if any, or no information about the type of vaccine used were excluded.

Exposure to mRNA vaccine against COVID-19

Exposure to mRNA vaccine against COVID-19 was defined as at least one injection of vaccine between one week before the date of LMP, or calculated LMP from first trimester ultrasound examination, and the end of pregnancy. Both mRNA vaccines authorized and recommended during pregnancy in Switzerland were assessed: BNT162b2 (Comirnaty®, Pfizer–BioNTech) and mRNA-1273 (SpikeVax®, Moderna) vaccine. Pregnancy exposure periods were stratified into peri-conceptional period (PCP), trimester 1, trimester 2, and trimester 3. The PCP was defined as an injection between one week before LMP and two weeks after LMP. Trimester 1 was defined as the period from two weeks after LMP to 11 weeks of gestation (wks) and 6 days to match the Swiss recommendations to prescribe the vaccine preferentially after 12 wks.[23] Trimester 2 was defined as the period from 12 wks to 27 wks and 6 days. Trimester 3 was defined as the period starting from 28 wks to the end of pregnancy. If the pregnancy due date related to the LMP differed by more than five days from the due date obtained by first trimester ultrasound, the due date was set by ultrasound.

Outcomes

Based on the outcomes of interest, the following additional inclusion and exclusion criteria were added to the study population.

Primary outcomes - early adverse events outcomes

Definition of outcomes. Early adverse events following vaccination were divided into three categories: local adverse events, systemic adverse events, and severe adverse events, observed within one month following an injection of mRNA vaccine against COVID-19. Local adverse events were defined as at least one of the following reactions at the injection site: redness, pain, swelling, warmth, itch, haematoma, induration, or other local findings. Systemic adverse events were defined as at least one of the following events: fever, fatigue, headache, chills, nausea, vomiting, diarrhoea, muscle pain, joint pain, malaise, or other events except those defined in the pregnancy and neonatal outcomes. Severe adverse events were defined as at least one of the following events occurring during the pregnancy: hospitalization potentially related to the vaccine, intensive care unit admission following vaccination, confirmed anaphylactic shock, or other potentially severe reaction related to the vaccine according to the patient and investigator interpretation.

Population 1a. For local and systemic adverse events, pregnant women with two mRNA vaccine injections between one week before LMP and the end of pregnancy were included in the analysis to compare the adverse events related to multiple doses. Patients who received only one injection were excluded.

Population 1b. For severe adverse event outcomes, pregnant women with at least one injection during pregnancy or the PCP were included.

Secondary outcomes — pregnancy and neonatal outcomes

Early spontaneous abortion

Definition of the outcome. Early spontaneous abortion was defined as a spontaneous pregnancy loss before 14 wks including spontaneous abortion, blighted ovum, or spontaneously arrested pregnancy. Elective terminations of pregnancy were excluded from this definition.

Population 2a. Pregnant women with at least one injection between one week before LMP and less than 14 wks were considered. Pregnant women with no pregnancy outcome data available at the time of analysis were excluded unless they received their second vaccine dose after 14 wks suggesting an ongoing pregnancy at the obstetrical visit following vaccination as no complications were reported in the questionnaire.

Late spontaneous abortion

Definition of the outcome. Late spontaneous abortion was defined as a spontaneous pregnancy loss between 14 wks and 19 wks and 6 days. Elective terminations of pregnancy were excluded by this definition.

Population 2b. Pregnant women with at least one injection between one week before LMP to 19 wks and 6 days were considered if pregnancy was ongoing after 14 wks. Pregnant women with no pregnancy outcome data available at the time of the analysis were excluded unless their second vaccine dose occurred after 20 wks, supporting ongoing pregnancy at the obstetrical visit following vaccination, as no complications were reported on the questionnaire.

Sensitivity analysis

To estimate the impact of the inclusion or exclusion of pregnant women lost to follow-up after 14 or 20 wks on the rate of early and late spontaneous abortion respectively, we conducted a "strict outcome scenario" sensitivity analysis.

We redefined our study population to include pregnant women exposed to at least one dose of vaccine between one week before LMP and 13 wks and 6 days for early spontaneous abortion and 19 wks and 6 days for late spontaneous abortion but restricted to pregnant women with a pregnancy outcome available at the time of the analysis. This analysis estimates the rate of spontaneous abortion with the hypothesis that patients with no pregnancy outcome available could have had a non-recorded spontaneous abortion following vaccination.

Preterm birth

Definition of the outcome — preterm birth. Preterm birth was defined as a live born infant between 24 wks and 36 wks and 6 days, and was classified as either spontaneous, defined as a delivery after spontaneous labour (assisted or non-assisted vaginal birth or caesarean section following spontaneous labour) or iatrogenic defined as an induction of labour or a caesarean delivery in the absence of spontaneous labour.

Population 2c. Pregnant women with at least one injection between one week before LMP to 36 wks and 6 days were included. Pregnant women with no pregnancy outcome data available at the time of the analysis were excluded as well as patients who terminated their pregnancy before 24 wks. Ongoing pregnancies that had not reached full term (37 wks) at the time of analysis were excluded, to avoid overestimation of an earlier adverse outcome such as preterm birth.

Delivery, livebirth, stillbirth, pre-viable fetus, gestational age at delivery, small for gestational age, neonatal intensive care unit, and neonatal death

Delivery was defined as vaginal birth, either spontaneous or assisted (i.e., by forceps or vacuum) or caesarean section. Livebirth was defined as a liveborn infant born at or after 24 wks. Stillbirth was defined as a fetal demise from 20 wks onwards. A pre-viable fetus was defined as a fetus born extremely preterm, between 20 to 23 wks and 6 days, without neonatal resuscitation. Gestational age (GA) at delivery was defined as the GA in wks at delivery. Small for gestational age (SGA) was defined as a birthweight below the 10th percentile for gestational age according to the INTERGROWTH 21 scale.[27] Neonatal intensive care unit (NICU) admission referred to the admission of the neonate into the NICU and was divided into four categories according to the cause of admission: prematurity, respiratory distress syndrome, sepsis, and any other cause. Neonatal death referred to the death within 28 days after birth of a liveborn infant born at 24 wks or more.

Population 2d. For the analysis of pregnancy and neonatal outcomes, pregnant women with at least one injection between one week before LMP and the end of pregnancy were included. Pregnant women with no pregnancy outcome data available at the time of analysis were excluded as well as patients who terminated their pregnancy before 20 wks.

Co-variates

Maternal age was divided into categories: <25 years (y), 25-29 y, 30-34 y, 35-39, and ≥40 y. For each injection, information on the type of vaccine (BNT162b2 or mRNA-1273), place of vaccination (i.e., vaccination centre/health authority, gynaecologist/midwife consultation, general practitioner, pharmacist), site of vaccine injection (i.e., right arm, left arm), and antipyretic intake around the time of injection was collected. Linguistic areas were defined according to the official language of each Swiss county: German, French, or Italian.

For analysis of pregnancy and preterm birth outcomes, maternal comorbidities (pulmonary, cardiac, hypertension, pregestational diabetes, obesity defined as a body mass index >30kg/m², immunosuppression, auto-immune diseases, hematologic, neurological, digestive, renal, urologic, oncologic, thyroid dysfunction, psychiatric disorders, and other comorbidities) and obstetric characteristics (nulliparity/multiparity, multiple pregnancy, and previous caesarean section status) were collected. Pregnancy due date was defined as 40 weeks after the LMP (LMP was reported by the patient or if unknown, calculated from a first trimester ultrasound examination).

Statistical analysis

Descriptive statistics were used to evaluate baseline demographics and characteristics, as well as the recorded prevalence of early adverse events by type of mRNA vaccine and by first or second doses and all pregnancy and neonatal outcomes overall. The 95% confidence intervals (95% CI) were calculated for each reported prevalence. Tests for normality were done for continuous variables. Statistical analyses were performed using Stata 16 (StataCorp. 2015. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP).

Role of the funding source

This research was supported by a grant from the Swiss Federal Office of Public Health and the CHUV Foundation. The funders had no role in study design, data collection, data analysis, interpretation and writing of the paper.

Results

Between March 1- December 27, 2021, a total of 1431 women were enrolled in the registry among which 1012 patients met the inclusion criteria (Figure 1). Results are reported according to the different outcomes of interest. Vaccination patterns represented in our cohort are described in figure S3 (supplementary materials).

Early adverse events outcomes

Among 1012 patients, 894 (88·3%) pregnant women had both injections between one week before LMP and the end of pregnancy and were included in this analysis (Figure 1).

Characteristics of the participants (population 1a) according to the type of vaccine received are presented in Table 1.

The number of patients who received two doses of Pfizer–BioNTech BNT162b2 or Moderna mRNA-1273 were 271 (30·3%) and 623 (69·7%), respectively. Most pregnant women were in the age category 30 to 34 y, with 107 (39·5%) and 283 (45·4%), followed by the category 35 to 39 y, with 99 (36·5%) and 199 (31·9%) for Pfizer–BioNTech BNT162b2 and Moderna mRNA-1273, respectively. Independent of vaccine type, 727 (81·3%) reported at least one local adverse event for the first dose and 720 (80·5%) for the second dose. At least one systemic adverse event was reported in 316 (35·4%) and 602 (67·3%), respectively for the first and second dose. Timing of the first vaccine dose was in the PCP for 32 (3·6%), first trimester for 10 (4·5%), second trimester for 623 (69·7%), and third trimester for 199 (22·3%). Timing of the second vaccine dose was in the PCP for 2 (0·2%), first trimester for 5 (0·6%), second trimester for 532 (59·5%), and third trimester for 355 (39·7%). Details by vaccine type are shown in Table 1.

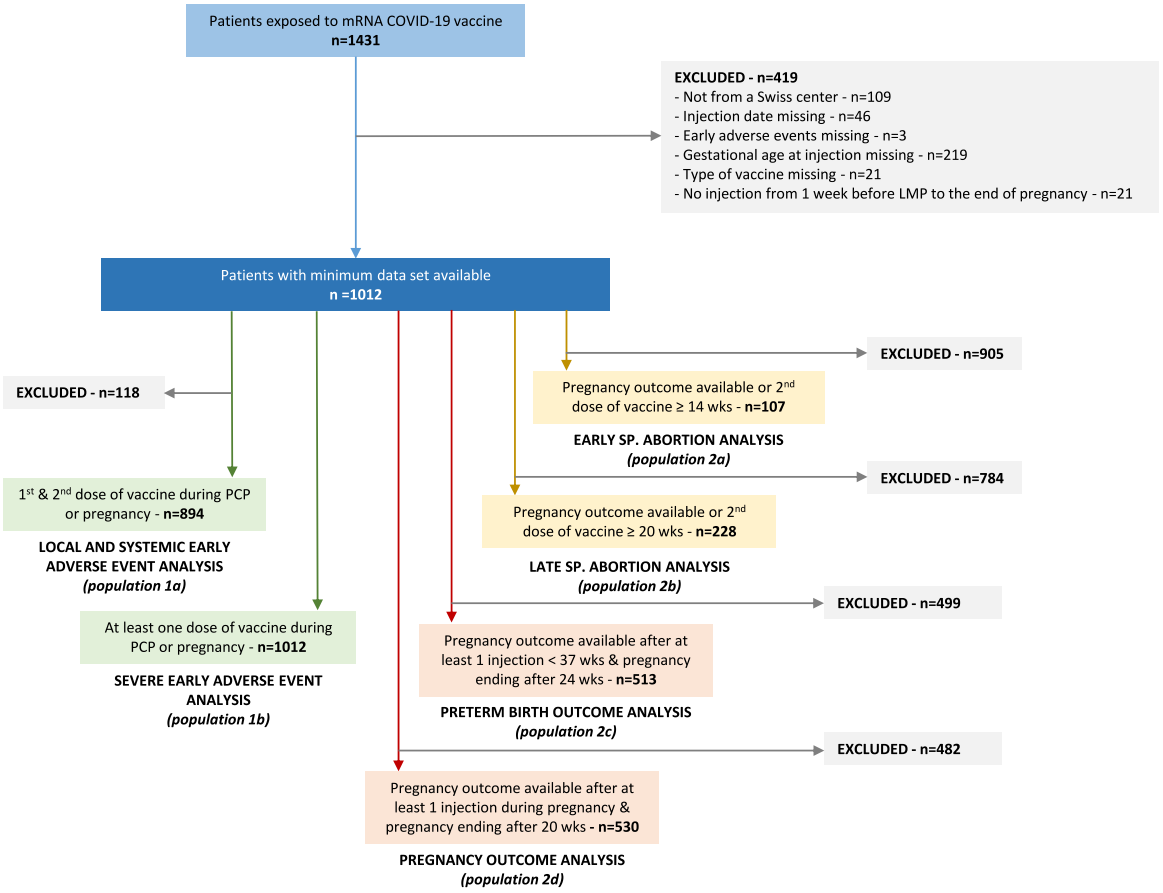


Figure 1. Flow chart of the study. The numbers of patients eligible for each analysis are displayed (Study populations 1a to 2d). Abbreviation: LMP: last menstrual period; PCP: peri-conceptional period; SP.: spontaneous; wks: weeks of gestation.

Local and systemic adverse events after the first and the second dose of vaccine, according to the type of vaccine received, are shown in Table 2 and represented in Figure 2. Local reactions were similar between the two vaccine types and the two doses, with pain representing two thirds of complains. The three most common systemic adverse events after the first dose were fatigue in 19·6% (95%CI [15·0-24·8]) and 25·2% (95%CI [21·8-28·8]), headache in 10·3% (95%CI [7·0-14·6]) and 16·1% (95%CI [13·3-19·2]), and muscle pain in 7·7% (95%CI [4·9-11·6]) and 11·6% (95%CI [9·2-14·3]) respectively for Pfizer–BioNTech BNT162b2 and Moderna mRNA-1273 vaccine. Systemic reactions, however, were higher after the second dose of Moderna mRNA-1273 vaccine, compared to the first dose of Moderna mRNA-1273 vaccine or compared to the first and second dose of Pfizer –BioNTech BNT162b2 vaccine. A total of 78·3% (95%CI [74·9-81·5]) of patients experienced at least one adverse systemic reaction after the second dose of Moderna mRNA-1273 vaccine with the 60·4% (95%CI [56·4-64·2]) reporting fatigue, 45·7% (95%CI [41·8-49·8]) reporting headache, 37·1% (95%CI [33·3-41·0]) reporting muscle pain, 25·2% (95%CI [21·8-28·8]) reporting joint pain, 24·6% (95%CI [21·2-28·1]) reporting chills, and 16·4% (95%CI [13·6-19·5]) reporting fever.

Baseline characteristics of the 1012 pregnant patients who had at least one injection (population 1b) are presented in table S1. A total of four (0·4%; 95%CI [0·1-1·0]) severe early adverse events were reported and are presented in Table 3: deep vein thrombosis associated with pulmonary embolism at 21 wks resolved with adapted treatment; preterm premature rupture of membranes (PPROM) with vaginal bleeding in the context of a partial placental abruption leading to emergency caesarean section at 31 wks; thoracic herpes zoster more than three weeks after the second injection performed at 17 wks; hospitalization for surveillance of fever at 32 wks following the second dose of vaccine. All patients of population 2d (n = 530) delivered liveborn infants, including a preterm neonate born at 31 wks.

Early spontaneous abortion outcome

A total of 135 patients out of 1012 were exposed to the vaccine before 14 wks and 28 women were excluded because they did not complete the follow-up

		Pfizer/BioNTech BNT162b2			Moderna mRNA-1273		
		N	*n* = 271 %		n	*n* = 623 %	
Maternal age at first dose (years)							
	<25	5	1.9	%	5	0.8	%
	25-29	34	12.6	%	72	11.6	%
	30-34	107	39.5	%	283	45.4	%
	35-39	99	36.5	%	199	31.9	%
	≥40	15	5.5	%	37	5.9	%
	Missing	11	4.1	%	27	4.3	%
Swiss linguistic area							
	German	175	64.6	%	452	72.6	%
	French	89	32.8	%	152	24.4	%
	Italian	7	2.6	%	19	3.1	%
EXPOSURE							
	1st dose of vaccine						
Trimester of injection							
	Peri-conception (7 days before LMP to 13 days after LMP)	7	2.6	%	25	4.0	%
	T1 - 14 days after LMP and <12 wks	12	4.4	%	28	4.5	%
	T2 - ≥12 and <28 wks	182	67.2	%	441	70.8	%
	T3 - ≥28 wks	70	25.8	%	129	20.7	%
Place of vaccination							
	Vaccination centre / Health authority	118	43.5	%	248	39.8	%
	Gynaecologist / Midwife consultation (PRIVATE PRACTICE)	0	-		4	0.6	
	Gynaecologist / Midwife consultation (HOSPITAL)	6	2.2	%	4	0.6	%
	GP (General practitioner)	2	0.7	%	6	1.0	%
	Occupational health service (at work)	5	1.9	%	9	1.4	%
	Pharmacist	2	0.7	%	16	2.6	%
	Unknown	2	0.7	%	1	0.2	%
	Missing	136	50.2	%	335	53.8	%
Injection site							
	Left arm	106	39.1	%	247	39.7	%
	Right arm	24	8.9	%	40	6.4	%
	Missing	141	52.0	%	336	53.9	%
Antipyretic intake around injection							
	Yes	15	5.5	%	24	3.9	%
	No	116	42.8	%	260	41.7	%
	Unknown	6	2.2	%	0	-	
	Missing	134	49.5	%	339	54.4	%
	2nd dose of vaccine						
Trimester of injection							
	Peri-conception (7 days before LMP to 13 days after LMP)	1	0.4	%	1	0.2	%
	T1 - 14 days after LMP and <12 wks	2	0.7	%	3	0.5	%
	T2 - ≥12 and <28 wks	156	57.6	%	376	60.4	%

Table 1 *(*Continued*)*

		Pfizer/BioNTech BNT162b2			Moderna mRNA-1273		
		N	*n* = 271 %		n	*n* = 623 %	
	T3 - ≥28 wks	112	41.3	%	243	39.0	%
Place of vaccination							
	Vaccination centre / Health authority	118	43.5	%	254	40.8	%
	Gynaecologist / Midwife consultation (PRIVATE PRACTICE)	0	-		3	0.5	%
	Gynaecologist / Midwife consultation (HOSPITAL)	6	2.2	%	2	0.3	%
	GP (General practitioner)	2	0.7	%	6	1.0	%
	Occupational health service (at work)	6	2.2	%	2	0.3	%
	Pharmacist	2	0.7	%	19	3.1	%
	Unknown	2	0.7	%	1	0.2	%
	Missing	135	49.8	%	336	53.9	%
Injection site							
	Left arm	107	39.5	%	234	37.6	%
	Right arm	20	7.4	%	52	8.4	%
	Missing	144	53.1	%	337	54.1	%
Antipyretic intake around injection							
	Yes	14	5.2	%	54	8.7	%
	No	110	40.6	%	227	36.4	%
	Unknown	8	3.0	%	1	0.2	%
	Missing	139	51.3	%	341	54.7	%

***Table 1*: Population 1a - Baseline characteristics of pregnant women exposed to 2 doses of COVID-19 mRNA vaccine.**
T1-3: trimester 1-3.
LMP: last menstrual period.
wks: weeks of gestation.

questionnaire regarding the second dose of vaccine after 14 wks or did not have an available pregnancy outcome at the time of analysis. Patient characteristics (population 2a) are presented in table S2 (supplementary materials). Among 107 patients included, 97 (90·7%; 95%CI [83·5-95·4]) had an ongoing pregnancy at the time of questionnaire completion after the second dose and only 10 patients' pregnancy outcome data were available at the time of the analysis. One patient (0·9%; 95%CI [0·0-5·1]) had an early spontaneous abortion at 8 wks, five weeks after a single dose of vaccine (Table 4).

Late spontaneous abortion analysis

Of 1012 pregnant women, a total of 399 were exposed to the vaccine before 20 wks. One case was excluded due to early spontaneous abortion, and 170 patients were excluded because they did not complete the questionnaire regarding the second dose of vaccine after 20 wks or pregnancy outcome data were not available. Patient characteristics (population 2b) are presented in Table S3. Among 228 patients included, 132 (57·9%; 95%CI [51·2-64·4]) patients had an ongoing pregnancy at the time completion of the questionnaire after the second dose and 96 patients had a pregnancy outcome available at the time of the analysis. A total of 95 (41·7%; 95%CI [35·2-48·4]) patients had a liveborn infant and one patient (0·4%; 95%CI [0·0-2·4]) had a late spontaneous abortion at 16 wks, related to chorioamnionitis three weeks after a first dose of vaccine (Table 4). The patient had no reported obstetric risk factors. Placenta pathology examination revealed placental inflammation compatible with incipient chorioamnionitis. Bacterial cultures and bacterial polymerase chain reaction testing were negative.

"Strict outcome scenario" sensitivity analysis

Patient baseline characteristics are presented in Tables S4 and S5 (supplementary materials).

Early spontaneous abortion - Among 135 patients exposed to the vaccine before 14 wks, 10 patients had a

	Comirnaty Pfizer/BioNTech - BNT162b2n = 271						Moderna - mRNA-1273n = 623					
	1st dose			2nd dose			1st dose			2nd dose		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
No reaction	**21**	**7.7%**	**4.9-11.6**	**25**	**9.2%**	**6.1-13.3**	**53**	**8.5%**	**6.4-11.0**	**13**	**2.1%**	**1.1-3.5**
Local reaction	**201**	**74.2%**	**68.5-79.3**	**191**	**70.5%**	**64.7-75.8**	**526**	**84.4%**	**81.3-87.2**	**529**	**84.9%**	**81.9-87.6**
Pain	196	72.3%	66.6-77.6	182	67.2%	61.2-72.7	499	80.1%	76.7-83.2	507	81.4%	78.1-84.4
Redness	5	1.8%	0.6-4.3	11	4.1%	2.0-7.1	60	9.6%	7.4-12.2	89	14.3%	11.6-17.3
Swelling	10	3.7%	1.8-6.7	14	5.2%	2.9-8.5	59	9.5%	7.3-12.0	85	13.6%	11.0-16.6
Induration	5	1.8%	0.6-4.3	4	1.5%	0.4-3.7	32	5.1%	3.5-7.2	37	5.9%	4.2-8.1
Warmth	7	2.6%	1.0-5.2	6	2.2%	0.8-4.8	24	3.9%	2.5-5.7	35	5.6%	3.9-7.7
Itch	1	0.4%	0.0-2.0	3	1.1%	0.2-3.2	14	2.2%	1.2-3.7	29	4.7%	3.1-6.6
Haematoma	5	1.8%	0.6-4.3	2	0.7%	0.1-2.6	7	1.1%	0.5-2.3	8	1.3%	0.6-2.5
Other	0	0.0%	0.0-1.4	1	0.4%	0.0-2.0	5	0.8%	0.3-1.9	4	0.6%	0.2-1.6
Systemic reaction	**82**	**30.3%**	**24.8-36.1**	**114**	**42.1%**	**36.1-48.2**	**234**	**37.6%**	**33.7-41.5**	**488**	**78.3%**	**74.9-81.5**
Fatigue	53	19.6%	15.0-24.8	80	29.5%	24.2-35.3	157	25.2%	21.8-28.8	376	60.4%	56.4-64.2
Headache	28	10.3%	7.0-14.6	56	20.7%	16.0-26.0	100	16.1%	13.3-19.2	285	45.7%	41.8-49.8
Muscle pain	21	7.7%	4.9-11.6	32	11.8%	8.2-16.3	72	11.6%	9.2-14.3	231	37.1%	33.3-41.0
Joint pain	7	2.6%	1.0-5.2	15	5.5%	3.1-9.0	24	3.9%	2.5-5.7	157	25.2%	21.8-28.8
Chills	2	0.7%	0.1-2.6	5	1.8%	0.6-4.3	14	2.2%	1.2-3.7	153	24.6%	21.2-28.1
Fever	1	0.4%	0.0-2.0	4	1.5%	0.4-3.7	13	2.1%	1.1-3.5	102	16.4%	13.6-19.5
Malaise	7	2.6%	1.0-5.2	10	3.7%	1.8-6.7	8	1.3%	0.6-2.5	57	9.1%	7.0-11.7
Nausea	6	2.2%	0.8-4.8	6	2.2%	0.8-4.8	8	1.3%	0.6-2.5	55	8.8%	6.7-11.3
Vomiting	2	0.7%	0.1-2.6	1	0.4%	0.0-2.0	5	0.8%	0.3-1.9	33	5.3%	3.7-7.4
Other	11	4.1%	2.0-7.1	6	2.2%	0.8-4.8	8	1.3%	0.6-2.5	32	5.1%	3.5-7.2
Diarrhea	5	1.8%	0.6-4.3	9	3.3%	1.5-6.2	8	1.3%	0.6-2.5	21	3.4%	2.1-5.1

***Table 2*: Local and systemic early adverse events among pregnant women receiving 2 injections of COVID-19 mRNA vaccine.**

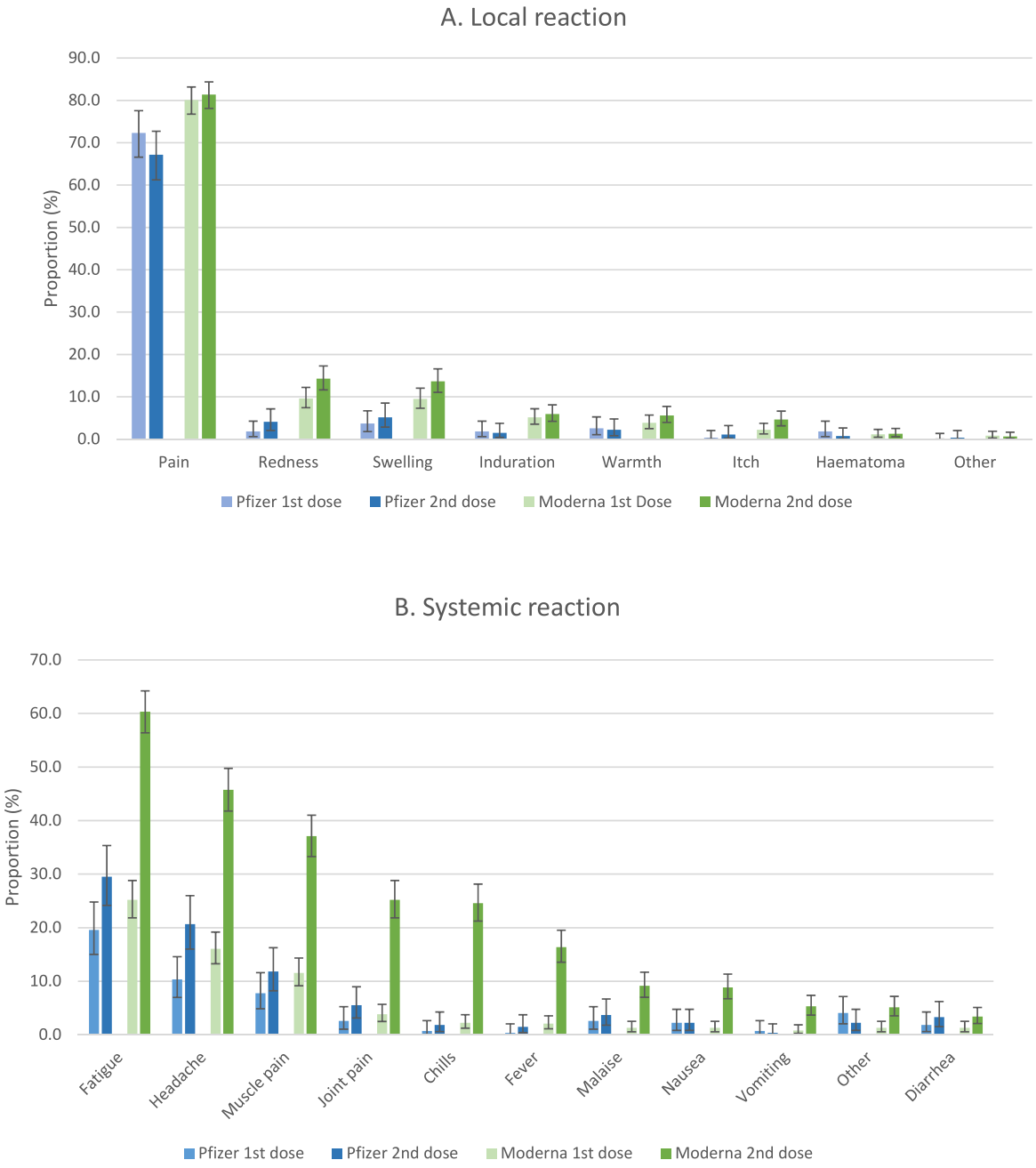


Figure 2. Local and systemic reactions reported within one month after each injection of mRNA COVID-19 vaccines in pregnancy. Proportions (%) are displayed and I bars represent 95% confidence intervals.

pregnancy outcome available, including one patient (1/10, 10·0%; 95%CI [0·3-44·5]) who had an early spontaneous abortion (Table 4).

Late spontaneous abortion - Among 398 patients exposed to the vaccine before 20 wks, after the exclusion of one case for early spontaneous abortion, 96 patients had a pregnancy outcome available. One (1/96, 1·0%; 95%CI [0·0-5·7]) patient had a late spontaneous abortion and 95 women had a livebirth (Table 4).

Preterm birth outcome

Of 1012 patients, 513 patients were included in this analysis because they were exposed to the vaccine before 37 wks, had a pregnancy outcome available, and delivered

	Patient 1	Patient 2	Patient 3	Patient 4
Maternal age at first dose	36	25	32	Unknown
Swiss linguistic area	German	German	German	French
Gravidity (G) Parity (P)	G2P1	G1P0	G1P0	G3P1
Obstetrical history	- Previous C-section (2017)			- Previous vaginal delivery (2007)
Medical condition	None	- Asthma treated by Salmeterol / Fluticason - 50/500 mcg - 1/day	None	- BMI = 34 kg/m2 - Allergic asthma without treatment - Psoriasis without treatment
Obstetrical condition		-	-	- Gestational diabetes requirering insuline
EXPOSURE				
Type of vaccine	BNT162b2	mRNA-1273	mRNA-1273	mRNA-1273
1st DOSE of vaccine				
Timing of injection (weeks from LMP)	13	15	26	28
Local reaction	Pain	Pain	Pain, Induration	Pain, Redness, Swelling, Warmth, Itch
Systemic reaction	Fatigue	Headache	Fatigue	Headache
Severe reaction	No	No	No	No
2nd DOSE of vaccine				
Timing of injection (weeks from LMP)	17	20	30	32
Local reaction	Pain	Pain	Pain, Induration	Pain, Warmth
Systemic reaction	Fatigue	Headache	-	Fever, Headache, Fatigue, Chills, Nausea, Muscle pain, Joint pain
Severe reaction	YES	YES	YES	YES
Timing	3 weeks after injection	Within 7 days after injection	Within 7 days after injection	Within 7 days after injection
Details	1st episode of herpes zoster on the right anterior thoracic wall - Spontaneously resolved with symptomatic treatment (paracetamol)	Deep venous thromboembolism and pulmonary embolism diagnosed 6 days after injection.	PPROM one day after vaccination - Hospital admission: complete fetal lung maturation. Active vaginal bleeding leading to emergency C-section five days after vaccination	Fever 38°C, one day after vaccination leading to hospital admission for clinical surveillance during 24 hours and discharged.
PREGNANCY OUTCOME	**Livebirth**	**Livebirth**	**Livebirth**	**Livebirth**
Gestational age at delivery (weeks)	38	40	31	38

***Table 3*: Severe early adverse events following vaccination.**
LMP: last menstrual period
BNT162b2: PfizerBioNTech mRNA vaccine
mRNA-1273: Moderna mRNA vaccine
C-section: cesarean section
PPROM: preterm premature rupture of membranes

	Early sp. abortion outcome			"Strict outcome scenario" sensitivity analysis		
EARLY SP. ABORTION ANALYSIS	n=107 n	%	95% CI	n=10 n	%	95% CI
Sp. abortion <14 wks	1	0.9%	0.0-5.1	1	10.0%	0.3-44.5
Sp. abortion ≥ 14 wks	1	0.9%	0.0-5.1	1	10.0%	0.3-44.5
Livebirth	8	7.5%	3.3-14.2	8	80.0%	44.4-97.5
2nd vaccine's dose ≥ 14 wks	97	90.7%	83.5-95.4	-		
	Late sp. abortion outcome			**"Strict outcome scenario" sensitivity analysis**		
LATE SP. ABORTION ANALYSIS	n= 228 n	%	95% CI	n=96 n	%	95% CI
Sp. abortion ≥ 14 wks	1	0.4%	0.0-2.4	1	1.0%	0.0-5.7
Livebirth	95	41.7%	35.2-48.4	95	99.0%	94.3-100.0
2nd vaccine's dose ≥ 20 wks	132	57.9%	51.2-64.4	-		

***Table 4*: Early and late spontaneous abortion outcomes analysis and sensitivity analysis following COVID-19 mRNA vaccination during PCP or pregnancy.**
wks: weeks of gestation
sp: spontaneous

after 24 wks (Figure 1). Patient baseline characteristics (population 2c) were very similar to the pregnancy outcome population (population 2d) (Tables 5 and 7). All patients gave birth to liveborn infants including five twin pregnancies. Preterm birth before 37 wks was reported in 33 (6·4%; 95%CI [4·5-8·9]) patients, with 19 (3·7%; 95%CI [2·2-5·7]) iatrogenic preterm births and 12 spontaneous preterm births (2·3%; 95%CI [1·2-4·1]) (Table 6).

Pregnancy and neonatal outcomes

Of 1012 patients, 530 patients had a pregnancy outcome available with a gestational age of at least 20 wks and were included in this analysis (Figure 1). Patient baseline characteristics (population 2d) are presented in Table 7. The majority (42·3% - *n* = 224) of patients were 30 to 34 y of age, 20·4% (*n* = 108) had a medical comorbidity, 41·5% (*n* = 220) were nulliparous, 0·9% (*n* = 5) had an ongoing twin pregnancy, and 14·5% (*n* = 77) had at least one previous caesarean section. Pfizer–BioNTech BNT162b2 vaccine was given to 28·3% (*n* = 150) of pregnant woman and Moderna mRNA-1273 vaccine to 71·7% (*n* = 380). A total of 46 (8·7%) patients did not receive a second dose, 28 (5·8%) had a second injection within six weeks after the end of the pregnancy, and 456 (86·0%) had a second injection during pregnancy. Most patients had a vaginal birth, including 302 (57·0%) spontaneous and 61 (11·5%) assisted, and 158 (29·8%) patients had a caesarean section. No stillbirths nor non-viable births were reported and all 530 patients delivered liveborn infants including five twin pregnancies. Of these 535 new-borns, 21 (3·9%; 95%CI [2·4-5·9]) were small for gestational age. A total of 25 (4·7%; 95%CI [3·0-6·8]) neonates were admitted to NICU, including 13 (2·4%; 95%CI [1·3-4·1] for prematurity, 6 (1·1% 95%CI [0·4-2·4]) for respiratory distress syndrome, 1 (0·2% 95%CI [0·0-1·0]) for sepsis, and 6 (1·1% 95%CI [0·4-2·4]) for other reasons. No neonatal death was recorded (Table 8).

Discussion

In this prospective cohort of 1012 pregnant patients from the Swiss COVI-PREG registry[25], we identified that pregnant women were vaccinated against COVID-19 throughout pregnancy but preferentially after 12 wks as recommended by the Swiss Society of Gynaecology and Obstetrics.[23] Most of the women (88·3%) received two doses just before or during pregnancy.

Local and systemic reactions after vaccination were primarily pain at the injection site, fatigue, headache, and muscle pain, with a higher rate of systemic reaction occurring after the second dose of vaccine (67·3% vs 35·3% after the first dose), especially with Moderna mRNA-1273 vaccine, which is consistent with already published data in the general population and during

	PRE-TERM BIRTH OUTCOME ANALYSIS n = 513	
	N	**%**
Maternal age at first dose (years		
<25	2	0.4%
25-29	53	10.3%
30-34	219	42.7%
35-39	170	33.1%
≥40	31	6.0%
Missing	38	7.4
Swiss linguistic area		
German	334	65.1%
French	172	33.5%
Italian	7	1.4%
Maternal medical condition	107	20.9%
Pulmonary comorbidities	10	1.9%
Cardiac comorbidities	20	3.9%
Hypertension	7	1.4%
Pregestational diabetes	4	0.8%
Obesity (BMI >30kg/m2)	28	5.5%
Immunosuppression	3	0.6%
Auto-immune diseases	7	1.4%
Hematologic comorbidities	3	0.6%
Neurological comorbidites	1	0.2%
Digestive comorbidities	3	0.6%
Renal comorbidities	4	0.8%
Urological comorbidities	1	0.2%
Oncological comorbidities	1	0.2%
Thyroid dysfunction	33	6.4%
Psychiatric disorders	6	1.2%
Other	9	1.8%
Pregnancy		
Nulliparous	215	41.9%
Twin pregnancy	5	1.0%
Previous cesarean section	74	14.4%
EXPOSURE		
Type of vaccine		
Pfizer/BioNTech - BNT162b2	144	28.1%
Moderna - mRNA-1273	369	71.9%
1st dose of vaccine		
Trimester of injection		
Peri-conception (7 days before LMP to 13 days after LMP)	0	-
T1 - 14 days after LMP and <12 wks	2	0.4%
T2 - ≥12 and <28 wks	303	59.1%
T3 - ≥28 wks	208	40.6%
Place of vaccination		
Vaccination center / Health authority	171	33.3%
Gynaecologist / Midwife consultation (PRIVATE PRACTICE)	1	0.2
Gynaecologist / Midwife consultation (HOSPITAL)	11	2.1%
GP (General practitioner)	5	1.0%
Occupational health service (at work)	8	1.6%
Pharmacist	8	1.6%
Unknown	4	0.8%
Missing	305	59.5%

Table 5 *(Continued)*

	PRE-TERM BIRTH OUTCOME ANALYSIS n = 513	
	N	**%**
Injection site		
Left arm	165	32.2%
Right arm	32	6.2%
Missing	316	61.6%
Antipyretic intake around injection		
Yes	22	4.3%
No	174	33.9%
Unknown	7	1.4%
Missing	310	60.4%
2nd dose of vaccine		
- During pregnancy	456	88.9%
Trimester of injection		
Peri-conception (7 days before LMP to 13 days after LMP)	0	-
T1 - 14 days after LMP and <12 wks	0	-
T2 - ≥12 and <28 wks	174	33.9%
T3 - ≥28 wks	282	55.0%
Place of vaccination		
Vaccination center / Health authority	154	30.0%
Gynaecologist / Midwife consultation (PRIVATE PRACTICE)	1	0.2%
Gynaecologist / Midwife consultation (HOSPITAL)	8	1.6%
GP (General practitioner)	4	0.8%
Occupational health service (at work)	6	1.2%
Pharmacist	7	1.4%
Unknown	3	0.6%
Missing	273	53.2%
Injection site		
Left arm	141	27.5%
Right arm	30	5.8%
Missing	285	55.6%
Antipyretic intake around injection		
Yes	31	6.0%
No	140	27.3%
Unknown	6	1.2%
Missing	279	54.4%

***Table 5*: Patient baseline characteristics for pregnant women exposed to mRNA COVID-19 vaccine before 37 wks and ending their pregnancy after 24 wks (population 2c).**
T1-3: trimester 1-3
LMP: last menstrual period
wks: weeks of gestation

pregnancy.[5,6,12,28] Comparisons across vaccine types revealed that receipt of the second dose, Moderna mRNA-1273 vaccine, younger age, female sex, and having had COVID-19 before vaccination were associated with greater odds of adverse effects.[29]

Severe adverse events were rare, including venous thromboembolism, fever requiring hospitalization, and herpes zoster, which can occur following any vaccine injection. In the general population, COVID-19 mRNA vaccine does not appear to increase the risk of deep vein thrombosis.[30] The risk of venous thromboembolism, however, is four times greater during pregnancy than in the non-pregnant population with an estimated incidence of 0·76 to 1·72 per 1000 and thus is expected to occur independently of vaccination.[31] Herpes zoster has been mentioned as a possible complication of mRNA COVID-19 vaccination, but a recent study of more than one million patients vaccinated in the US showed a similar prevalence to historical cohorts.[32] During pregnancy, herpes zoster remains a rare condition with no risk associated for the mother or her infant.[33] The case of preterm birth resulted from PPROM followed by

PRE-TERM BIRTH ANALYSIS	n	%	95% CI
Pregnant women	513		
Twin pregnancies	5		
Number of foetuses	518		
DELIVERY			
Vaginal delivery	354	69.0%	64.8-73.0
Spontaneous	291	56.7%	52.3-61.1
Assisted (forceps, vacuum)	59	11.5%	8.9-14.6
Unknown	4	0.8%	0.2-2.0
Caesarean section	154	30.0%	26.1-34.2
Unknown	5	1.0%	0.3-2.3
PRE-TERM BIRTH (among pregnant women)			
Preterm <37 wks	33	6.4%	4.5-8.9
Iatrogenic preterm birth	19	3.7%	2.2-5.7
Spontaneous preterm birth	12	2.3%	1.2-4.1
Unknown	2	0.4%	0.0-1.4
PREGNANCY OUTCOMES			
Stillbirth (Fetal demise ≥ 20 wks)	0	-	
Livebirth	518	100%	
GA at delivery (in wks) - median (IQR)	39 wks	(38-40)	
NEONATAL OUTCOMES (among livebirth infants)			
- Small for gestational age*	21	4.1%	2.5-6.1
- NICU admission (any cause)**	25	4.8%	3.1-7.0
NICU admission for prematurity	13	2.5%	1.3-4.3
NICU admission for respiratory distress	6	1.2%	0.4-2.5
NICU admission for sepsis	1	0.2%	0.0-1.1
NICU admission for other cause	6	1.2%	0.4-2.5
- Neonatal death	0	-	

***Table 6*: Pregnancy and neonatal outcomes among pregnant women exposed to COVID-19 mRNA vaccine before 37 wks and ending their pregnancy after 24 wks (population 2c).**

* <10th percentile for gestational age according to INTERGROWTH 21GA: gestational agewks: weeks of gestationNICU: neonatal Intensive Care Unit

** reason for NICU admission can be multiple

vaginal haemorrhage 48 hours later, leading to an emergency caesarean section, which is likely not secondary to the vaccine.

With respect to spontaneous abortion, our study showed very low rates of early and late spontaneous abortion of 0·9% and 0·4%, respectively. The only identified late spontaneous abortion occurred three weeks after the first vaccine dose at 16 wks in the context of chorioamnionitis. However these findings were constrained by limited outcome data on most of the pregnancies vaccinated before 14 wks (10/135; 7·4%) and before 20 weeks (96/398; 24·1%). Several studies have not shown an increased risk of spontaneous abortion following COVID-19 vaccination.[13,34,35] Further studies once outcome data is obtained may confirm findings noted by other authors.

All infants delivered from mothers exposed to mRNA COVID-19 vaccine in pregnancy were liveborn. A low prevalence (6·4%; 95%CI [4·5-8·9]) of preterm birth before 37 wks was reported in this study. This is similar to the rates for the last four years in Switzerland ranging from 6·4 to 7·0% and in Europe ranging from 5·5 to 11·4%.[36,37] A low rate of SGA (3·8%; 95%CI [2·3-5·8]) was reported using the INTERGROWTH 21 scale.[27] NICU admission was also low (3·7%; 95%CI [2·9-6·7]) in our cohort, compared to a recently published rate of 6·3% in a cohort of neonates born after 35 wks in the US, which did not include very preterm births.[38]

These results are consistent with a recent US study stemming from a retrospective cohort of more than 40,000 pregnant women, where COVID-19 vaccine exposure was not associated with increased risk of preterm birth or small for gestational age at birth.[39] Similarly, a nationwide Scottish study reported that despite the low prevalence of vaccination among pregnant women, it was safe and reduced maternal and perinatal complications associated with COVID-19.[40]

The prospective design of the study enabled exhaustive and precise collection of adverse events following vaccination directly from a nation-wide cohort of vaccine recipients. This study is limited, however, by a relatively small number of pregnant women at the time of analysis, making it difficult to assess rare events such as serious adverse events following vaccination or stillbirths, which would require several thousands of patients.

	PREGNANCY OUTCOME ANALYSIS n = 530	
	n	**%**
Maternal age at first dose (years)		
<25	2	0.4%
25-29	53	10.0%
30-34	224	42.3%
35-39	178	33.6%
≥40	32	6.0%
Missing	41	7.7
Swiss linguistic area		
German	344	64.9%
French	179	33.8%
Italian	7	1.3%
Maternal medical condition	108	20.4%
Pulmonary comorbidities	11	2.1%
Cardiac comorbidities	20	3.8%
Hypertension	7	1.3%
Pre-gestational diabetes	4	0.8%
Obesity (BMI >30kg/m2)	28	5.3%
Immunosuppression	3	0.6%
Auto-immune diseases	7	1.3%
Hematologic comorbidities	3	0.6%
Neurological comorbidities	1	0.2%
Digestive comorbidities	3	0.6%
Renal comorbidities	4	0.8%
Urological comorbidities	1	0.2%
Oncological comorbidities	1	0.2%
Thyroid dysfunction	33	6.2%
Psychiatric disorders	6	1.1%
Other	9	1.7%
Pregnancy		
Nulliparous	220	41.5%
Twin pregnancy	5	0.9%
Previous caesarean section	77	14.5%
EXPOSURE		
Type of vaccine		
Pfizer/BioNTech - BNT162b2	150	28.3%
Moderna - mRNA-1273	380	71.7%
1st dose of vaccine		
Trimester of injection		
Peri-conception (7 days before LMP to 13 days after LMP)	0	-
T1 - 14 days after LMP and <12 wks	2	0.4%
T2 - ≥12 and <28 wks	303	57.2%
T3 - ≥28 wks	225	42.5%
Place of vaccination		
Vaccination centre / Health authority	177	33.4%
Gynaecologist / Midwife consultation (PRIVATE PRACTICE)	1	0.2
Gynaecologist / Midwife consultation (HOSPITAL)	11	2.1%
GP (General practitioner)	5	0.9%
Occupational health service (at work)	8	1.5%
Pharmacist	8	1.5%
Unknown	4	0.8%
Missing	316	59.6%

Table 7 *(Continued)*

	PREGNANCY OUTCOME ANALYSIS n = 530	
	n	**%**
Injection site		
Left arm	171	32.3%
Right arm	32	6.0%
Missing	327	61.7%
Antipyretic intake around injection		
Yes	22	4.2%
No	180	34.0%
Unknown	7	1.3%
Missing	321	60.6%
2nd dose of vaccine		
- During pregnancy	456	86.0%
Trimester of injection		
Peri-conception (7 days before LMP to 13 days after LMP)	0	-
T1 - 14 days after LMP and <12 wks	0	-
T2 - ≥12 and <28 wks	174	32.8%
T3 - ≥28 wks	282	53.2%
Place of vaccination		
Vaccination centre / Health authority	154	29.1%
Gynaecologist / Midwife consultation (PRIVATE PRACTICE)	1	0.2
Gynaecologist / Midwife consultation (HOSPITAL)	8	1.5%
GP (General practitioner)	4	0.8%
Occupational health service (at work)	6	1.1%
Pharmacist	7	1.3%
Unknown	3	0.6%
Missing	273	51.5%
Injection site		
Left arm	153	28.9%
Right arm	33	6.2%
Missing	298	56.2%
Antipyretic intake around injection		
Yes	31	5.8%
No	168	31.7%
Unknown	6	1.1%
Missing	279	52.6%

***Table 7*: Patient baseline characteristics for pregnant women exposed to mRNA COVID-19 vaccine and ending their pregnancy during pregnancy after 20 wks (population 2d).**
T1-3: trimester 1-3
LMP: last menstrual period
wks: weeks of gestation

Most women were exposed during the second and third trimesters, limiting the assessment of the vaccine impact on early pregnancy and embryogenesis. This could explain the very low rate of early spontaneous abortion. Our study was not designed to specifically target these early pregnancy outcomes as most of the enrolled patients were vaccinated after 12 wks according to national recommendations in Switzerland in 2021. Thus, the available population to estimate the rate of early spontaneous abortion may not appropriately represent the population at risk for spontaneous abortion. Spontaneous abortion incidence rates are sensitive to gestational age at enrollment as the risk decreases over gestation, later enrollees caring a lower risk or no risk of the outcome. Some selection biases may have lowered the spontaneous abortion risk estimates as well. Women may have not known that they were pregnant at the time of vaccination or had an early pregnancy loss and did not consult with a gynaecologist. Furthermore, patients that presented to a gynaecologist for the first time with a diagnosis of early spontaneous abortion, may have simply declined to participate in the study because their psychological state was not conducive to scientific research. Finally, this study does not provide a

PREGNANCY OUTCOMES ANALYSIS	n	%	95% CI
Pregnant women	530		
Twin pregnancies	5		
Number of fetuses	535		
DELIVERY			
Vaginal delivery	367	69.2%	65.1–73.2
Spontaneous	302	57.0%	52.6–61.2
Assisted (forceps, vacuum)	61	11.5%	8.9–14.5
Unknown	4	0.8%	0.2–1.9
Caesarean section	158	29.8%	25.9–33.9
Unknown	5	0.9%	0.3–2.2
PREGNANCY OUTCOMES			
Stillbirth (Fetal demise ≥ 20 wks)	0	-	
Pre-viable fetus (≥ 20 and <24 wks)	0	-	
Livebirth	535	100%	
GA at delivery (in wks) - median (IQR)	39 wks	(38-40)	
NEONATAL OUTCOMES (among livebirth infants)			
- Small for gestational age*	21	3.9%	2.4–5.9
- NICU admission (any cause)**	25	4.7%	3.0–6.8
NICU admission for prematurity	13	2.4%	1.3–4.1
NICU admission for respiratory distress	6	1.1%	0.4–2.4
NICU admission for sepsis	1	0.2%	0.0–1.0
NICU admission for other cause	6	1.1%	0.4–2.4
- Neonatal death	0	-	

***Table 8*: Pregnancy and neonatal outcomes among pregnant women exposed to COVID-19 mRNA vaccine and ending their pregnancy during pregnancy after 20 wks (population 2d).**

* <10th percentile for gestational age according to INTERGROWTH 21GA: gestational agewks: weeks of gestationNICU: neonatal Intensive Care Unit

** Reason for NICU admission can be multiple

control group of non-vaccinated pregnant women for comparison, which could have given more strength to our results and allow for evaluation of association between exposure and outcomes. This study was also not designed to test the efficacy of the vaccine during pregnancy.

The results may not be representative of the general pregnant population as the COVID-19 mRNA vaccine was first offered to pregnant patients with comorbidities three months before being extended to all pregnant women in Switzerland. This led to the inclusion of more high-risk pregnancies with maternal comorbidities, as shown in Table 5. Because maternal comorbidities are associated with increased adverse pregnancy outcomes, our results may have overestimated the rate of adverse outcomes. As they were, however, not increased compared to the general population, this reinforces the evidence of safety of the mRNA vaccines observed in our cohort.

In conclusion, this prospective study has provided further evidence that mRNA vaccination against SARS-CoV-2 during pregnancy seems safe in terms of early adverse events, pregnancy, and neonatal outcomes, within the limitation of the information provided by a descriptive non-controlled study design. Exposure to mRNA vaccine anytime in pregnancy seemed not associated with higher adverse pregnancy or neonatal outcomes as compared to historical data. In addition, pregnant patients exposed to the vaccine before 37 wks seemed not at increased risk of preterm birth as compared to the data on neonatal health from the Swiss Federal statistical office. Long term outcomes, however, such as infant developmental outcomes were not within the available time frame of this study and would require further studies. Efforts must be made to continue to monitor the safety and efficacy of these already marketed mRNA COVID-19 vaccines in larger sample of pregnant women and appropriate control groups to provide risk estimates. The focus should be on first trimester exposure, rare adverse events and long-term outcomes (e.g. infant developmental outcomes).

Contributors

GF, EM, DB, and AP conceived and designed the study. GF, DB and AP were in charge of the funding acquisition and of the project administration. GF, EM, LP, and AP analysed and interpreted the data. GF, EM, DB, and AP drafted the manuscript. DB and AP provided supervision of the work. All authors (GF, EM, LP, UW, CD, BMT, DD, SC, MM, MTB, SS, IH, CM, BFT, SK, CB,

JM, RZ, APR, DS, DB, AP) contributed to data collection, reviewed and edited the manuscript. 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.

Data sharing statement

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

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 a malpractice case, outside the submitted work. All other authors declare no conflicts of interest.

Acknowledgments

We thank every patient who agreed to participate in this study. We are very grateful to our collaborators (listed in Table S6) who recruited patients and collected data for this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanepe.2022.100410.

References

1 Lokken EM, Taylor GG, Huebner EM, et al. Higher severe acute respiratory syndrome coronavirus 2 infection rate in pregnant patients. *Am J Obstet Gynecol*. 2021;225(1). 75.e1-75.e16.
2 Vouga M, Favre G, Martinez-Perez O, et al. Maternal outcomes and risk factors for COVID-19 severity among pregnant women. *Sci Rep*. 2021;11(1):13898.
3 Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. 2020;370:m3320.
4 DeSisto CL, Wallace B, Simeone RM, et al. Risk for stillbirth among women with and without COVID-19 at delivery hospitalization - United States, March 2020-September 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(47):1640–1645.
5 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603–2615.
6 Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403–416.
7 Buchan SA, Chung H, Brown KA, et al. *Effectiveness of COVID-19 Vaccines Against Omicron or Delta infection [Internet]*. 2022. [cited 2022 Jan 11]. Available from: https://www.medrxiv.org/content/10.1101/2021.12.30.21268565v1.
8 Barda N, Dagan N, Cohen C, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *The Lancet*. 2021;398(10316):2093–2100.
9 Hansen CH, Schelde AB, Moustsen-Helm IR, et al. Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: a Danish cohort study [Internet]. 2021 [cited 2022 Jan 11]. Available from: https://www.medrxiv.org/content/10.1101/2021.12.20.21267966v3.
10 Collie S, Champion J, Moultrie H, Bekker L-G, Gray G. Effectiveness of BNT162b2 vaccine against Omicron Variant in South Africa. *N Engl J Med*. 2021;0(0). null.
11 Dashraath P, Nielsen-Saines K, Madhi SA, Baud D. COVID-19 vaccines and neglected pregnancy. *Lancet*. 2020;396(10252):e22.
12 Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary findings of mRNA Covid-19 vaccine safety in pregnant persons. *N Engl J Med*. 2021;384(24):2273–2282.
13 Zauche LH, Wallace B, Smoots AN, et al. Receipt of mRNA Covid-19 vaccines and risk of spontaneous abortion. *N Engl J Med*. 2021;385(16):1533–1535.
14 Morgan JA, Biggio JR, Martin JK, et al. Maternal outcomes after severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection in vaccinated compared with unvaccinated pregnant patients. *Obstet Gynecol*. 2022;139(1):107–109.
15 Dagan N, Barda N, Biron-Shental T, et al. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. *Nat Med*. 2021;27(10):1693–1695.
16 Goldshtein I, Nevo D, Steinberg DM, et al. Association Between BNT162b2 Vaccination and Incidence of SARS-CoV-2 Infection in Pregnant Women. *JAMA*. 2021;326(8):728–735.
17 Bookstein Peretz S, Regev N, Novick L, et al. Short-term outcome of pregnant women vaccinated with BNT162b2 mRNA COVID-19 vaccine. *Ultrasound Obstet Gynecol*. 2021;58(3):450–456.
18 Theiler RN, Wick M, Mehta R, Weaver AL, Virk A, Swift M. Pregnancy and birth outcomes after SARS-CoV-2 vaccination in pregnancy. *Am J Obstet Gynecol MFM*. 2021;3:(6) 100467.
19 Wainstock T, Yoles I, Sergienko R, Sheiner E. Prenatal maternal COVID-19 vaccination and pregnancy outcomes. *Vaccine*. 2021;39(41):6037–6040.
20 Rottenstreich M, Sela HY, Rotem R, Kadish E, Wiener-Well Y, Grisaru-Granovsky S. Covid-19 vaccination during the third trimester of pregnancy: rate of vaccination and maternal and neonatal outcomes, a multicentre retrospective cohort study. *BJOG*. 2022;129(2):248–255.
21 Blakeway H, Prasad S, Kalafat E, et al. COVID-19 vaccination during pregnancy: coverage and safety. *Am J Obstet Gynecol*. 2022;226(2). 236.e1-236.e14.
22 Trostle ME, Limaye MA, Avtushka V, Lighter JL, Penfield CA, Roman AS. COVID-19 vaccination in pregnancy: early experience from a single institution. *Am J Obstet Gynecol MFM*. 2021;3:(6) 100464.
23 SGGG - Recommandation of the Swiss Society of Gynecologists and Obstetricians on Vaccination with COVID-19 mRNA vaccine during pregnancy [Internet]. 2021 [cited 2021 Dec 15]; Available from: https://www.sggg.ch/fr/nouvelles/detail/1/infection-a-coronavirus-covid-19-et-grossesse/.
24 Stuckelberger S, Favre G, Ceulemans M, et al. SARS-CoV-2 vaccine willingness among pregnant and breastfeeding women during the first pandemic wave: a cross-sectional study in Switzerland. *Viruses*. 2021;13(7):1199.
25 Panchaud A, Favre G, Pomar L, Vouga M, Aebi-Popp K, Baud D. An international registry for emergent pathogens and pregnancy. *Lancet*. 2020;395(10235):1483–1484.
26 von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453–1457.
27 Papageorghiou AT, Kennedy SH, Salomon LJ, et al. The INTERGROWTH-21st fetal growth standards: toward the global

integration of pregnancy and pediatric care. *Am J Obstet Gynecol*. 2018;218(2S):S630–S640.
28 Kachikis A, Englund JA, Singleton M, Covelli I, Drake AL, Eckert LO. Short-term reactions among pregnant and lactating individuals in the first wave of the COVID-19 vaccine rollout. *JAMA Netw Open*. 2021;4:(8) e2121310.
29 Beatty AL, Peyser ND, Butcher XE, et al. Analysis of COVID-19 vaccine type and adverse effects following vaccination. *JAMA Netw Open*. 2021;4:(12) e2140364.
30 Houghton DE, Padmanabhan A, Ashrani AA, et al. Deep vein thrombosis after COVID-19 vaccinations. *Blood*. 2021;138:291.
31 Marik PE, Plante LA. Venous thromboembolic disease and pregnancy. *N Engl J Med*. 2008;359(19):2025–2033.
32 Birabaharan M, Kaelber DC, Karris MY. Risk of herpes zoster reactivation after messenger RNA COVID-19 vaccination: a cohort study. *J Am Acad Dermatol*. 2021;S0190-9622(21). 02892-9.
33 Enders G, Miller E, Cradock-Watson J, Bolley I, Ridehalgh M. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. *Lancet*. 1994;343(8912):1548–1551.
34 Kharbanda EO, Haapala J, DeSilva M, et al. Spontaneous abortion following COVID-19 vaccination during pregnancy. *JAMA*. 2021;326(16):1629–1631.
35 Magnus MC, Gjessing HK, Eide HN, Wilcox AJ, Fell DB, Håberg SE. Covid-19 vaccination during pregnancy and first-trimester miscarriage. *N Engl J Med*. 2021;385(21):2008–2010.
36 Office Fédérale de la Statistique Suisse (Swiss Federal Statistical Office). Santé des nouveau-nés [Internet]. [cited 2022 Feb 25]; Available from: https://www.bfs.admin.ch/bfs/fr/home/statistiken/gesundheit/gesundheitszustand/gesundheit-neugeborene.html.
37 Zeitlin J, Mohangoo A, Cuttini M. The European Perinatal Health Report: comparing the health and care of pregnant women and newborn babies in Europe. *J Epidemiol Commun Health*. 2009;63(9):681–682.
38 Haidari ES, Lee HC, Illuzzi JL, Phibbs CS, Lin H, Xu X. Hospital variation in admissions to neonatal intensive care units by diagnosis severity and category. *J Perinatol*. 2021;41(3):468–477.
39 Lipkind HS, Vazquez-Benitez G, DeSilva M, et al. Receipt of COVID-19 vaccine during pregnancy and preterm or small-for-gestational-age at birth - eight integrated health care organizations, United States, December 15, 2020-July 22, 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(1):26–30.
40 Stock SJ, Carruthers J, Calvert C, et al. SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. *Nat Med*. 2022.

Clinical Microbiology and Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

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

Guillaume Favre [1, †], Emeline Maisonneuve [1, 2, †], Léo Pomar [3], Charlotte Daire [1], Cécile Monod [4], Begoña Martinez de Tejada [5], Thibaud Quibel [6], Monya Todesco-Bernasconi [7], Loïc Sentilhes [8], Carolin Blume [9], Andrea Papadia [10], Stephanie Sturm [11], Dirk Bassler [12], Claudia Grawe [13], Anda Petronela Radan [14], Marie-Claude Rossier [15], Jérôme Mathis [16], Romina Capoccia-Brugger [17], Karine Lepigeon [1], Eva Gerbier [1], Marie Claude Addor [1], Ursula Winterfeld [18], David Baud [1, *, †], Alice Panchaud [2, 19, †]on behalf of the COVI-PREG group[§]

[1)] *Materno-fetal and Obstetrics Research Unit, Department "Femme-Mère-Enfant", University Hospital, Lausanne, Switzerland*
[2)] *Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland*
[3)] *School of Health Sciences (HESAV), University of Applied Sciences and Arts Western Switzerland, Lausanne, Switzerland*
[4)] *Department of Obstetrics, Basel, University Hospital, Basel, Switzerland*
[5)] *Obstetrics Division, Department of Pediatrics, Gynecology, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland*
[6)] *Department of Obstetrics, Maternité Poissy Saint Germain, Poissy, France*
[7)] *Department of Obstetrics, Cantonal Hospital Aarau, Aarau, Switzerland*
[8)] *Department of Obstetrics and Gynecology, Bordeaux University Hospital, Bordeaux, France*
[9)] *Kantonsspital Graubünden, Frauenklinik Fontana, Chur, Switzerland*
[10)] *Department of Gynecology and Obstetrics, Ente Ospedaliero Cantonale, Lugano, Switzerland*
[11)] *Frauenpraxis Schaffhausen, Schaffhausen, Switzerland*
[12)] *Neonatal Department, University Hospital Zürich, Zürich, Switzerland*
[13)] *Department of Obstetrics, Gynecology Stadtspital Triemli Zürich, Zürich, Switzerland*
[14)] *Department of Obstetrics and Feto-maternal Medicine, University Hospital of Bern, University of Bern, Bern, Switzerland*
[15)] *Department of Obstetrics and Gynecology, Hospital Riviera Chablais, Rennaz, Switzerland*
[16)] *Department of Obstetrics and Gynecology, Centre Hospitalier Bienne, Bienne, Switzerland*
[17)] *Department of Obstetrics and Gynecology, RHNE, Neuchâtel, Switzerland*
[18)] *Swiss Teratogen Information Service, Clinical Pharmacology Service, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland*
[19)] *Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland*

ARTICLE INFO

Article history:
Received 4 April 2023
Received in revised form
11 June 2023
Accepted 12 June 2023
Available online xxx

Editor: L. Leibovici

Keywords:
Congenital anomaly
COVID-19
Pregnancy
Pregnant women
SARS-CoV-2

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 foetus 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 with 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 of 0.89 (95% CI: 0.12–6.80) with no significant changes after adjustment through exploratory analysis.

* Corresponding author. David Baud, Materno-fetal and Obstetrics Research Unit, Department of Obstetrics and Gynecology, Centre Hospitalier Universitaire Vaudois (CHUV), 1011 Lausanne, Switzerland.
E-mail address: David.baud@chuv.ch (D. Baud).
† These authors contributed equally to this work.
§ The members of the The COVI-PREG group were listed in the section The COVI-PREG group.

https://doi.org/10.1016/j.cmi.2023.06.015

Teratogenicity
Vaccine

Conclusions: Pregnant women exposed to mRNA COVID-19 vaccine before 12 weeks of gestation did not have an increased risk of congenital malformation compared with women exposed outside the teratogenic window. Because vaccination is safe and effective, emphasis must be placed on promoting vaccination during pregnancy. **Guillaume Favre, Clin Microbiol Infect 2023;▪:1**

Introduction

COVID-19 vaccines have been accessible since December 2020 [1,2]. Because 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 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 first trimester of pregnancy, which represents the exposure period with the highest risk of teratogenicity, are lacking [12,17,18].

Ruderman et al. [19] 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 before the pregnancy to 14 weeks of gestation (weeks) with a group composed of both unvaccinated pregnant women and pregnant women vaccinated after 14 weeks. Another study by Calvert et al. [20] 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 with unvaccinated patients. 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 with 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 before 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 were 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 timepoints: (a) patient's baseline characteristics, medical/obstetrical history, and vaccine exposure were collected at time of inclusion; and (b) pregnancy outcomes including congenital malformations diagnosed via ultrasonography and confirmed at birth or diagnosed after birth (up to 5 days after birth) were recorded using the maternal hospital discharge letters. Patient data were extracted from electronic medical records and stored using the 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].

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 5 days compared with the measured CRL by ultrasound, the GA was set based on the CRL measured by ultrasound. If the difference was less than 5 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 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 and 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 10th version 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, 26–30, 31–35, 36–40, and >40 years), 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 covariates 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/foetuses 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 2 patients vaccinated after the first trimester of pregnancy were excluded because of unknown pregnancy outcome status. Among the 1450 remaining patients, 124 were exposed to an 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 is 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, 2 (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 after 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 after conception, had a late spontaneous abortion that occurred at 16 weeks in a context of chorioamnionitis.

Among women exposed from 12 weeks of pregnancy, 2 (0.15%; 95% CI: 0.02–0.54; n = 2/1326) had a late spontaneous abortion at 14 and 16 weeks after 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 with 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.

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

	1st trimester exposure[a]		2nd/3rd trimester exposure[b]		
	$n = 124$		$n = 1326$		
	n	%	*n*	%	Std. Diff.
Patients baseline characteristics					
Maternal age (y) at first dose					
≤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					
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 (wk) median; [IQR] (min–max)	3	[2–5] (2–11)	23	[17–28] (12–40)	—
GA at second injection (wk) median; [IQR] (min–max)	8	[7–9] (5–11)	27	[22–32] (14–40)	—

GA, gestational age; PPROM, preterm premature rupture of membranes.
[a] First trimester exposure: exposure to the vaccine from conception to 11 weeks of gestation and 6 days.
[b] Second and third trimester exposure: exposure to the vaccine from 12 weeks of gestation to the end of pregnancy.

Our results align with current literature. On the basis of patients exposed from 30 days before conception to 14 weeks, Ruderman et al. [19] reported no increased risk of congenital anomaly compared with 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 2–10 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 have 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 before anatomical screening at 18–24 weeks may have led to a medically indicated TOP, which were not considered in their study. In addition, cases identified during third trimester ultrasonography or at birth may also have been inadvertently excluded [25]. The study from Calvert et al. [20] 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 before conception to 19^{+6} weeks with 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

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

	1st trimester exposure			2nd/3rd trimester exposure						
	$n = 124$			$n = 1326$						
	n	%	95%CI	*n*	%	95%CI	RR	95%CI	adj. RR[b]	95%CI
Congenital malformation[a]	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	0.15%	0.02–0.54	-			

adj. RR, adjusted risk ratio; RR, risk ratio.
[a] Congenital malformation classification (major + minor) according to the EUROCAT classification.
[b] Adjusted analysis on unbalanced potential confounders: maternal age >40 y, 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			2nd/3rd trimester exposure		
$n = 1/124$			$n = 11/1326$		
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 wk	Q620	Congenital hydronephrosis >10 mm	18 wk
			Q660	Right club foot	26 wk
			Q254	Congenital heart defect (right aortic arch + patent ductus arteriosus + perimembranous ventricular septal defect)	12 wk
			Q54	Hypospadias	14 wk
			D180	Haemangioma (on the right cheek)	15 wk
			Q278	Isolated aberrant right subclavian artery	18 wk
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 wk
			Q179	Right ear hypoplasia	20 wk
			Q179	Bilateral ear fistulas	15 wk
			P835	Bilateral hydrocele of testis	14 wk
			Q669	Left foot malposition (abduction, dorsal extension, and valgus)	27 wk

GA, gestational age; ICD-10-BPA, International Classification of Disease Version 10 – British Paediatric Association.

that 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. Because 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 remains 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 with a maximum of 5 days after birth in our study. This difference impacts the proportion of congenital malformation because 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 because 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 who had an early spontaneous abortion were not excluded, underestimating the proportion of malformation, however likely marginal because of 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 second/third trimester vaccination. This may have led to unreported malformations leading to fetal death before inclusion. Fourth, our reference group consisted of women who were vaccinated during the second/third trimesters therefore representing an exposed population. It is

unlikely, however, that exposure to a COVID-19 vaccine could induce a malformation, because major malformations 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 with women exposed during the second/third trimester of pregnancy, in the limits of small sample size, leading to imprecise risk estimates. Although these data are reassuring, additional studies are required to confirm our findings. Pregnant women 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. Because willingness for vaccination remains low among pregnant women, emphasis must be placed on promoting vaccination during pregnancy.

The COVI-PREG group

Irene Hoesli: Department of Obstetrics, Basel, University Hospital, Basel, Switzerland.

Sonia Campelo : Research Platform, Department of Pediatrics, Gynecology, and Obstetrics, Faculty of Medicine, University of Geneva, Geneva, Switzerland.

Véronique Othenin-Girard: Research Platform, Department of Pediatrics, Gynecology, and Obstetrics, Faculty of Medicine, University of Geneva, Geneva, Switzerland.

Mirjam Moser: Department of Obstetrics, Cantonal Hospital Aarau, Aarau, Switzerland.

Amaury Brot: Department of Obstetrics and Gynecology, Bordeaux University Hospital, Bordeaux, France.

Alizée Froeliger: Department of Obstetrics and Gynecology, Bordeaux University Hospital, Bordeaux, France.

Clémence Houssin: Department of Obstetrics and Gynecology, Bordeaux University Hospital, Bordeaux, France.

Stylianos Kalimeris: Kantonsspital Graubünden, Frauenklinik Fontana, Chur, Switzerland

Maria Luisa Gasparri M: Department of Gynecology and Obstetrics Ente Ospedaliero Cantonale, Lugano, Switzerland.

Antonilli Morena: Department of Gynecology and Obstetrics Ente Ospedaliero Cantonale, Lugano, Switzerland.

Christian Polli: Department of Gynecology and Obstetrics Ente Ospedaliero Cantonale, Lugano, Switzerland

Edoardo Taddei: Department of Gynecology and Obstetrics Ente Ospedaliero Cantonale, Lugano, Switzerland.

Daniel Surbek: Department of Obstetrics and Feto-maternal Medicine, University Hospital of Bern, University of Bern, Bern, Switzerland.

Luigi Raio: Department of Obstetrics and Feto-maternal Medicine, University Hospital of Bern, University of Bern, Bern, Switzerland.

Edouard Ha: Department of Obstetrics and Gynecology, Centre hospitalier Bienne, Bienne, Switzerland.

Carolin Eggemann: Department of Obstetrics and Gynecology, Centre hospitalier Bienne, Bienne, Switzerland.

Author contributions

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 contributed to data collection. All authors made a significant contribution in reviewing the manuscript drafting or revision and accept accountability for the overall work. All authors approved the final version of the report.

Transparency declaration

Conflict of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. AP 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. BMdT 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. LS 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.

Funding

The study was funded by a grant from the Swiss Federal Office of Public Health and the Foundation CHUV.

Ethics statement

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

Data availability

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

Acknowledgements

We thank the patients, obstetricians, and midwives who agreed to participate in this study.

References

[1] Office of the Commissioner. FDA approves first COVID-19 vaccine. FDA; 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine. [Accessed 15 November 2022].

[2] EMA. Ema Recommends first COVID-19 vaccine for authorisation in the EU. European Medicines Agency; 2020. https://www.ema.europa.eu/en/news/

ema-recommends-first-covid-19-vaccine-authorisation-eu. [Accessed 15 November 2022].
[3] Favre G, Pomar L, Baud D. Coronavirus disease 2019 during pregnancy: do not underestimate the risk of maternal adverse outcomes. Am J Obstet Gynecol MFM 2020;2:100160. https://doi.org/10.1016/j.ajogmf.2020.100160.
[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 2020;370:m3320. https://doi.org/10.1136/bmj.m3320.
[5] Vouga M, Favre G, Martinez-Perez O, Pomar L, Acebal LF, Abascal-Saiz A, et al. Maternal outcomes and risk factors for COVID-19 severity among pregnant women. Sci Rep 2021;11:13898. https://doi.org/10.1038/s41598-021-92357-y.
[6] Favre G, Mazzetti S, Gengler C, Bertelli C, Schneider J, Laubscher B, et al. Decreased fetal movements: a sign of placental SARS-CoV-2 infection with perinatal brain injury. Viruses 2021;13:2517. https://doi.org/10.3390/v13122517.
[7] Dashraath P, Nielsen-Saines K, Madhi SA, Baud D. COVID-19 vaccines and neglected pregnancy. Lancet 2020;396:e22. https://doi.org/10.1016/S0140-6736(20)31822-5.
[8] Office fédéral de la santé publique. Coronavirus: vaccination contre le COVID-19. https://www.bag.admin.ch/bag/fr/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/information-fuer-die-aerzteschaft/covid-19-impfung.html. [Accessed 9 December 2022].
[9] Stratégie de vaccination contre le SARS-CoV-2 – actualisation des facteurs de risque de formes graves de la COVID-19 et des recommandations sur la stratégie de priorisation des populations à vacciner. Haute Autorité de Santé. https://www.has-sante.fr/jcms/p_3240117/fr/strategie-de-vaccination-contre-le-sars-cov-2-actualisation-des-facteurs-de-risque-de-formes-graves-de-la-covid-19-et-des-recommandations-sur-la-strategie-de-priorisation-des-populations-a-vacciner. [Accessed 20 January 2023].
[10] Villar J, Conti CPS, Gunier RB, Ariff S, Craik R, Cavoretto PI, et al. Pregnancy outcomes and vaccine effectiveness during the period of omicron as the variant of concern, INTERCOVID-2022: a multinational, observational study. Lancet 2023;401:447–57. https://doi.org/10.1016/S0140-6736(22)02467-9.
[11] Schrag SJ, Verani JR, Dixon BE, Page JM, Butterfield KA, Gaglani M, et al. Estimation of COVID-19 mRNA vaccine effectiveness against medically attended COVID-19 in pregnancy during periods of Delta and Omicron variant predominance in the United States. JAMA Netw Open 2022;5:e2233273. https://doi.org/10.1001/jamanetworkopen.2022.33273.
[12] Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, et al. Preliminary findings of mRNA COVID-19 vaccine safety in pregnant persons. N Engl J Med 2021;384:2273–82. https://doi.org/10.1056/NEJMoa2104983.
[13] Favre G, Maisonneuve E, Pomar L, Winterfeld U, Daire C, Martinez de Tejada B, et al. COVID-19 mRNA vaccine in pregnancy: results of the Swiss COVI-PREG registry, an observational prospective cohort study. Lancet Reg Health Eur 2022;18:100410. https://doi.org/10.1016/j.lanepe.2022.100410.
[14] Stock SJ, Carruthers J, Calvert C, Denny C, Donaghy J, Goulding A, et al. SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. Nat Med 2022;28:504–12. https://doi.org/10.1038/s41591-021-01666-2.
[15] Zauche LH, Wallace B, Smoots AN, Olson CK, Oduyebo T, Kim SY, et al. Receipt of mRNA Covid-19 vaccines and risk of spontaneous abortion. N Engl J Med 2021;385:1533–5. https://doi.org/10.1056/NEJMc2113891.
[16] Watanabe A, Yasuhara J, Iwagami M, Miyamoto Y, Yamada Y, Suzuki Y, et al. Peripartum outcomes associated with COVID-19 vaccination during pregnancy: a systematic review and meta-analysis. JAMA Pediatr 2022;176:1098–106. https://doi.org/10.1001/jamapediatrics.2022.3456.
[17] Mascolo A, di Mauro G, Fraenza F, Gaio M, Zinzi A, Pentella C, et al. Maternal, fetal and neonatal outcomes among pregnant women receiving COVID-19 vaccination: the preg-co-vax study. Front Immunol 2022;13:965171. https://doi.org/10.3389/fimmu.2022.965171.
[18] Blakeway H, Prasad S, Kalafat E, Heath PT, Ladhani SN, Le Doare K, et al. COVID-19 vaccination during pregnancy: coverage and safety. Am J Obstet Gynecol 2022;226:236. e1–14. https://doi.org/10.1016/j.ajog.2021.08.007.
[19] Ruderman RS, Mormol J, Trawick E, Perry MF, Allen EC, Millan D, et al. Association of COVID-19 vaccination during early pregnancy with risk of congenital fetal anomalies. JAMA Pediatr 2022;176:717–9. https://doi.org/10.1001/jamapediatrics.2022.0164.
[20] Calvert C, Carruthers J, Denny C, Donaghy J, Hillman S, Hopcroft LEM, et al. A population-based matched cohort study of early pregnancy outcomes following COVID-19 vaccination and SARS-CoV-2 infection. Nat Commun 2022;13:6124. https://doi.org/10.1038/s41467-022-33937-y.
[21] Panchaud A, Favre G, Pomar L, Vouga M, Aebi-Popp K, Baud D, et al. An international registry for emergent pathogens and pregnancy. Lancet 2020;395:1483–4. https://doi.org/10.1016/S0140-6736(20)30981-8.
[22] Moore KL, Persaud TVN, Torchia MG. Before we are born: essentials of embryology and birth defects. 9th ed. United States: Elsevier; 2020.
[23] European platform on rare disease registration. https://eu-rd-platform.jrc.ec.europa.eu. [Accessed 24 February 2021].
[24] World Health Organization. ICD-10: International statistical classification of diseases and related health problems: tenth revision. World Health Organization; 2004.
[25] Syngelaki A, Hammami A, Bower S, Zidere V, Akolekar R, Nicolaides KH. Diagnosis of fetal non-chromosomal abnormalities on routine ultrasound examination at 11–13 weeks' gestation. Ultrasound Obstet Gynecol 2019;54:468–76. https://doi.org/10.1002/uog.20844.
[26] Dossier thématique – vaccins contre le COVID-19 et femmes encei – ANSM. https://ansm.sante.fr/dossiers-thematiques/covid-19-vaccins/covid-19-vaccins-et-femmes-enceintes. [Accessed 20 January 2023].
[27] EUROCAT. Eurocat Guide 1.4: instruction for the registration of congenital anomalies. EUROCAT central registry. University of Ulster; 2013. Updated, https://eu-rd-platform.jrc.ec.europa.eu/eurocat_en. [Accessed 1 December 2020].
[28] Liu CL, Li P, Cai GF, Morse A, Liu J, Chen ZH, et al. Optimal follow-up duration for assessment of birth defects after in vitro fertilization-embryo transfer: a multicenter 5-year cohort study in China. Front Endocrinol (Lausanne) 2022;13:817397. https://doi.org/10.3389/fendo.2022.817397.
[29] Qin J, Sheng X, Wang H, Liang D, Tan H, Xia J. Assisted reproductive technology and risk of congenital malformations: a meta-analysis based on cohort studies. Arch Gynecol Obstet 2015;292:777–98. https://doi.org/10.1007/s00404-015-3707-0.
[30] Stuckelberger S, Favre G, Ceulemans M, Nordeng H, Gerbier E, Lambelet V, et al. SARS-CoV-2 vaccine willingness among pregnant and breastfeeding women during the first pandemic wave: a cross-sectional study in Switzerland. Viruses 2021;13:1199. https://doi.org/10.3390/v13071199.

scientific reports

Check for updates

OPEN

Mental health in pregnant individuals during the COVID-19 pandemic based on a Swiss online survey

Guillaume Favre[1,9]✉, Cléa Kunz[1], Simone Schwank[2,3], Ho-Fung Chung[4,5], Anda Petronela Radan[6], Luigi Raio[6], Mihaela Fluri[6], Ursula Winterfeld[7], David Baud[1] & Léo Pomar[1,8]

The aim of our study was to evaluate the mental health of pregnant individuals during the early COVID-19 pandemic and the potential factors associated. A Swiss online survey was proposed to individuals who gave birth during the pandemic period from March 2020. The Edinburgh Postnatal Depression Scale (EPDS), Generalized Anxiety Disorder 7 questions (GAD-7), and Impact Event Scale-Revised (IES-R) were evaluated and used to defined mental health impairment as a composite outcome. From October, 2020 to February, 2021, 736 participants responded. The anxiety GAD-7 score was moderate in 9.6% and severe in 2.0%. The EPDS was moderate in 21.5% and severe in 32.9%. The IES-R was moderate in 10.3% and severe in 3.9%. Mental health impairment was reported in 37.0%. The association between the risk of mental health impairment and foreign nationality was significant (OR = 1.48; 95%CI [1.06–2.05]) as well as fetal and pregnancy worries because of coronavirus (OR = 1.46; 95% CI [1.08–1.98]) and 1.65; 95% CI [1.22–2.24]). Adjusted ORs were significant for foreign nationality (aOR = 1.51; 95%CI [1.07–2.13]) and pregnancy worries because of coronavirus (aOR = 1.62; 95%CI [1.10–2.40]). Pregnant people and especially foreign national have a high risk of mental health impairment during the pandemic.

Following the first coronavirus disease 2019 (COVID-19) case in Switzerland in February 25, 2020, the situation rapidly escalated, with closure of all non-essential shops and services and the implementation of restrictions on social interactions[1].

The measures undertaken to control viral spread have had multiple repercussions. While the Swiss confederation did not impose a complete lockdown as seen in many countries, the mental health of Swiss citizens was nonetheless severely impacted. Many factors contributed to this situation including potential financial instability, lack of social contact, drastic changes to routines, and health concerns amongst others. In the Swiss Corona Stress Study, while the proportion of participants reporting moderate depressive symptoms was 11.8% before the pandemic, this proportion rose to 24.7% after isolation measures were introduced. Severe depressive symptoms were reported in 2.4% and 9.1%, respectively. Furthermore, 57% of participants felt more anxious during the pseudo-lockdown[2]. Of note, a longitudinal study in Argentina also reported that the pandemic had contributed to a deterioration of mental health, leading to increased susceptibility to depressive and anxiety symptoms among pregnant individuals[3].

[1]Materno-Fetal and Obstetrics Research Unit, Department Woman-Mother-Child, Lausanne University Hospital, Lausanne, Switzerland. [2]Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, Stockholm, Sweden. [3]Columbia University, College of Physicians and Surgeons, Center for Psychoanalytic Training and Research, New York, USA. [4]Department of Psychology, The University of Hong Kong, Hong Kong, China. [5]Department of Anthropology, The Chinese University of Hong Kong, Hong Kong, China. [6]Department of Obstetrics and Gynecology, University Hospital of Bern and University of Bern, Bern, Switzerland. [7]Swiss Teratogen Information Service, Clinical Pharmacology Service, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. [8]School of Health Sciences (HESAV), University of Applied Sciences and Arts Western Switzerland, Lausanne, Switzerland. [9]Materno-Fetal & Obstetrics Research Unit, Department of Obstetrics and Gynecology, Centre Hospitalier Universitaire Vaudois (CHUV), 1011 Lausanne, Switzerland. ✉email: guillaume.favre@chuv.ch

Pregnant individuals are particularly vulnerable to mental health disorders due to life changes, stress and hormonal adaptations. Furthermore, depression and anxiety are frequently underdiagnosed during pregnancy[4]. Additionally, concerns regarding medication safety rise during pregnancy and many patients discontinue their antidepressant or anxiolytic medications, increasing the risk of relapse[5]. In Switzerland, one in six pregnant people require mental health services each year, with depression being the most prevalent perinatal mental health related diagnosis[6]. Maternal distress, including depression, anxiety, and stress, are critical as they increase the risk of miscarriage[7]. Low birth weight, as well as preterm birth, are also increased in pregnancies affected by maternal mental health disorders[8,9]. It can also impact the long-term health of children with a higher rate of severe psychological diagnoses, ranging from autism to schizophrenia[10,11].

The COVID-19 pandemic intensified the mental strain of pregnancy due to legitimate concerns consisting in an increased vulnerability to a severe COVID-19 infection compared to non-pregnant individuals of the same age, along with the consequence of their fetus[12]. Depression and anxiety amongst pregnant people have substantially increased during this outbreak worldwide[13–15]. Alongside from general fears arising during pregnancy, health concerns for pregnant individuals following a COVID-19 infection have emerged[16]. It has been established that pregnant people are at higher risk of infection and progression to a severe form of COVID-19, with a higher risk of intensive care unit admission, mechanical ventilation, and death[12,17,18]. Preterm birth is increased in pregnancies to mothers that tested positive for the virus, and potential dramatic neonatal issues have also been reported in the literature[19,20]. Fear of COVID-19 infection led some pregnant individuals to not adhere to routine antenatal surveillance deepening their anxiety state and indirectly increasing the rate of stillbirth[21]. Additionally, social isolation, poor access to support, and economic uncertainty have amplified depressive symptoms. Previous studies have reported that the first wave of the pandemic may have had a severe impact on pregnant individuals' mental health in Switzerland and suggested to set up specific prevention and support strategies for this high risk group[22]. A recent study in Sweden reported high prevalence of depression and anxiety in pregnancy during the COVID-19 highlighting the need to prevent and support this population even late in the pandemic. So far, no study so far has evaluated the mental health of pregnant people later in the pandemic in Switzerland.

The aim of our study was to evaluate the mental health status of pregnant individuals during the late COVID-19 pandemic in Switzerland and to explore the potential factors associated with altered mental health outcomes.

Methods

Design and data collection. The study was conducted from October 28, 2020 to February 23, 2021. Participants were recruited with an announcement on Lausanne University Hospital (CHUV) and Bern University Hospital (Inselspital) public social media platforms (Facebook). The announcement included the link to the online survey (powered by Qualtrics, Provo, UT). After voluntarily signing an informed consent form, participants accessed the online questionnaire. This form was available in French, German, and Italian, and required approximately 20 min to complete. Anonymous data was self-reported by individuals who consented to participate in the study. Data was collected in accordance with the General Data Protection Regulation (GDPR 2016/679) on privacy in the European Union and the European Economic Area. Institutional review board (IRB) approval from Lausanne University Hospital was obtained. During the study period, measures to fight coronavirus in Switzerland have varied over time and included compulsory masks in every closed space including transportations and public spaces, prohibition of classroom courses, private events with more than 5 to 10 persons and cultural/sports manifestation. Nightclubs/discos and bars were also closed. People travelling to Switzerland from foreign countries were quarantined. Measures have been reinforced from December2020–January 2021 with the closing of every non-essential shops and the recommendation to avoid unnecessary private gatherings. People were asked to stay at home[23].

Participants. Individuals who were pregnant at the time of the questionnaire were eligible. Exclusion criteria were pregnant people who were not of legal age (< 18 years old), not able or willing to consent to participate in the study or who did not speak any of the survey languages.

Co-variates. Maternal age was divided into categories: ≤ 25 years (y), 26 to 30 y, 31 to 35 y, 35 to 40 y, and > 40 y. Baseline characteristics of participants were also collected as follows: ethnicity, nationality, marital status, work hours per week, family income per year, and educational level. Foreign nationality was defined as a participant who is not Swiss. Amount of work hours per weeks (h/w) were divided into categories: less than 40 h/w, 40 h/w, and more than 40 h/w. Higher education was reported as having a bachelor's degree or more. High family income was considered as 90,000 Swiss francs (CHF) or more per year according to the mean household incomes in Switzerland[24].

Primary outcome: COVID-19 concerns, depressive symptoms, anxiety and impact of events. The questionnaire was composed of several blocks of questions, based on participants' concerns about the pandemic as well as three mental health evaluation scales: the Edinburgh Postnatal Depression Scale (EPDS), the Generalized Anxiety Disorder 7 questions (GAD-7), and the Impact Event Scale–Revised (IES-R).

COVID-19 pandemic concerns. Questions about the COVID-19 pandemic were specifically designed for this study, based on authors' expertise from clinical experience and patients feedbacks at the beginning of the pandemic. Questions assessed participants' concerns about their health, anxiety, pregnancy, fetus, as well as the concerns from family members about the respondent being pregnant during the pandemic. The 9 questions were (1) Are you concerned about your health status because of the Coronavirus?, (2) Are you anxious about the coronavirus?, (3) Are you worried about being pregnant during the coronavirus period?, (4) Are you worried

about your fetus in relation to the coronavirus?, (5) Are you worried about your fetus in relation to the coronavirus?, (6) Are your family members concerned of you being pregnant during the coronavirus?, (7) How does the media information impact your worries about the coronavirus?, (8) Is the health care professional's information useful to reduce your questions and concerns regarding the coronavirus ?, (9) Would you like more information regarding the coronavirus related to pregnancy? For the first 6 questions, answers were evaluated on a scale of 0 to 10, 0 being "not anxious at all" and 10 "very anxious". For the last three questions, answers were evaluated on a scale of 0 to 10, 0 being "not at all" and 10 "extremely". Answers were pooled into 5 category scores: 0–1, 2–4, 5–7, and 8–10 for visual interpretation.

General anxiety. General anxiety was evaluated by the generalized anxiety disorder 7 questions (GAD-7); a 7 item self-reported anxiety scale assessing the severity of general anxiety over the last 2 weeks. The scale involves indicating the frequency at which the patient is bothered by specific situations using a four-point Likert scale, ranging from not at all to nearly every day (score 0 to 3, respectively), giving a total score out of 21. Total GAD-7 scores were classified into minimal (0–4), mild (5–9), moderate (10–14), and severe anxiety (15–21)[25].

Depressive symptoms. Depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS), a self-reported questionnaire composed of 10 questions. For each question, four suggestions are present, each corresponding to a score from 0 to 3, rating the intensity of depressive symptoms over the last 7 days for a final score out of 30. A score of ≥ 13 was considered representative of major depressive symptoms[26].

Impact of events. The impact event scale-revised (IES-R) is a 22-item self-reported measure of subjective distress caused by traumatic events. Patients are asked to identify a specific stressful life event and indicate how much they were distressed or bothered by it during the past seven days by each difficulty listed. Total score ranged from 0 to 88 and were categorized into mild (0–39), moderate (40–55), and severe (56–88) symptoms[27].

Secondary outcome: mental health impairment. Mental health impairment was a composite outcome built for this study, defined as at least one of the following conditions: (i) GAD-7 score ≥ 10 (ii) EPDS score ≥ 13 or (iii) IES-R score ≥ 40. This was not a validated instrument and it was only used to analyze potential associated cofactors.

Statistical analysis. A descriptive analysis was performed regarding participants' basic characteristics, COVID-19 situation concerns, and mental health scores reporting absolute numbers of participants, proportions in percentages, means and 95% confidence intervals.

A case control analysis was performed, assessing the association between potential risk factors and risk of mental health impairment. Risk factors assessed were foreign nationality, maternal age > 35 (as it represents a known risk factor for pregnant individuals)[28,29], married status, working hours more than 40 h/w, high educational level, high family income, fetal worries because of COVID-19 score ≥ 5/10, and pregnancy worries because of COVID-19 score ≥ 5/10. Univariate logistic regression was performed, reporting crude Odds Ratios (OR). A multivariate logistic regression analysis was performed. All potential risk factors were considered in the model. A p value less than 0.05 was considered as statistically significant. Statistical analyses were performed using Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

From October 28, 2020, to February 23, 2021, 736 participants that gave birth during the pandemic period responded to the questionnaire and were included. Mean maternal age was 32 years (interquartile range 30–35). Most participants (n = 559; 76.0%) were married or were cohabitating with their partner and 72.3% (n = 532) respondents were Swiss. The percentage of participants that were working more than 40 h a week was 28.1% (n = 207), had a family income of more than 90,000 CHF per year was 59.1% (n = 435), and had a higher education with a bachelor's degree or more was 78.0% (n = 574) (Table 1).

Primary outcome. *COVID-19 pandemic concerns.* Participants' concerns regarding the COVID-19 pandemic are presented in Fig. 1.

18 to 34% of individuals (131 to 253/736) reported being very anxious about COVID-19-related concerns with a score of ≥ 8 out of 10. A proportion of 40% (296/736) of participants reported that they were concerned about their health status because of coronavirus with a score ≥ 5/10 (mean score 4.6; 95%CI 4.4–4.8). The major concern was the global coronavirus situation with an anxiety score ≥ 5/10 in 67% (493/736—mean score 5.5; 95%CI 5.3–5.7). Concerns about being pregnant during the coronavirus period and worries about their fetus in relation to the coronavirus was reported with a score ≥ 5/10 in 40% (295/736—mean score 4.25; 95%CI 4.0–4.5) and 49% (364/736—mean score 5.0: 95%CI 4.7–5.3) respectively. A total of 53% (388/736) reported one of their family member being worried about their pregnancy in the COVID-19 context with a score ≥ 5/10 (mean score 4.5; 95%CI 4.2–4.7). Half of the participants concerns were impacted by the media (50.4%, 371/736—mean score 4.4; 95%CI 4.2–4.7) with a score ≥ 5/10. The majority of individuals reported that information from health care professionals was useful in reducing anxiety associated with pregnancy during the coronavirus pandemic, with a score ≥ 5/10 in 61% (448/736—mean score 5.2; 95%CI 5.0–5.4). The majority expressed their interest in receiving more information on SARS-CoV.2 and pregnancy with a score ≥ 5/10 in 73% (538/736—mean score 6.1; 95%CI 5.9–6.4).

	Patients n = 736		
	n	%	IQR
Maternal age in years (y)			
18–25 y	24	3.3	2.1–4.8
26–30 y	219	29.8	26.5–33.2
31–35 y	350	47.6	43.9–51.2
36–40 y	117	15.9	13.3–18.7
> 40 y	26	3.5	2.3–5.1
	n	**%**	**95% CI**
Marital/relationship status			
Single	57	7.7	5.9–9.9
Married	421	57.2	53.5–60.8
Cohabitation	138	18.8	16.0–21.8
In relationship	118	16.0	13.5–18.9
Divorced	2	0.3	0.0–1.0
Nationality			
Swiss	532	72.3	68.9–75.5
French	122	16.6	14.0–19.5
Belgium	31	4.2	2.9–5.9
German	13	1.8	0.9–3.0
Italian	8	1.1	0.5–2.1
Other	30	4.1	2.8–5.8
Working hours per week			
Less than 40 h a week	419	56.9	53.3–60.5
40 h a week	110	14.9	12.4–17.7
More than 40 h a week	207	28.1	24.9–31.5
Family income per year (CHF-Swiss francs)			
Less than 90,000 CHF	216	29.3	26.1–32.8
Around 90,000 CHF	71	9.6	7.6–12.0
More than 90,000 CHF	435	59.1	55.5–62.7
Unknown	14	1.9	1.0–3.2
Higher educational level			
No scholar education	4	0.5	0.1–1.4
Secondary school 12–15 years	19	2.6	1.6–4.0
Secondary school 15–18 years	16	2.2	1.2–3.5
Diploma	120	16.3	13.7–19.2
Bachelor degree	167	22.7	19.7–25.9
Master degree	312	42.4	38.8–46.1
Doctorate degree/PhD	95	12.9	10.6–15.5
Unknown	3	0.4	0.1–1.2

Table 1. Basic characteristics of participants.

General anxiety, depressive symptoms, and impact of events. The mental health score assessment of respondents is reported in Table 2. Anxiety disorder was evaluated by the GAD-7 as mild in 38.3% (n = 282), moderate in 9.6% (n = 71), severe in 2.0% (n = 15), and missing in 0.3% (n = 2). Depressive symptoms were evaluated by the EPDS as minimal in 45.7% (n = 336), moderate in 21.5% (n = 158), and severe in 32.9% (n = 242). The IES-R score that assessed distress caused by traumatic events was reported as mild in 85.7% (n = 631), moderate in 10.3% (n = 76), severe in 3.9% (n = 29), and missing in 14.3% (n = 105).

Secondary outcome. *Mental health impairment.* A total of 272 (37.0%) participants were identified to have a mental health impairment. Baseline characteristics of patients, according to mental health impairment status, are described in supplementary materials—Table S1. The association between the risk of mental health impairment and foreign nationality was significant with an OR of 1.48 (95%CI [1.06–2.05]; p = 0.021) as well as fetal and pregnancy worries because of coronavirus with a crude OR of 1.46 (95% CI [1.08–1.98]; p = 0.014) and 1.65 (95% CI [1.22–2.24]; p = 0.001). All other covariates, maternal age ≥ 35 years, marital status, working more than 40 h a week, high educational level, and low family income were not significant. Adjusted ORs were only significant for foreign nationality (aOR = 1.51; 95%CI [1.07–2.13]; p = 0.020) and pregnancy worries because of coronavirus (aOR = 1.62; 95%CI [1.10–2.40]; p = 0.016). Other covariates adjusted ORs were not significant (Table 3).

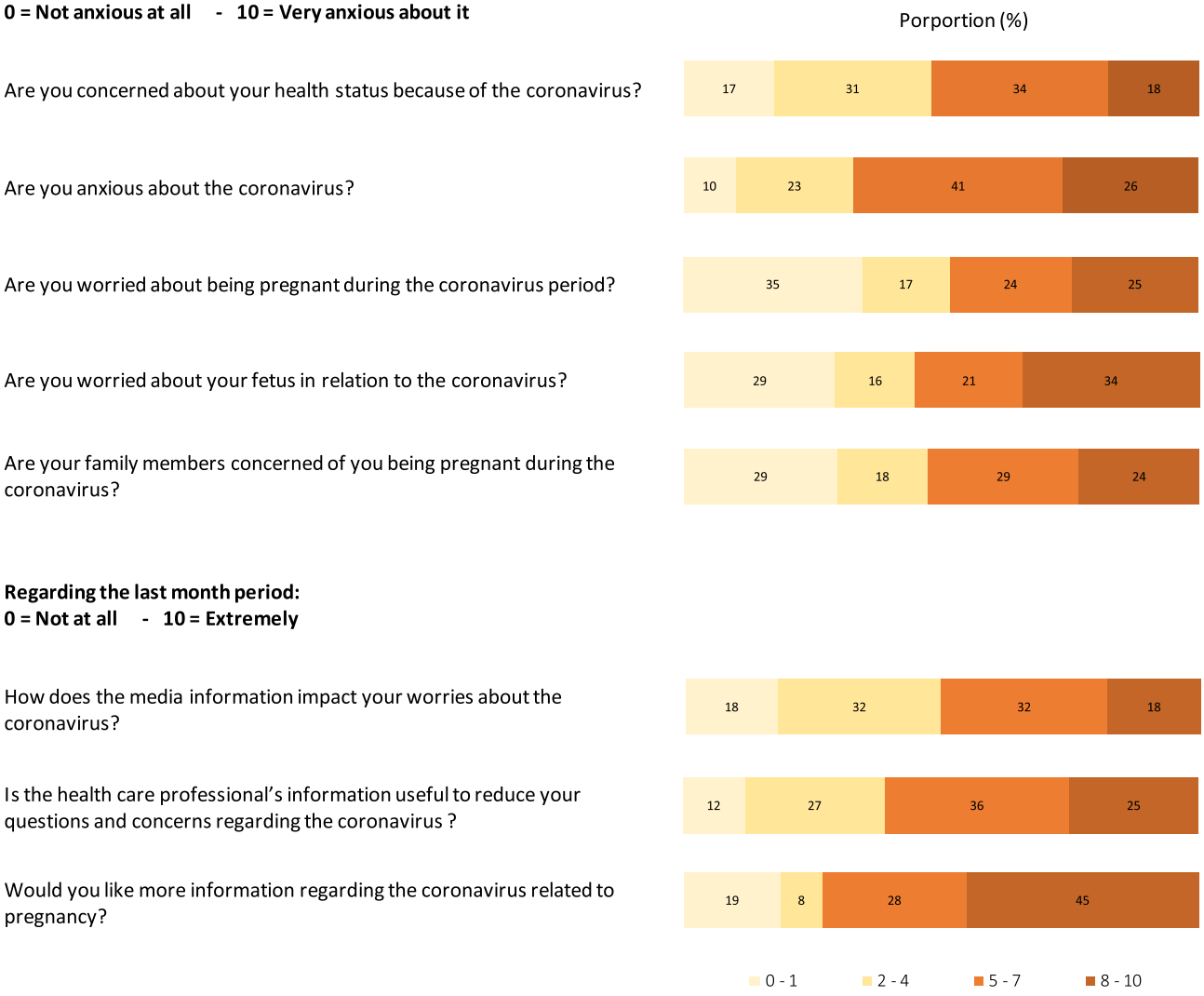


Figure 1. COVID-19 concerns of participants.

		Patients n = 736		
		n	%	95% CI
GAD-7	Minimal (0–4)	366	49.7	46.1–53.4
	Mild (5–9)	282	38.3	34.8–41.9
	Moderate (10–14)	71	9.6	7.6–12.0
	Severe (15–21)	15	2.0	1.1–3.3
	Missing	2	0.3	0.0–1.0
EPDS	Minimal (< 10)	336	45.7	42.0–49.3
	Moderate (10–12)	158	21.5	18.6–24.6
	Severe (≥ 13)	242	32.9	29.5–36.4
IES-R	Mild (< 40)	631	85.7	83.0–88.2
	Moderate (40–55)	76	10.3	8.2–12.8
	Severe (> 55)	29	3.9	2.7–5.6
	Missing	105	14.3	11.8–17.0

Table 2. Mental health assessment using GAD-7, EPDS and IES-R among participants.

	Patients without mental health impairment			Patients with mental health impairment								
	n = 464			n = 272								
	n	%	95% CI	n	%	95% CI	OR	95% CI	p	aOR	95% CI	p
Foreign nationality	115	24.8	20.9–29.0	89	32.7	27.2–38.6	1.48	1.06–2.05	0.021	1.51	1.07–2.13	0.020
Maternal age > 35 y	134	28.9	24.8–33.2	64	23.5	18.6–29.0	0.76	0.54–1.07	0.115	0.78	0.55–1.11	0.168
Married/cohabitation	358	77.2	73.1–80.9	201	73.9	68.3–79.0	0.84	0.59–1.19	0.318	0.85	0.59–1.21	0.355
Working hours more than 40 h/w	123	26.5	22.5–30.8	84	30.9	25.4–36.7	1.24	0.89–1.72	0.203	1.30	0.93–1.83	0.123
High educational level (bachelor or more)	368	79.3	75.3–82.9	209	76.8	71.4–81.7	0.87	0.60–1.24	0.432	0.80	0.55–1.16	0.239
High family income (more than 90,000 CHF/year)	335	72.2	67.9–76.2	185	68.0	62.1–73.5	0.82	0.59–1.13	0.229	0.91	0.65–1.28	0.597
Fetal worries because of COVID-19	240	51.7	47.1–56.4	166	61.0	55.0–66.9	1.46	1.08–1.98	0.014	1.11	0.75–1.65	0.606
Pregnancy worries because of COVID-19	203	43.8	39.2–48.4	153	56.3	50.1–62.2	1.65	1.22–2.24	0.001	1.62	1.10–2.40	0.016

Table 3. Associations between mental health impairment and baseline characteristics as potential risk factors using a univariate and a multivariate logistic regression model. y: years; h/w: hours per week; OR: crude odd ratio; aOR: adjusted OR; Adjustment with all cofactors listed in the table.

Discussion

This study reports that pregnant individuals seemed to have been particularly impacted by the COVID-19 pandemic with almost one third of participants experiencing severe symptoms of depression. In addition, 11.6% of participants experienced moderate to severe symptoms of anxiety with a GAD-7 score of ≥ 10 and 14.2% reported a moderate or severe impact caused by traumatic events. During the pandemic, 37.0% of pregnant individuals reported as having a mental health impairment.

The impact of the COVID-19 pandemic on mental health is potentially serious with most participants stating that they were concerned about their health, their pregnancy, and their unborn child due to coronavirus and two thirds of the participants reporting anxiety surrounding the pandemic situation.

Information given by health care providers was perceived as reassuring and the participants expressed their interest in receiving more information. Persons experiencing worries about their pregnancy because of COVID-19 were at higher risk of mental health impairment highlighting that pregnancy represents a relevant risk factor itself. Pregnant individuals identified as foreign nationals were also significantly more at risk for mental health impairment suggesting that possible interventions should target this population.

Our results align with current literature. International studies have found that severe depressive symptoms affected 13.9% and moderate to severe anxiety affected 16.7% of people during and after pregnancy[30]. Our results suggest a much higher proportion of mothers experiencing symptoms of depression in Switzerland and less generalized anxiety. Switzerland has not imposed a strict lockdown unlike many other countries, suggesting that the lack of social interactions may not be the main cause of perinatal depression. Our results, however, suggest a significant association between mental health impairment and foreign nationality during the pandemic. Switzerland is composed of approximately 25% foreign nationals in 2020[31]. Border closures could have mimicked lock down conditions on a larger scale, limiting foreign nationals from returning to their family for support during this critical life event. While the prevalence of perinatal maternal disorders is on the rise, especially during this global pandemic, studies have suggested that psychiatric supports for these individuals are deficient in Switzerland, and highlights in particular the lack of guidelines, routine evaluations, as well as progress in the field[32]. These results are comparable to already published data with a similar methodology, reporting higher mental health impairment according to Khoury et al. in a similar high educated pregnant population. Lack of social support was associated as a risk factor for exacerbating mental health symptoms mirroring our results regarding foreign nationality[33]. Low socioeconomic status (SES) appears to have played a role as a risk factor for impaired mental health during the pandemic period, as reported in a study of a non-pregnant population in Switzerland. However, low SES was also associated with fear of employment loss due to the crisis, which can be compared with the situation of pregnant people, who are more vulnerable to the risk of job loss. Pregnancy can be considered as a constraint because of the employer's obligation to adapt the job and working hours of the person concerned. The health crisis has increased this precariousness because the pregnant person is at risk of a severe form of COVID-19 and the employer is responsible for the safety of its employee[34]. Dismissal is therefore a legitimate fear for the pregnant person during this period and probably plays an additional role thus explaining that SES could not be as protective in pregnant individuals than in the general population.

Our study has several limitations including a selection bias as the survey was voluntary and only accessible via the online maternity social platform. Participants with a higher SES and educational background who were concerned by the current situation may have had easier access to the survey, which is consistent with the basic characteristics of our participants. The mental health assessment was limited to score scales not evaluating the medical history of mental health disorders or any other medical conditions that could have added to participant concerns. The COVID-19 concerns questions were built for the study only to try to describe maternal concerns but are not a validated tool. Similarly, the mental health impairment status outcome was constructed for the study based on 3 validated scores as previously described. This composite outcome is not a validated score but allowed us to extend the analysis to potential covariates associated with this outcome. Additionally, the study did not collect information about maternal disease and pregnancy conditions arising during pregnancy that

have been reported to play a role on mental health[35]. Finally, these results were collected at a time where the pandemic had led to the implementation of strong protective social measures. The results do not necessarily apply to the current situation due to various reasons including current less severe SARS-CoV 2 variants and massive vaccination campaigns.

This study, however, provides a snapshot of how the mental health status of pregnant individuals during a difficult situation may have been affected and provides us with clues on how to better manage such worries in an already stressed context that represents pregnancy.

The study suggests that pregnant persons were at risk of mental health disorder even at distance of the first wave of COVID-19 and first scientific evidences that came a few months after the beginning of the pandemic. This emphasize that clinicians should be aware of pregnant individuals during these periods and give particular attention to foreign individuals even with a high educational background or a high income. These results could be useful for any resurgence of a new mutation of SARS-CoV-2 or potential new emerging pathogens such as monkey pox-virus or still unknown future pathogens[36].

Further studies are needed, especially later in the pandemic, to distinguish the impact of social restrictions from that of the pandemic itself, on psychological distress among pregnant individuals.

Conclusion

This study suggests that pregnant people have a high risk of mental health impairment during the pandemic. Pregnant individuals should therefore be better informed about the impacts of the pandemic on pregnancy, and this should be a key focus of health care professionals. Emphasis should be placed on vulnerable populations, for example foreign nationals regardless of SES or educational status.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available. Participants have signed an informed consent stating that data are not publicly available but only to the dedicated research team or collaborators of the research team for additional research work only. Data can be available from the corresponding author on reasonable request under joint research agreement.

Received: 24 February 2022; Accepted: 5 October 2022
Published online: 02 November 2022

References

1. Federal Office of Public Health. New Coronavirus 2019-nCoV: first confirmed case in Switzerland. https://www.bag.admin.ch/bag/en/home/das-bag/aktuell/medienmitteilungen.msg-id-78233.html (Accessed 20 Oct 2021).
2. de Quervain, D. *et al.* The Swiss Corona Stress Study. (2020) https://osf.io/jqw6a/ (Accessed 20 Oct 2021)
3. López-Morales, H. *et al.* Mental health of pregnant women during the COVID-19 pandemic: A longitudinal study. *Psychiatry Res.* **295**, 113567 (2021).
4. Faisal-Cury, A., Rodrigues, D. M. O. & Matijasevich, A. Are pregnant women at higher risk of depression underdiagnosis?. *J. Affect. Disord.* **283**, 192–197 (2021).
5. Trinh, N. T. H., Nordeng, H. M. E., Bandoli, G., Eberhard-Gran, M. & Lupattelli, A. Antidepressant and mental health care utilization in pregnant women with depression and/or anxiety: An interrupted time-series analysis. *J. Affect. Disord.* **308**, 458–465 (2022).
6. Berger, A. *et al.* Perinatal mental disorders in Switzerland: prevalence estimates and use of mental-health services. *Swiss Med. Wkly.* (9) (2017).
7. Qu, F. *et al.* The association between psychological stress and miscarriage: A systematic review and meta-analysis. *Sci. Rep.* **7**(1), 1731 (2017).
8. Grote, N. K. *et al.* A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Arch. Gen. Psychiatry* **67**(10), 1012–1024 (2010).
9. Lilliecreutz, C., Larén, J., Sydsjö, G. & Josefsson, A. Effect of maternal stress during pregnancy on the risk for preterm birth. *BMC Pregnancy Childbirth* **16**(1), 5 (2016).
10. Austin, M.-P., Hadzi-Pavlovic, D., Leader, L., Saint, K. & Parker, G. Maternal trait anxiety, depression and life event stress in pregnancy: Relationships with infant temperament. *Early Hum. Dev.* **81**(2), 183–190 (2005).
11. Kinsella, M. T. & Monk, C. Impact of maternal stress, depression & anxiety on fetal neurobehavioral development. *Clin. Obstet. Gynecol.* **52**(3), 425–440 (2009).
12. Allotey, J. *et al.* Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis. *BMJ* **370**, m3320 (2020).
13. Lebel, C., MacKinnon, A., Bagshawe, M., Tomfohr-Madsen, L. & Giesbrecht, G. Elevated depression and anxiety symptoms among pregnant individuals during the COVID-19 pandemic. *J. Affect. Disord.* **277**, 5–13 (2020).
14. Durankuş, F. & Aksu, E. Effects of the COVID-19 pandemic on anxiety and depressive symptoms in pregnant women: A preliminary study. *J. Matern. Fetal Neonatal Med.* 1–7 (2020).
15. Kotabagi, P., Fortune, L., Essien, S., Nauta, M. & Yoong, W. Anxiety and depression levels among pregnant women with COVID-19. *Acta Obstet. Gynecol. Scand.* **99**(7), 953–954 (2020).
16. Favre, G., Pomar, L., Musso, D. & Baud, D. 2019-nCoV epidemic: What about pregnancies?. *Lancet* **395**(10224), e40 (2020).
17. Lokken, E. M. *et al.* Higher severe acute respiratory syndrome coronavirus 2 infection rate in pregnant patients. *Am. J. Obstet. Gynecol.* **225**(1), 75.e1-75.e16 (2021).
18. Vouga, M. *et al.* Maternal outcomes and risk factors for COVID-19 severity among pregnant women. *Sci. Rep.* **11**(1), 13898 (2021).
19. Ryan, L. *et al.* Neonates and COVID-19: state of the art: Neonatal Sepsis series. *Pediatr. Res.* (2021).
20. Favre, G. *et al.* Decreased fetal movements: A sign of placental SARS-CoV-2 infection with perinatal brain injury. *Viruses* **13**(12), 2517 (2021).
21. Khalil, A. *et al.* Change in the incidence of stillbirth and preterm delivery during the COVID-19 pandemic. *JAMA* **324**(7), 705–706 (2020).
22. Lambelet, V. *et al.* Impact of the COVID-19 pandemic on Swiss pregnant and breastfeeding women—A cross-sectional study covering the first pandemic wave. *Swiss. Med. Wkly.* **151**, w30009 (2021).

23. Federal Office of Public Health. Coronavirus: Measures and ordinances. https://www.bag.admin.ch/bag/en/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/massnahmen-des-bundes.html (Accessed 31 Aug 2022).
24. Federal Statistical Office. Household income and expenditure. https://www.bfs.admin.ch/bfs/en/home/statistiken/wirtschaftliche-soziale-situation-bevoelkerung/einkommen-verbrauch-vermoegen/haushaltsbudget.html (Accessed 1 Sept 2022).
25. Spitzer, R. L., Kroenke, K., Williams, J. B. W. & Löwe, B. A brief measure for assessing generalized anxiety disorder: The GAD-7. *Arch. Intern. Med.* **166**(10), 1092 (2006).
26. Cox, J. L., Holden, J. M. & Sagovsky, R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br. J. Psychiatry* **150**, 782–786 (1987).
27. Weiss, D. S. & Marmar, C. R. The impact of event scale—revised. In *Assessing Psychological Trauma and PTSD*, 399–411 (The Guilford Press, 1997).
28. Gantt, A. *et al.* Pregnancy at age 35 years or older: ACOG obstetric care consensus No. 11. *Obstet. Gynecol.* **140**(2), 348–366 (2022).
29. Tearne, J. E. *et al.* Older maternal age is associated with depression, anxiety, and stress symptoms in young adult female offspring. *J. Abnorm. Psychol.* **125**(1), 1–10 (2016).
30. Ceulemans, M. *et al.* Vaccine willingness and impact of the COVID-19 pandemic on women's perinatal experiences and practices—A multinational, cross-sectional study covering the first wave of the pandemic. *Int. J. Environ. Res. Public Health* **18**(7), 3367 (2021).
31. Office fédéral de la statistique. Population de nationalité étrangère. https://www.bfs.admin.ch/bfs/fr/home/statistiken/bevoelkerung/migration-integration/auslaendische-bevoelkerung.html (Accessed 20 Oct 2021).
32. Castro, R. T. A. *et al.* Perinatal mental health service provision in Switzerland and in the UK. *Swiss Med. Wkly.* (7) (2015).
33. Khoury, J. E., Atkinson, L., Bennett, T., Jack, S. M. & Gonzalez, A. COVID-19 and mental health during pregnancy: The importance of cognitive appraisal and social support. *J. Affect. Disord.* **282**, 1161–1169 (2021).
34. Docteur, mon employeur vous demande un certificat médical. Revue Medicale Suisse. https://www.revmed.ch/revue-medicale-suisse/2020/revue-medicale-suisse-712/docteur-mon-employeur-vous-demande-un-certificat-medical (Accessed 25 Jan 2022).
35. Biaggi, A., Conroy, S., Pawlby, S. & Pariante, C. M. Identifying the women at risk of antenatal anxiety and depression: A systematic review. *J. Affect. Disord.* **191**, 62–77 (2016).
36. Dashraath, P. *et al.* Monkeypox and pregnancy: Forecasting the risks. *Am. J. Obstet. Gynecol.* **S0002–9378**(22), 00651–00652 (2022).

Acknowledgements

We thank Elise Méan and all members of the communication service of Lausanne University Hospital (CHUV) and Bern University Hospital (Inselspital) with study management as well as data collection. We also would like to thank the participants who volunteered for this study.

Author contributions

S.S. and H-F.C. conceived and designed the online survey. G.F. S.S. H-F.C. A.R. L.R. M.F. participated in the data collection. G.F., C.K. and L.P. performed the statistical analysis of the study. G.F., C.K., S.S., H-F.C., A.R., L.R., U.W., D.B., and L.P. interpreted the results. G.F. wrote the first draft of the manuscript. S.S., H-F.C., A.R., L.R., U.W., D.B., participated in the study design and revision of the manuscript. All authors provided critical inputs to the paper, reviewed, and approved the final version.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-022-21881-2.

Correspondence and requests for materials should be addressed to G.F.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Maternal and perinatal outcomes following pre-Delta, Delta, and Omicron SARS-CoV-2 variants infection among unvaccinated pregnant women in France and Switzerland: a prospective cohort study using the COVI-PREG registry

Guillaume Favre,[a,ab] Emeline Maisonneuve,[a,b,ab] Léo Pomar,[a,c] Charlotte Daire,[a] Christophe Poncelet,[d] Thibaud Quibel,[e] Cécile Monod,[f] Begoña Martinez de Tejada,[g] Leonhard Schäffer,[h] Andrea Papadia,[i] Anda Petronela Radan,[j] Monya Todesco-Bernasconi,[k] Yves Ville,[l] Cora Alexandra Voekt,[m] Béatrice Eggel-Hort,[n] Romina Capoccia-Brugger,[o] Silke Johann,[p] Claudia Grawe,[q] Sophie Defert,[r] Nicolas Mottet,[s] Christian R. Kahlert,[t] Charles Garabedian,[u] Loïc Sentilhes,[v] Brigitte Weber,[w] Steffi Leu,[x] Dirk Bassler,[y] Karine Lepigeon,[a] Ursula Winterfeld,[z] Alice Panchaud,[b,aa,ab] and David Baud,[a,ab,*] on behalf of the French and Swiss COVI-PREG group[ac]

[a]Materno-fetal and Obstetrics Research Unit, Department "Femme-Mère-Enfant", University Hospital, Lausanne, Switzerland
[b]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland
[c]School of Health Sciences (HESAV), University of Applied Sciences and Arts Western Switzerland, Lausanne, Switzerland
[d]Department of Obstetrics and Gynecology, Pontoise Hospital, Pontoise, France
[e]Department of Obstetrics and Gynecology, Poissy-Saint Germain Hospital, Poissy, France
[f]Department of Obstetrics, Basel University Hospital, Basel, Switzerland
[g]Obstetrics Division, Department of Pediatrics, Gynecology and Obstetrics, Geneva University Hospitals, Faculty of Medicine, Geneva, Switzerland
[h]Division of Obstetrics, Baden Cantonal Hospital, Baden, Switzerland
[i]Department of Gynecology and Obstetrics, Ente Ospedaliero Cantonale, Lugano, Switzerland
[j]Department of Obstetrics and Fetal–Maternal Medicine, University Hospital of Bern, University of Bern, Bern, Switzerland
[k]Department of Obstetrics, Cantonal Hospital Aarau, Aarau, Switzerland
[l]Necker-Enfants Malades Hospital, Department of Obstetrics, Paris, France
[m]Department of Obstetrics, Grabs Hospital, Grabs, Switzerland
[n]Obstetrics and Gynecology Unit, Sion Hospital, Sion, Switzerland
[o]Département de gynécologie-obstétrique, RHNE, Neuchâtel, Switzerland
[p]Department of Gynecology and Obstetrics, Hospital of the Upper Valais, Visp, Switzerland
[q]Department of Obstetrics, Gynecology Stadtspital Triemli, Zürich, Switzerland
[r]Department of Gynecology, Mont-de-Marsan Hospital, Mont-de-Marsan, France
[s]Department of Obstetrics and Gynecology, Besançon University Hospital, Besançon, France
[t]Infectious Diseases and Hospital Epidemiology, Children's Hospital of Eastern Switzerland, St. Gallen, Switzerland
[u]Department of Obstetrics, CHU de Lille, Lille, France
[v]Department of Obstetrics and Gynecology, Bordeaux University Hospital, Bordeaux, France
[w]Department of Obstetrics and Gynecology, Obwald Cantonal Hospital, Sarnen, Switzerland
[x]Department of Obstetrics and Gynecology, Nidwald Cantonal Hospital, Stans, Switzerland
[y]Neonatal Department, University Hospital Zürich, Zürich, Switzerland
[z]Swiss Teratogen Information Service, Clinical Pharmacology Unit, Lausanne University Hospital and University of Lausanne, Switzerland
[aa]Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Switzerland

Summary

Background SARS-CoV-2 positive pregnant women are at higher risk of adverse outcomes, but little evidence is available on how variants impact that risk. We aim to evaluate maternal and perinatal outcomes among unvaccinated pregnant women that tested positive for SARS-CoV-2, stratified by pre-Delta, Delta, and Omicron periods.

Methods This prospective study enrolled women from March 2020 to September 2022. Exposure to the different SARS-CoV-2 variants was defined by their periods of predominance. The primary outcome was severe maternal adverse outcome defined as either intensive care unit admission, acute respiratory distress syndrome, advanced

The Lancet Regional Health - Europe 2023;26: 100569

Published Online 5 January 2023
https://doi.org/10.1016/j.lanepe.2022.100569

*Corresponding author. Materno-fetal & Obstetrics Research Unit, Department of Obstetrics and Gynecology, Centre Hospitalier Universitaire Vaudois (CHUV), 1011, Lausanne, Switzerland.
E-mail address: David.baud@chuv.ch (D. Baud).
[ab]Contributed equally to the work.
[ac]The COVI-PREG co-authors are listed at the end.

oxygen supplementation, or maternal death. The secondary outcomes were preterm birth and other perinatal outcomes.

Findings Overall, 1402, 262, and 391 SARS-CoV-2 positive pregnant women were enrolled during the pre-Delta, Delta, and Omicron periods respectively. Severe maternal adverse outcome was reported in 3.4% (n = 947/1402; 95% confidence intervals (95%CI) 2.5–4.5), 6.5% (n = 7/262; 95%CI 3.8–10.2), and 1.0% (n = 4/391; 95%CI 0.3–2.6) of women during the pre-Delta, Delta, and Omicron periods. The risk of severe maternal adverse outcome was higher during the Delta vs pre-Delta period (adjusted risk ratio (aRR) = 1.8; 95%CI 1.1–3.2) and lower during the Omicron vs pre-Delta period (aRR = 0.3; 95%CI, 0.1–0.8). The risks of hospitalization for COVID-19 were 12.6% (n = 176/1402; 95%CI 10.9–14.4), 17.2% (n = 45/262; 95%CI 12.8–22.3), and 12.5% (n = 49/391; 95%CI 9.4–16.2), during the pre-Delta, Delta, and Omicron period, respectively. Pregnancy complications occurred after SARS-CoV-2 exposure in 30.0% (n = 363/1212; 95%CI 27.4–32.6), 35.2% (n = 83/236; 95%CI 29.1–41.6), and 30.3% (n = 105/347; 95%CI 25.5–35.4) of patients during the pre-Delta, Delta, and Omicron periods, respectively. Stillbirths were reported in 0.5% (n = 6/1159; 95%CI 0.2–1.1), 2.8% (n = 6/210; 95%CI 1.0–6.0), and 0.9% (n = 2/213; 95%CI 0.1–3.4) or patients during the pre-Delta, Delta, and Omicron periods respectively.

Interpretation The Delta period was associated with a higher risk of severe maternal adverse outcome and the Omicron period with a lower risk of severe adverse outcome compared to pre-Delta era. The reported risk of hospitalization was high during the Omicron period and should not be trivialized.

Funding Swiss Federal Office of Public Health, Fondation CHUV.

Keywords: SARS-CoV-2; Omicron; Variant; COVID-19; Pregnant women; Pregnancy

Research in context

Evidence before this study

Pregnant women that test positive for SARS-CoV-2 are at higher risk of maternal and neonatal adverse outcomes. Several variants of concern have emerged since the beginning of the pandemic. The Delta variant has been reported to be more severe compared to pre-Delta or Omicron, in adults as well as in pregnant women. However, limited data is available on the Omicron variant during pregnancy. We searched on PubMed and SSRN available as of November 3, 2022 for English articles studying severe maternal adverse outcomes following SARS-CoV-2 infection among unvaccinated pregnant women, according to the Omicron variant found few articles using the search terms "pregnancy", "pregnant women", "COVID-19", "SARS-CoV-2", "Delta" and "Omicron". The studies identified were all retrospective and the majority included both vaccinated and unvaccinated pregnant women in the same cohort. A recent Scottish study based on more than 9000 pregnancies evaluating both vaccinated and unvaccinated pregnant women, reported lower risks of maternal and pregnancy adverse outcomes in the Omicron period based on a national registry database. A study performed in Malawi, including 55 pregnant women in the fourth local wave of SARS-CoV-2 assumed to be the Omicron variant, also reported less severe maternal outcome than in previous waves, regardless of the vaccination status.

Added value of this study

Our research is the first to report results from a prospective and dedicated designed study that compared the risk of adverse maternal outcome according to the pre-Delta, Delta, and Omicron variant among unvaccinated pregnant women. The risk of severe maternal adverse outcome was lower during the Omicron period compared to the pre-Delta and Delta period. Conversely, pregnant women requiring inpatient management for COVID-19 during the Omicron period remained high.

Implications of all the available evidence

Our study reported a lower risk of severe maternal adverse outcome during the Omicron period compared to the pre-Delta and Delta periods among unvaccinated pregnant women. However, the reported risk of hospitalization for COVID-19 remained high during the Omicron period. This emphasizes the need to pursue the promotion of COVID-19 vaccination for pregnant women, especially given that the potential long-term consequences of the virus are still unknown.

Introduction

During the SARS-CoV-2 pandemic, pregnant women were reported to have a higher susceptibility to COVID-19 infection.[1] Pregnant women that tested positive for SARS-CoV-2 are at higher risk of a severe form of COVID-19, associated with higher rates of intensive care unit (ICU) admission and increased needs for respiratory support, compared to the age-matched non-pregnant population.[2,3] Women infected during pregnancy also have an increased risk of adverse pregnancy outcomes including preterm-birth, with a significant proportion secondary to iatrogenic preterm birth due to maternal illness.[3,4] Infection with SARS-CoV-2 during pregnancy has also been reported to be associated with a higher risk of stillbirth directly or indirectly caused by the virus.[5] Rare cases of confirmed viral vertical transmission have been reported, associated with critical neonatal adverse outcomes.[6,7]

SARS-CoV-2 has already mutated into five main variants of concern (VOC), as designated by the WHO. The Alpha, the Beta and the Gamma variants, were the first VOC of the pandemic (pre-Delta period), followed by the Delta variant, which was rapidly predominant, and finally replaced by the current Omicron variant.[8] The Delta variant was associated with increased COVID-19 severity, including a higher hospitalization rate and poorer clinical outcomes in the general population, compared to pre-Delta variants.[9,10] The Omicron variant has been reported to spread very rapidly with a rate of re-infection up to 15%. The severity of the disease with this variant, however, was lower, with a decreased risk of hospitalization and less clinically severe illness, regardless of previous acquired immunity status.[11–13] COVID-19 reinfection has been reported to be less severe than primary infection, making it difficult to interpret the real pathogenicity of emerging variants.[14] Similar results were observed among unvaccinated pregnant women exposed to the Delta variant during pregnancy, with a higher risk of severe disease and a higher risk of preterm birth.[15–17] Little evidence is available on the impact of the Omicron variant on unvaccinated pregnant women and it is urgent to assess the impact of this variant as COVID-19 vaccine hesitancy remains high in pregnant women despite its safety and efficacy.[18–20]

The primary aim of this study was to compare the risk of maternal adverse outcomes among unvaccinated pregnant women that tested positive for SARS-CoV-2 during one of three different periods of variant predominance: pre-Delta, Delta, and Omicron. The secondary aim was to describe the rate of preterm birth and other perinatal outcomes in women stratifying by variant predominance.

Methods

Settings

This prospective cohort study enrolled patients from March 24, 2020 to September 28, 2022, in France and Switzerland, using the COVI-PREG registry. This registry aims to evaluate the impact of SARS-CoV-2 infection among pregnant women.[21] Hospitals with an antenatal clinic and/or labor ward were able to participate in this multicenter registry. An oral and written consent was obtained from all patients included in the study. 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 were included at the time of a positive SARS-CoV-2 test. Local investigators completed 3 different forms: 1) the enrollment form at initial inclusion documenting the patient's baseline characteristics, medical/obstetrical history, and SARS-CoV-2 exposure/testing information; 2) a first follow-up form dedicated to the COVID-19 event management and COVID-19 maternal outcomes; 3) a second follow-up form completed at the end of the pregnancy, after the patient's discharge from maternity, collecting pregnancy and neonatal outcomes. Data were collected individually from medical records and stored as de-identified data using the REDCap (Research Electronic Data Capture) online database.

Participants

Only pregnant women who tested positive for SARS-CoV-2 were included in the study. They were tested either because of symptoms compatible with COVID-19, potential SARS-CoV-2 exposure, or local universal screening protocols. Only patients with a confirmed positive nasopharyngeal reverse transcriptase polymerase chain reaction (RT-PCR) or an antigen test were included in the study. Patients vaccinated for COVID-19 before or during the current pregnancy were excluded. No information was available regarding any previous SARS-CoV-2 infection prior to pregnancy. Patients who were under the legal age of 18 years and/or who were not able to consent were not included.

Exposure to pre-Delta, Delta, and Omicron SARS-CoV-2 variants

As the information on specific viral strains impacting patients was not available (i.e. genome sequencing of SARS-CoV-2 was not universally performed), we assumed that a pregnant woman enrolled in the study was infected with the predominant variant of that specific period. The date of the positive SARS-CoV-2 test was used to assign the patient to one of these periods. If the date of the test was missing, the date of onset of symptoms was used.

Variant predominance was determined using the GISAID data platform. French and Swiss health

authorities provided national relative variant frequency on a weekly basis by sequencing viral strains obtained from representative national samples.[22] Using the relative variant frequency, the three different periods of interest were defined as follows: the pre-Delta period, corresponding to the period before the emergence of the Delta variant (i.e., Alpha, Beta, Gamma), defined as the period with Delta variant infection in <20% of national samples; the Delta period, considered as the period when the Delta variant was reported in ≥80% of national samples; the Omicron period, considered as the period when the Omicron variant was reported in ≥80% of national samples. Between these periods of interest, we have defined two transition periods: the period between pre-Delta and Delta periods (>20% and <80% of Delta variant) and the period between Delta and Omicron periods (>20% and <80% of Omicron variant). The different periods are illustrated in Fig. S1 – supplementary materials. Patients who were included in COVI-PREG during the two transition periods were excluded to prevent exposure misclassification.

Maternal adverse outcomes

Maternal severe adverse outcome was a composite outcome defined as a patient experiencing at least one of the following outcomes related to COVID-19 only: ICU admission, acute respiratory distress syndrome (ARDS), high flow oxygen requirement, non-invasive ventilation requirement, or mechanical ventilation, and maternal death of any cause. Other maternal outcomes included inpatient management for the COVID-19 event (e.g., standard unit admission, ICU admission), length of stay in ICU >7 days, supplemental oxygen requirement (including standard oxygen, high-flow oxygen, non-invasive ventilation, and mechanical ventilation), and extracorporeal membrane oxygenation (ECMO) requirement. All patients included in this study were considered for this analysis.

Pre-term birth outcome

Preterm birth was defined as a birth occurring before 37 weeks of gestation (wks) and was divided into three categories: <37 wks (23–36 wks and 6 days), <32 wks (23–31 wks and 6 days), and <28 wks (23–27 wks and 6 days). Preterm birth was also categorized as either spontaneous (occurring after a spontaneous labor) or induced (medically indicated birth, after an induction of labor or a caesarean section without spontaneous labor). Iatrogenic preterm birth due to COVID-19 was defined as an induced preterm birth directly related to COVID-19 either for maternal or fetal reasons. For this analysis, only pregnancies resulting in a livebirth occurring at or after 23 wks and patients exposed to SARS-CoV-2 before 37 wks were considered. Patients with a pregnancy that did not reach an expected due date of 42 wks during the study period were also excluded to ensure only exposures who had the potential to develop the outcome of interest were included.

Pregnancy and neonatal outcomes

Pregnancy complications were defined as pregnancy related conditions that arose after the positive test (preeclampsia, gestational diabetes, intrauterine growth restriction, abnormal fetal Doppler, suspected macrosomia, threatened preterm labor, preterm premature rupture of membranes, post-partum hemorrhage). Labor was defined as either spontaneous or induced. Vaginal birth was defined as either spontaneous or assisted (i.e., by vacuum extractor, forceps). Cesarean section was defined as either emergent out of labor/induction, emergent during labor/induction, or planned out of labor. Emergency cesarean section could be directly related to COVID-19 when the reason for delivery was for a maternal or fetal indication secondary to COVID-19. Livebirth was defined as a birth of a live born neonate occurring at or after 23 wks. The delivery of a pre-viable fetus was defined as a birth occurring from 20 wks to 22 wks and 6 days without neonatal resuscitation. Stillbirth was defined as an in utero fetal demise at 20 weeks or more. Late termination of pregnancy was any medically indicated termination of pregnancy at 20 weeks or more. For this analysis, pregnant women with a known pregnancy outcome from 20 wks were included.

Neonatal weight at birth was defined as the weight in grams measured just after the delivery. Small for gestational age (SGA) was defined as a weight at birth less than 10th and intrauterine growth restriction as less than 3rd percentile for gestational age according to the INTERGROWTH charts.[23] Apgar score was collected at 5 min after birth and a poor Apgar score at 5 min was defined as less than 7. Neonatal intensive care unit (NICU) admission and neonatal death for any reason were also collected.

Co-variables

Patients' demographic characteristics were collected, including maternal age categories (≤25 years (y), 26–30 y, 31-35 y, 36–40 y, and >40 y, marital status, ethnicity, country of residence, educational level, body mass index (BMI) at inclusion (kg/m^2), medical history, addiction during pregnancy, obstetrical history including previous pregnancies complications and ongoing pregnancy characteristics, conditions arising in pregnancy before exposure to the virus. Trimester of pregnancy at infection were defined as last menstrual period date to 13 wks and 6 days for the 1st trimester, 14 wks–27 wks and 6 days for the 2nd trimester, and 28 wks until the end of pregnancy for the 3rd trimester.

Statistical analysis

Descriptive statistics were used to assess the baseline characteristics of patients and different outcomes of interest. Proportions were reported with their 95% confidence intervals (95%CI). To evaluate the association between outcomes severe adverse maternal composite outcome and the three periods of interest, we performed a univariate and a multivariate generalized linear regression model to estimate Risk Ratios (RR) with 95%CI to compare the pre-Delta versus Delta and the pre-Delta versus Omicron period. In the multivariate analysis, the model included all unbalanced baseline characteristics between groups, defined as a standardized difference (SD) of more than 10% between groups. Statistical analyses were performed using Stata (StataCorp. 2015. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Results

A total of 2244 pregnant women that tested positive for SARS-CoV-2 were enrolled in COVI-PREG. The 15 and 174 patients infected during the pre-Delta/Delta and Delta/Omicron transition periods, respectively, were excluded (Table S1 supplementary materials). Overall, 2055 patients were included with 1402 patients during the pre-Delta period, 262 patients during the Delta, and 391 patients during the Omicron. Variants time periods are reported in supplementary materials Table S2.

Overall, the mean maternal age was 31.7 years with 21.9% (n = 450/2055) aged more than 35 years. Most patients were of white ethnicity (67.8%; n = 1394/2055). With regards to location, 36.8% (n = 756/2055) and 63.2% (n = 1299/2055) of patients were living in France and Switzerland respectively. Maternal BMI was above 35 kg/m^2 in 5.8% (n = 120/2055) of cases. Overall, pregnant women were infected during the first trimester in 14.4% (n = 295/2055) of cases, second in 34.6% (n = 711/2055), and third in 50.0% (1028/2050). Trimester of infection was unknown for 21 patients (1.0%). Baseline characteristics are presented according to the three periods of interest in Table 1. In three patients, the date of the SARS-CoV-2 test was missing and the date of symptom onset was used instead. All three patients had symptoms in the pre-Delta period (August 2020, January 2021, and March 2021) with no possibility of exposure misclassification.

Maternal adverse outcomes

Among patients that tested positive for SARS-CoV-2, a severe maternal adverse outcome was reported in 3.4% (n = 47/1402; 95%CI 2.5–4.5), 6.5% (n = 17/262; 95%CI 3.8–10.2), and 1.0% (n = 4/391; 95%CI 0.3–2.6) of patients during the pre-Delta, Delta, and Omicron period, respectively. ICU admission was reported in 3.2% (n = 45/1402; 95%CI 2.4–4.3) during the pre-Delta period, 5.0% (n = 13/262; 95%CI 2.7–8.3) during the Delta, and 1.0% (n = 4/391; 95%CI 0.3–2.6) during the Omicron. Mechanical ventilation was required in 0.9% (n = 14/1402; 95%CI 0.5–1.7) of patients during the pre-Delta period and 2.7% (n = 7/262; 95%CI 1.1–5.4) during the Delta period. No patients required high-flow oxygen, non-invasive ventilation, or mechanical ventilation during the Omicron period. During the pre-Delta and Delta periods, 0.9% (n = 12/1402 95%CI 0.1–1.5) and 1.9% (n = 5/262; 95%CI 0.6–4.4) of patients admitted to the ICU stayed more than 7 days, and none (0/391) during the Omicron. A total of three (n = 3/1402; 0.2%; 95%CI 0.0–0.6) maternal deaths were reported in the pre-Delta period and none in the Delta and Omicron (Table 2). Maternal deaths were directly related to extremely severe COVID-19. Maternal outcomes of patients that tested positive during the transition periods are reported in Table S3 supplementary materials.

Delta vs. pre-Delta

The Delta period was associated with more severe maternal adverse outcomes when compared to the pre-Delta period, with a crude RR of 1.9 (95%CI, 1.1–3.3). This association persisted after adjustment for the unbalanced potential confounders, with an adjusted risk ratio (aRR) of 1.8 (95%CI 1.1–3.2) for severe adverse maternal outcome during the Delta period, compared to the pre-Delta one (Table 3).

Omicron vs pre-Delta

The Omicron period was associated with fewer severe maternal adverse outcomes compared to the pre-Delta, with a crude RR of 0.3 (95%CI, 0.1–0.8) and an aRR of 0.3 (95%CI, 0.1–0.8) after adjustment for the unbalanced potential confounders (Table 3).

Preterm birth outcomes

A total of 1544 pregnant women with a pregnancy resulting in a livebirth at 23 weeks or later were exposed to SARS-CoV-2 before 37 wks. Patient characteristics are presented in Table S4 supplementary materials. Overall, 993 patients were included during the pre-Delta period, 168 during the Delta, and 245 during the Omicron. Preterm birth less than 37 wks occurred in 9.3% (n = 92/993; 95%CI 7.5–11.2) of patients during the pre-Delta period, 13.7% (n = 23/168; 95%CI 8.9–20.5) during the Delta, and 11.0% (n = 27/245; 95%CI 7.4–15.6) during the Omicron. Preterm birth less than 32 wks occurred in 2.0% (n = 19/993; 95%CI, 1.2–3.1), 4.8% (n = 8/168; 95%CI 2.1–9.2), and 2.0% (n = 5/245; 95%CI 0.7–4.7) of patients during the pre-Delta, Delta, and Omicron periods, respectively. Extremely preterm birth less than 28 wks occurred in 0.6% (n = 6/993; 95%CI 0.2–1.4) and in 0.8% (n = 2/245; 95%CI 0.1–2.9) of patients during the pre-Delta and Omicron periods, respectively and none during the Delta (Table 4).

	Pre-Delta		Delta			Omicron		
	n = 1402		n = 262			n = 391		
	n	%	n	%	Std. Diff.	n	%	Std. Diff.
Maternal age at first dose - n %								
≤25	148	10.6%	28	10.7%	−0.4	41	10.5%	0.2
26-30	421	30.0%	76	29.0%	2.2	117	29.9%	0.2
31-35	520	37.1%	98	37.4%	−0.7	145	37.1%	0.0
36-40	243	17.3%	49	18.7%	−3.6	70	17.9%	−1.5
>40	63	4.5%	9	3.4%	5.4	16	4.1%	2.0
Missing	7	0.5%	2	0.8%	−3.3	2	0.5%	−0.2
Marital status - n %								
Married or domestic partnership	1187	84.7%	222	84.7%	−0.2	325	83.1%	4.2
Single never married	126	9.0%	30	11.5%	−8.1	25	6.4%	9.7
Divorced or separated	14	1.0%	2	0.8%	2.5	6	1.5%	−4.8
Unknown	36	2.6%	4	1.5%	7.4	9	2.3%	1.7
Missing	39	2.8%	4	1.5%	8.7	26	6.6%	−18.3
Ethnicity - n %								
White	947	67.5%	181	69.1%	−3.3	266	68.0%	−1.0
Hispanic or Latino	55	3.9%	6	2.3%	9.4	11	2.8%	6.2
Black or African American	156	11.1%	32	12.2%	−3.4	38	9.7%	4.6
Asian or Pacific islander	50	3.6%	3	1.1%	16.0	12	3.1%	2.8
Other	67	4.8%	22	8.4%	−14.6	15	3.8%	4.6
Unknown	75	5.3%	11	4.2%	5.4	20	5.1%	1.1
Missing	52	3.7%	7	2.7%	5.9	29	7.4%	−16.2
Country of residence - n %								
France	531	37.9%	92	35.1%	5.7	133	34.0%	8.0
Switzerland	871	62.1%	170	64.9%	−5.7	258	66.0%	−8.0
Educational level - n %								
University/college or equivalent	467	33.3%	68	26.0%	16.2	128	32.7%	1.2
Intermediate	212	15.1%	55	21.0%	−15.3	84	21.5%	−16.5
Secondary school	116	8.3%	31	11.8%	−11.9	22	5.6%	10.4
Primary school or less	18	1.3%	3	1.1%	1.3	2	0.5%	8.2
Unknown	503	35.9%	95	36.3%	−0.8	120	30.7%	11.0
Missing	86	6.1%	10	3.8%	10.7	35	9.0%	−10.7
Maternal BMI (kg/m2) - n %								
BMI >30	266	19.0%	49	18.7%	0.7	58	14.8%	11.1
BMI >35	93	6.6%	11	4.2%	10.8	16	4.1%	11.3
Maternal addiction								
Any	85	6.2%	21	8.2%	−7.5	29	7.9%	−6.5
Drug	3	0.2%	3	1.1%	−11.4	2	0.5%	−5.0
Tobacco	76	5.4%	19	7.3%	−7.5	28	7.2%	−7.2
Alcohol	9	0.6%	1	0.4%	3.6	5	1.3%	−6.5
Obstetrical history								
Nulliparous	604	43.1%	101	38.5%	9.2	191	48.8%	−11.6
Previous cesarean section	233	16.6%	38	14.5%	5.8	45	11.5%	14.7
Medical history								
Pulmonary	38	2.7%	3	1.1%	11.4	9	2.3%	2.6
Cardiac	13	0.9%	6	2.3%	−10.8	9	2.3%	−10.9
Hypertensive	24	1.7%	4	1.5%	1.5	6	1.5%	1.4
Diabetes	19	1.4%	4	1.5%	−1.4	1	0.3%	12.3
Immunosuppression	6	0.4%	0	0.0%	9.3	0	0.0%	9.3
Neurological	15	1.1%	8	3.1%	−14.0	5	1.3%	−1.9
Digestive	19	1.4%	0	0.0%	16.6	1	0.3%	12.3
Renal	10	0.7%	3	1.1%	−4.5	4	1.0%	−3.3

(Table 1 continues on next page)

	Pre-Delta		Delta			Omicron		
	n = 1402		n = 262			n = 391		
	n	%	n	%	Std. Diff.	n	%	Std. Diff.
(Continued from previous page)								
Urological	13	0.9%	1	0.4%	6.8	1	0.3%	8.8
Oncological	9	0.6%	1	0.4%	3.6	1	0.3%	5.8
Thyroid imbalance	59	4.2%	13	5.0%	−3.6	14	3.6%	3.2
Other	189	13.5%	36	13.7%	−0.8	52	13.3%	0.5
No comorbidities	988	70.5%	183	69.8%	1.4	288	73.7%	−7.1
Previous pregnancy complications								
Preeclampsia	18	1.3%	4	1.5%	−2.1	4	1.0%	2.4
Intrauterine growth restriction	30	2.1%	4	1.5%	4.6	3	0.8%	11.5
Fetal malformation	17	1.2%	2	0.8%	4.5	2	0.5%	7.6
Preterm birth	23	1.6%	3	1.1%	4.2	1	0.3%	14.3
Postpartum hemorrhage	26	1.9%	16	6.1%	−21.9	11	2.8%	−6.4
Other	86	6.1%	23	8.8%	−10.1	24	6.1%	0.0
None	1202	85.7%	210	80.2%	14.9	346	88.5%	−8.2
Ongoing pregnancy								
Singletons	1372	97.9%	259	98.9%	−7.8	382	97.7%	1.1
Twins	30	2.1%	3	1.2%	7.1	9	2.3%	−1.4
Ongoing pregnancy condition (before exposure to the virus)								
Preeclampsia	13	0.9%	1	0.4%	6.8	2	0.5%	4.9
Gestational diabetes	145	10.3%	22	8.4%	6.7	29	7.4%	10.3
Intrauterine growth restriction	29	2.1%	2	0.8%	11.1	5	1.3%	6.2
Abnormal fetal Doppler	6	0.4%	0	0.0%	9.3	1	0.3%	3.0
Macrosomia	13	0.9%	2	0.8%	1.8	3	0.8%	1.7
Threatened preterm labor	15	1.1%	6	2.3%	−9.5	7	1.8%	−6.1
Placenta praevia	8	0.6%	2	0.8%	−2.4	0	0.0%	10.7
PPROM	8	0.6%	1	0.4%	2.7	1	0.3%	4.9
Other	107	7.6%	18	6.9%	2.9	33	8.4%	−3.0
None	1058	75.5%	208	79.4%	−9.4	310	79.3%	−9.1
EXPOSURE - Trimester of infection								
Trimester 1	253	18.0%	15	5.7%	38.8	27	6.9%	34.2
Trimester 2	517	36.9%	85	32.4%	9.3	109	27.9%	19.3
Trimester 3	628	44.8%	157	59.9%	−30.6	243	62.1%	−35.3
Unknown	4	0.3%	5	1.9%	−15.6	12	3.1%	−21.8

BMI: body mass index, PPROM: preterm premature rupture of membranes.

Table 1: **Patient characteristics according to the variant time periods.**

Maternal outcomes and pregnancy conditions following SARS-CoV-2 exposure as well as mode of delivery according to the periods of interest are presented in supplementary materials Table S5. Preterm birth outcomes as well as maternal/pregnancy outcomes and mode of delivery for transition periods are reported in supplementary materials Table S6.

Pregnancy and neonatal outcomes

Pregnancy outcomes

A total of 1964 pregnancies that tested positive for SARS-CoV-2 had a known pregnancy outcome from 20 wks onwards. Patient characteristics and maternal outcomes are presented in the supplementary materials Tables S7 and S8 respectively. Overall, 1212 patients were included during the pre-Delta period, 236 during the Delta, and 347 during the Omicron. Pregnancy complications arising after COVID-19 infection were reported in 30.0% (n = 363/1212; 95%CI 27.4–32.6), 35.2% (n = 83/236; 95%CI 29.1–41.6), and 30.3% (n = 105/347; 95%CI 25.5–35.4) of patients during the pre-Delta, Delta, and Omicron periods, respectively (Table 5). Stillbirths were reported in 0.5% (n = 6/1159; 95% CI 0.2–1.1), 2.8% (n = 6/210; 95%CI 1.0–6.0), and 0.9% (n = 2/213; 95%CI 0.1–3.4) of patients during the pre-Delta, Delta, and Omicron periods respectively (Table 5).

	Pre-Delta			Delta			Omicron		
	n = 1402			n = 262			n = 391		
	n	%	95%CI	n	%	95% CI	n	%	95% CI
Maternal adverse outcome	**47**	**3.4%**	2.5–4.4	**17**	**6.5%**	3.8–10.2	**4**	**1.0%**	0.3–2.6
Inpatient management	176	**12.6%**	10.9–14.4	45	**17.2%**	12.8–22.3	49	**12.5%**	9.4–16.2
Standard unit	131	**9.3%**	7.9–11.0	32	**12.2%**	8.5–16.8	45	**11.5%**	8.5–15.1
ICU admission	45	**3.2%**	2.4–4.3	13	**5.0%**	2.7–8.3	4	**1.0%**	0.3–2.6
Length ICU >7 days	12	**0.9%**	0.4–1.5	5	**1.9%**	0.6–4.4	0	**0.0%**	0.0–0.9
Maternal complications									
Pneumonia	33	**2.4%**	1.6–3.3	5	**1.9%**	0.6–4.4	0	**0.0%**	0.0–0.9
ARDS	56	**4.0%**	3.0–5.2	8	**3.1%**	1.3–5.9	0	**0.0%**	0.0–0.9
Oxygen supply requirement	66	**4.7%**	3.7–6.0	26	**9.9%**	6.6–14.2	2	**0.5%**	0.1–1.8
Standard oxygen	35	**2.5%**	1.7–3.5	13	**5.0%**	2.7–8.3	2	**0.5%**	0.1–1.8
High Flow oxygen	12	**0.9%**	0.4–1.5	3	**1.1%**	0.2–3.3	0	**0.0%**	0.0–0.9
Non-invasive ventilation	5	**0.4%**	0.1–0.8	3	**1.1%**	0.2–3.3	0	**0.0%**	0.0–0.9
Mechanical ventilation	14	**1.0%**	0.5–1.7	7	**2.7%**	1.1–5.4	0	**0.0%**	0.0–0.9
ECMO	7	**0.5%**	0.2–1.0	0	**0.0%**	0.0–1.4	0	**0.0%**	0.0–0.9
Maternal death (any reason)	3	**0.2%**	0.0–0.6	0	**0.0%**	0.0–1.4	0	**0.0%**	0.0–0.9

ICU: intensive care unit, ARDS: acute respiratory distress syndrome, ECMO: extracorporeal membrane oxygenation.

Table 2: **Maternal adverse outcomes among pregnant women tested positive for SARS-CoV-2 according to the pre-Delta, Delta, and Omicron periods.**

Neonatal outcomes

A total of 1226, 233, and 352 livebirths were recorded during the pre-Delta, Delta, and Omicron periods, respectively. Small weight for gestational age was reported in 6.9% (n = 85/1226; 95%CI 5.6–8.5), 4.7% (n = 11/233; 95%CI 2.4–8.3), and 6.0% (n = 21/352; 95% CI 3.7–9.0) of neonates for the pre-Delta, Delta, and Omicron periods respectively. Apgar scores less than 7 were reported in 3.2% (n = 39/1226; 95%CI 1.3–3.1), 2.9% (n = 6/233; 95%CI 1.1–6.1), and 2.3% (n = 9/352; 95%CI 0.8–5.4) of neonates during the pre-Delta, Delta, and Omicron periods (Table 5). Four (0.4%; n = 4/1226; 95%CI 01–0.8) neonates died, during the pre-Delta period and two (0.6%; 2/352; 95%CI 0.1–2.0 during the Omicron (Supplementary materials Table S9). Maternal, pregnancy, and neonatal outcomes for transition periods are presented in supplementary materials Table S10.

Discussion

This study showed that the risk for a severe maternal adverse outcome differed between time periods associated with specific SARS-CoV-2 variant predominance with a risk of 3.4%, 6.5%, and 1.0% during the pre-Delta, Delta, and Omicron periods, respectively.

In this study, the Delta variant period was associated with a higher risk of severe maternal adverse outcome compared to the pre-Delta period. Pregnant women that tested positive during the Delta period had trends of higher risks of hospitalization, ICU admission, and advanced oxygen requirements than during the pre-Delta period. Similar results were reported in the unvaccinated general population with a significantly higher risk of hospitalization and presentation to emergency care in patients that tested positive for the Delta compared to pre-Delta variants.[9,24] Our results are also consistent with the current literature regarding the Delta variant that reported higher risk of adverse maternal outcomes including oxygen requirements, hospitalization, and ICU admission.[15–17] The Delta variant remains the variant with the highest pathogenicity potential to date.

Our results show that the Omicron variant period was associated with a lower risk of severe maternal adverse outcome and a lower risk of ICU admission compared to pre-Delta. This could be interpreted to suggest that Omicron variant induces less severe disease during pregnancy, compared to the previous SARS-CoV-2 strains. Conversely, in our study, pregnant women requiring inpatient management for COVID-19 during the Omicron period remained high with 12.5% of patients needing hospitalization. Nevertheless, no advanced oxygen supplementation was required for these patients and the risk of ICU admission (1%) was lower than during the pre-Delta (3.2%) or Delta (5.0%) periods. Additionally, none of the women that tested positive during the Omicron period were admitted to the ICU for more than 7 days, suggesting that Omicron induced a less severe disease. These results are consistent with the already published data that reported a less severe disease during the Omicron period in unvaccinated adults with a reduced risk of severe disease compared with previous strains.[25] Our results confirmed already published data on pregnant women reporting a trend of a less severe disease during the Omicron

	Pre-Delta			Delta			Omicron			Delta Vs Pre-Delta				Omicron Vs Pre-Delta			
	n = 1402			n = 262			n = 391										
	n	%	95%CI	n	%	95%CI	n	%	95%CI	Crude RR	95%CI	adj. RR[a]	95%CI	Crude RR	95%CI	adj. RR[b]	95%CI
Severe maternal adverse outcome	**47**	**3.4%**	2.5–4.4	**17**	**6.5%**	3.8–10.2	**4**	**1.0%**	0.3–2.6	**1.9**	**1.1–3.3**	**1.8**	**1.1–3.2**	**0.3**	**0.1–0.8**	**0.3**	**0.1–0.8**
ICU admission	45	**3.2%**	2.4–4.3	13	**5.0%**	2.7–8.3	4	**1.0%**	0.3–2.6	–		–		–		–	
Length of ICU admission >7 days	12	**0.9%**	0.4–1.5	5	**1.9%**	0.6–4.4	0	**0.0%**	0.0–0.9	–		–		–		–	
High Flow oxygen	12	**0.9%**	0.4–1.5	3	**1.1%**	0.2–3.3	0	**0.0%**	0.0–0.9	–		–		–		–	
Non-invasive ventilation	5	**0.4%**	0.1–0.8	3	**1.1%**	0.2–3.3	0	**0.0%**	0.0–0.9	–		–		–		–	
Mechanical ventilation	14	**1.0%**	0.5–1.7	7	**2.7%**	1.1–5.4	0	**0.0%**	0.0–0.9	–		–		-		–	
Maternal death (any reason)	4	**0.3%**	0.1–0.7	0	**0.0%**	0.0–1.4	0	**0.0%**	0.0–0.9	–		–		–		–	

In bold: 95% CI does not includes 1. RR: risk ratio, adj. RR: adjusted risk ratio, ICU: intensive care unit. [a]Adjusted for ethnicity, educational level, BMI >35 kg/m^2, drug use, pulmonary, cardiac, neurological and digestive medical history, previous pregnancy with post-partum hemorrhage or other complication, ongoing pregnancy with intrauterine growth restriction, and trimester of infection. [b]Adjusted for marital status, ethnicity, educational level, BMI >30 kg/m^2, nulliparity, history of cesarean section, cardiac, diabetes, and digestive medical history, previous pregnancy with intrauterine growth restriction or preterm birth, current pregnancy with gestational diabetes or placenta praevia, and trimester of infection.

Table 3: **Association of Delta vs. pre-Delta and Omicron vs pre-Delta periods of infection with adverse maternal outcomes.**

period, with lower rates of oxygen requirement.[16] Additionally, a recent nationwide study from Scotland reported a significantly lower rate of critical care admission, adjusted by vaccination status, among pregnant women who tested positive for COVID-19, regardless of the indication of admission.[17] Acquired immunity from previous SARS-CoV-2 infections and improved management of pregnant women infected with SARS-CoV-2 over time might partially explain the decreased risk observed in our study during the Omicron period.

Preterm birth prior to 37 wks among patients that tested positive for SARS-CoV-2 remained high, with reported rates of 9.3%, 13.7%, and 11% in the pre-Delta, Delta, and Omicron periods respectively remain higher than the national rates (5–7% in the previous years).[26,27] Nevertheless, the infection itself may induces systemic inflammatory mechanisms that could lead to higher risks of preterm birth as observed in other systemic infections during pregnancy.[28] Regardless of the period of interest, low rates of adverse neonatal were reported.

The strength of this research is its prospective design and the large number of patients included in each period of interest with high quality and detailed data, and brings very timely evidence. However, several points limit the interpretation. First, the centers participating in the COVI-PREG registry were regional/university hospitals. This may have introduced a selection bias in the recruitment of patients, such as more severe patients who needed hospital care or dedicated maternity level admission but also in selecting patient with higher comorbidities as they have required care in antenatal clinics as previously observed.[3,19] Our study population is thus, probably, not representative of the

	Pre-Delta			Delta			Omicron		
	n = 993			n = 168			n = 245		
	n	%	95%CI	n	%	95%CI	n	%	95%CI
PREMATURITY (<37 weeks)	92	**9.3%**	7.5–11.2	23	**13.7%**	8.9–19.8	27	**11.0%**	7.4–15.6
- Spontaneous	33	**3.3%**	2.3–4.6	7	**4.2%**	1.7–8.4	10	**4.1%**	2.0–7.4
- Iatrogenic birth directly related to COVID-19	15	**1.5%**	0.8–2.5	7	**4.2%**	1.7–8.4	0	**0.0%**	0.0–1.5
<32 weeks	19	**2.0%**	1.2–3.1	8	**4.8%**	2.1–9.2	5	**2.0%**	0.7–4.7
- Spontaneous	6	**0.6%**	0.2–1.4	2	**1.2%**	0.1–4.2	1	**0.4%**	0.0–2.3
- Iatrogenic birth directly related to COVID-19	4	**0.4%**	0.1–1.1	2	**1.2%**	0.1–4.2	0	**0.0%**	0.0–1.5
<28 weeks	6	**0.6%**	0.2–1.4	0	**0.0%**	0.0–2.2	2	**0.8%**	0.1–2.9
- Spontaneous	1	**0.1%**	0.0–0.6	0	**0.0%**	0.0–2.2	1	**0.4%**	0.0–2.3
- Iatrogenic birth directly related to COVID-19	1	**0.1%**	0.0–0.6	0	**0.0%**	0.0–2.2	0	**0.0%**	0.0–1.5

In bold: 95% CI does not includes 1.

Table 4: **Preterm birth outcomes according to the variants' periods among patients exposed to SARS-CoV-2 before 37 weeks of gestation with a pregnancy resulting in a livebirth after 23 weeks of pregnancy.**

	Pre-Delta			Delta			Omicron		
	n = 1212			n = 236			n = 347		
	N	%	95%CI	n	%	95%CI	n	%	95%CI
Pregnancy complications (after viral exposure)	**363**	**30.0%**	27.4–32.6	**83**	**35.2%**	29.1–41.6	**105**	**30.3%**	25.5–35.4
Preeclampsia	**35**	**2.9%**	2.0–4.0	**7**	**3.0%**	1.2–6.0	**8**	**2.3%**	1.0–4.5
Gestational Diabetes	**111**	**9.2%**	7.6–10.9	**28**	**11.9%**	8.0–16.7	**41**	**11.8%**	8.6–15.7
Intrauterine growth restriction	**56**	**4.6%**	3.5–6.0	**12**	**5.1%**	2.7–8.7	**13**	**3.7%**	2.0–6.3
Abnormal fetal Doppler	**8**	**0.7%**	0.3–1.3	**2**	**0.8%**	0.1–3.0	**2**	**0.6%**	0.1–2.1
Suspected macrosomia	**24**	**2.0%**	1.3–2.9	**5**	**2.1%**	0.7–4.9	**12**	**3.5%**	1.8–6.0
Threatened preterm labor	**38**	**3.1%**	2.2–4.3	**9**	**3.8%**	1.8–7.1	**9**	**2.6%**	1.2–4.9
Preterm Premature Rupture Of Membranes	**23**	**1.9%**	1.2–2.8	**5**	**2.1%**	0.7–4.9	**7**	**2.0%**	0.8–4.1
Post-partum hemorrhage	**12**	**1.0%**	0.5–1.7	**1**	**0.4%**	0.0–2.3	**2**	**0.6%**	0.1–2.1
Other	**127**	**10.5%**	8.8–12.3	**28**	**11.9%**	8.0–16.7	**31**	**8.9%**	6.2–12.4
Labour									
Spontaneous	633	**52.2%**	49.4–55.1	**123**	**52.1%**	45.5–58.6	**185**	**53.3%**	47.9–58.7
Induction of labor	353	**29.1%**	26.6–31.8	**68**	**28.8%**	23.1–35.0	**113**	**32.6%**	27.7–37.8
Cesarean out of labor/induction	206	**17.0%**	14.9–19.2	**39**	**16.5%**	12.0–21.9	**45**	**13.0%**	9.6–17.0
Unknown	20	**1.7%**	1.0–2.5	**6**	**2.5%**	0.9–5.5	**4**	**1.2%**	0.3–2.9
Mode of delivery									
Vaginal birth	**835**	**68.9%**	66.2–71.5	**169**	**71.6%**	65.4–77.3	**261**	**75.2%**	70.3–79.7
- Assisted	**109**	**9.0%**	7.4–10.7	**20**	**8.5%**	5.3–12.8	**32**	**9.2%**	6.4–12.8
Cesarean section	**357**	**29.5%**	26.9–32.1	**61**	**25.8%**	20.4–31.9	**82**	**23.6%**	19.3–28.5
- Emergency during labor/induction	**151**	**12.5%**	10.7–14.5	**22**	**9.3%**	5.9–13.8	**37**	**10.7%**	7.6–14.4
- Emergency out of labor	**52**	**4.3%**	3.2–5.6	**5**	**2.1%**	0.7–4.9	**13**	**3.7%**	2.0–6.3
Related directly to COVID-19	**23**	**1.9%**	1.2–2.8	**12**	**5.1%**	2.7–8.7	**1**	**0.3%**	0.0–1.6
- Planned cesarean section	**154**	**15.5%**	13.317.9	**34**	**14.4%**	10.2–19.5	**32**	**9.2%**	6.4–12.8
Unknown	20	**1.7%**	1.0–2.5	**6**	**2.5%**	0.9–5.5	**4**	**1.2%**	0.3–2.9
Prematurity									
<37 weeks	108	**8.9%**	7.4–10.7	32	**13.6%**	9.5–18.6	32	**9.2%**	6.4–12.8
- Spontaneous	35	**2.9%**	2.0–4.0	9	**3.8%**	1.8–7.1	9	**2.6%**	1.2–4.9
- Iatrogenic birth related directly to COVID-19	16	**1.3%**	0.8–2.1	7	**3.0%**	1.2–6.0	0	**0.0%**	0.0–1.1
<32 weeks	30	**2.5%**	1.7–3.5	13	**5.5%**	3.0–9.2	8	**2.3%**	1.0–4.5
- Spontaneous	6	**0.5%**	0.2–1.1	2	**0.8%**	0.1–3.0	2	**0.6%**	0.1–2.1
- Iatrogenic birth related directly to COVID-19	5	**0.4%**	0.1–1.0	2	**0.8%**	0.1–3.0	0	**0.0%**	0.0–1.1
<28 weeks	13	**1.1%**	0.6–1.8	2	**0.8%**	0.1–3.0	4	**1.2%**	0.3–2.9
- Spontaneous	6	**0.5%**	0.2–1.1	2	**0.8%**	0.1–3.0	2	**0.6%**	0.1–2.1
- Iatrogenic birth related directly to COVID-19	2	**0.2%**	0.0–0.6	0	**0.0%**	0.0–1.6	0	**0.0%**	0.0–1.1
Pregnancy outcomes									
Number of fetuses	**n = 1238**			**n = 239**			**n = 356**		
Livebirths	**1226**	**99.0%**	98.3–99.5	**233**	**97.5%**	94.6–99.1	**352**	**98.9%**	97.1–99.7
Pre-viable fetus birth (≥20 and < 24 weeks)	**4**	**0.3%**	0.1–0.8	**0**	**0.0%**	0.0–1.5	**1**	**0.3%**	0.0–1.6
Late termination of pregnancy (≥20 weeks	**2**	**0.2%**	0.0–0.6	**0**	**0.0%**	0.0–1.5	**1**	**0.3%**	0.0–1.6
Stillbirths	**6**	**0.5%**	0.2–1.1	**6**	**2.5%**	0.9–5.4	**2**	**0.6%**	0.1–2.0
Neonatal outcomes	**n = 1226**			**n = 233**			**n = 352**		
Weight at birth (mean in g.; SD)	3226	**609**		3226	**675**		3246	**596**	
<10th percentile for gestational age[a]	85	**6.9%**	5.6–8.5	11	**4.7%**	2.4–8.3	21	**6.0%**	3.7–9.0
<3rd percentile for gestational age[a]	25	**2.0%**	1.3–3.0	3	**1.3%**	0.3–3.7	3	**0.9%**	0.2–2.5
Apgar score 5 min (mean; SD)	9.5	**1.1**		9.4	**1.2**		9.5	**1.1**	
Apgar score <7	39	**3.2%**	2.3–4.3	6	**2.6%**	1.0–5.5	9	**2.6%**	1.2–4.8
NICU admission	153	**12.5%**	10.7–14.5	23	**9.9%**	6.4–14.4	34	**9.7%**	6.8–13.2
Neonatal death	4	**0.3%**	0.1–0.8	0	**0.0%**	0.0–1.6	2	**0.6%**	0.1–2.0

In bold: 95% CI does not includes 1. PPROM: preterm premature rupture of membranes, NICU: neonatal intensive care unit admission, SD: standard deviation. [a]Neonatal weight <10th and <3rd percentile defined according to the INTERGROWTH 21st scale (Villar J, Giuliani F, Bhutta ZA et al. Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-up Study of the INTERGROWTH-21st Project. The Lancet Global Health 2015; 3(11):e681–91).

Table 5: **Pregnancy and neonatal outcomes according to the variant time period among patients exposed to SARS-CoV-2 with a known pregnancy outcome from 20 weeks of gestation.**

entire pregnancy population. Through the registry, we did not have access to information regarding the indication for the SARS-CoV-2 test (e.g., symptoms compatible with COVID-19, routine screening) or the location of the test (e.g., hospital, pharmacy, or community). This may have impacted our results as SARS-CoV-2 testing may have changed over time and therefore could have introduced a selection bias if testing patterns selected a differential proportion of more severe or less severe women from one period to the next. Additionally, we did not have access to the sequencing of the SARS-CoV-2 variant that caused the infection in our patients, and we assumed that a woman infected during the predominant variant's period was infected by this predominant variant. No clear standard exists to define variant time periods using variant predominance to ensure accurate allocation of individuals to specific variants. The Centers for Disease Control (CDC) defines predominance of a variant as accounting for more than 50% of national circulating SARS-CoV-2 linages among infections.[29–31] Within the literature, variant predominance is defined between 70 and 95% of the samples of interest. As such, we selected an empirical threshold of 80% for predominance identified in national samples in order to ensure a relatively high threshold per specific period without excluding too many patients. For this reason, there is a potential for exposure misclassification as up to 20% of patients might had an infection to another variant then the one they have been classified for. This may have caused exposure misclassification. Furthermore, the study did not collect the immune status of women who could have been infected prior to the pregnancy, influencing the severity of the current reinfection during the pregnancy, and may have underestimated the real risk of the Delta or Omicron variants for non-immune individuals. Prior to the Omicron wave, COVID-19 reinfection in adults has been reported to have 90% lower odds of leading to hospitalization or death compared to primary infection among unvaccinated individuals.[14] The risk of SARS-CoV-2 re-infection has been reported to be up to 15% in a population including both vaccinated and unvaccinated adults.[32] In a study from Denmark, the rate of hospitalized in re-infected adults was 0.16% compared to 1.33% in primary infected individuals, with a significant adjusted hazard ratio of 0.13 (95%CI 0.03–0.54).[33] Finally, the outcome defined as ICU admission is difficult to standardized as it is subject to variability in clinician choices and local management protocols. No clear standards were available to guide clinicians on timing of and need for admission to the ICU. The management of pregnant women during the Omicron wave could have been influenced by the previous Delta wave as it was associated with more severe adverse maternal outcomes prompting a tendency for additional precautions.

This study presents evidence on maternal adverse outcomes of SARS-CoV-2 variants during pregnancy with less severe disease associated with the Omicron strain. However, our results support Nealon et al.[34] stating that Omicron severity is "milder but not mild". Omicron was reported to still induce a high risk of hospitalization and should not be trivialized. Our results should be interpreted carefully as widespread disease could potentially severely affect pregnant women. As the pandemic is not over, a new viral strain with a potentially more severe impact on pregnancy outcomes may emerge in the future. Furthermore, very scarce information is available regarding long-term implications of COVID-19 in pregnant women, such as long COVID-19 following infection during pregnancy and the potential impact of the virus on the development of infants born from mothers exposed to COVID-19 during pregnancy.[35] Thus, health care providers and public health authorities should not be complacent about COVID-19 infection during pregnancy. Focus should be placed on promoting vaccination against COVID-19 in pregnant women, before and during pregnancy, as many remain reluctant to vaccinate while pregnant.[18]

In conclusion, pregnant women exposed to SARS-CoV-2 during the Delta period, attending an antenatal clinic, were at higher risk of severe maternal outcomes with increased ICU admissions and increased need for advanced oxygen support, compared to pre-Delta and Omicron variants. Omicron was associated with less severe maternal adverse outcome. Nevertheless, the rate of hospitalization remained high with Omicron, emphasizing the need to pursue the promotion of COVID-19 vaccination for pregnant women.

Contributors

GF, EM, DB, and AP conceived and designed the study. GF, EM, LP, and AP analyzed 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, CP, TQ, CM, BMT, LS, AP, APR, MTB, YV, CAV, BEH, RCB, SJ, CG, SD, NM, CRK, CG, LS, BW, SL, DB, KL, UW, AP, and DB) 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.

Data sharing statement

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

Ethics statement

This research project was reviewed and approved the Swiss Ethical Board (CER-VD-2020-00548).

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. All other authors declare no conflicts of interest.

Acknowledgments

We thank every patient who agreed to participate in this study.

The French and Swiss COVI-PREG group

Co-authors:

Irene Hoesli[1], Sonia Campelo[2], Véronique Othenin-Girard[2], Anett Hernadi[3], Maria Luisa Gasparri[4], Antonilli Morena[4], Christian Polli[4], Edoardo Taddei[4], Daniel Surbek[5], Luigi Raio[5], Karoline Aebi-Popp[6], Mirjam Moser[7], Johana Sichitiu[8], Laurent J. Salomon[8], Julien Stirnemann[8], Jérôme Dimet[9], Tina Fischer[10], Louise Ghesquiere[1], Amaury Brot[12], Aurélien Mattuizzi[12], Clémence Houssin[12], Stefanie Sturm[13], Jérôme Mathis[14], Edouard Ha[14], Caroline Eggemann[14], Marie-Claude Rossier[15], Andrea Bloch[16], Martin Kaufmann[17], Panagiotis Kanellos[18], Carina Britschgi[18], Bénédicte Breton[19], Carolin Blume[20], Stylianos Kalimeris[20], Arnaud Toussaint[21], Guillaume Ducarme[22], Hélène Pelerin[23], Chloé Moreau[23], Gaetan Plantefeve[24], Cecile Le Parco[24], Mohamed Derouich[24], Anis Feki[25], Gaston Grant[25], Ina Hoffmann[26], Kathrin Bütikofer[26], Elke Barbara Prentl[27], Jessica Maisel[27], Grit Vetter[28], Brigitte Frey Tirri[28], Lucie Sedille[29], Michel Boulvain[30], Annina Haessig[31]

Affiliations

[1] Department of Obstetrics, University Hospital Basel, Basel, Switzerland
[2] Obstetrics Division, Department of Pediatrics, Gynecology, and Obstetrics, Geneva University Hospitals, Geneva Switzerland
[3] Division of Obstetrics, Baden Cantonal Hospital Baden Switzerland
[4] Department of Gynecology and Obstetrics, Ente Ospedaliero Cantonale, Lugano, Switzerland
[5] Department of Obstetrics and feto-maternal Medicine, University Hospital of Bern, University of Bern, Bern, Switzerland
[6] Department of Infectious Diseases, University Hospital Bern, Bern, Switzerland
[7] Department of Obstetrics, Cantonal Hospital Aarau, Aarau, Switzerland
[8] Necker-Enfants Malades Hospitals, Department of Obstetrics, Paris, France
[9] Department of Gynecology, Mont-de-Marsan Hospital, Mont-de-Marsan, France
[10] Infectious Diseases and Hospital Epidemiology, Children's Hospital of Eastern Switzerland, St. Gallen, Switzerland
[11] Department of Obstetrics, CHU de Lille, Lille, France
[12] Department of Obstetrics and Gynecology, Bordeaux University Hospital, Bordeaux, France
[13] Frauenpraxis Schaffhausen, Schaffhausen, Switzerland
[14] Department of Obstetrics and Gynecology, Centre hospitalier Bienne, Bienne, Switzerland
[15] Department of Obstetrics and Gynecology, Hospital Riviera Chablais, Rennaz, Switzerland
[16] Obstetric and Gynecology Unit, Hopital du Jura, Delemont, Switzerland
[17] Department of Obstetrics, Spital Bülach, Bülach, Switzerland
[18] Department of Gynecology and Obstetrics, Kantonal Hospital of Uri, Altdorf, Switzerland
[19] Departement of obstetrics and Gynecology, Annecy Genevois Hospital Centre, Annecy, France
[20] Kantonsspital Graubünden, Frauenklinik Fontana, Chur, Switzerland
[21] Department of Gynecology and Obstetrics, Intercantonal Hospital of Broye, Payerne, Switzerland
[22] Department of Obstetrics and Gynecology, Centre Hospitalier Departemental de Vendée, La-Roche-sur-Yon, France
[23] Clinical Research Department, Centre Hospitalier Départemental de Vendée, La-Roche-sur-Yon, France
[24] Victor Dupouy Hospital, Argenteuil, France
[25] Département de gynécologie et obstétrique, HFR, Fribourg, Switzerland
[26] Department of Obstetrics and Gynecology, Olten cantonal hospital, Olten, Switzerland
[27] Department of Obstetrics and Gynecology, Winterthur cantonal hospital, Winterthur, Switzerland
[28] Department of obstetrics, Kantonsspital Baselland, Liestal, Switzerland
[29] Department of Obstetrics and Gynecology, La Rochelle Hospital, La Rochelle, France
[30] Faculty of Medicine, University of Geneva, Geneva, Switzerland
[31] Department of Obstetrics and Gynecology, Zuger Kantonsspital, Zug, Switzerland

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2022.100569.

References

1 Lokken EM, Taylor GG, Huebner EM, et al. Higher severe acute respiratory syndrome coronavirus 2 infection rate in pregnant patients. *Am J Obstet Gynecol*. 2021;225(1):75.e1–75.e16.
2 Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. 2020;370:m3320.
3 Vouga M, Favre G, Martinez-Perez O, et al. Maternal outcomes and risk factors for COVID-19 severity among pregnant women. *Sci Rep*. 2021;11(1):13898.
4 Villar J, Ariff S, Gunier RB, et al. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: the INTERCOVID multinational cohort study. *JAMA Pediatr*. 2021;175(8):817–826.
5 Khalil A, von Dadelszen P, Draycott T, Ugwumadu A, O'Brien P, Magee L. Change in the incidence of stillbirth and preterm delivery during the COVID-19 pandemic. *JAMA*. 2020;324(7):705–706.
6 Favre G, Mazzetti S, Gengler C, et al. Decreased fetal movements: a sign of placental SARS-CoV-2 infection with perinatal brain injury. *Viruses*. 2021;13(12):2517.
7 Sichitiu J, Bourgon N, Guilleminot T, Bessieres B, Leruez-Ville M, Ville Y. Third trimester placentitis: an under-reported complication of SARS-CoV-2 infection. *Am J Obstet Gynecol MFM*. 2022:100703.
8 Tracking SARS-CoV-2 variants [internet]. [cited 2022 Sep 20]. Available from: https://www.who.int/activities/tracking-SARS-CoV-2-variants.
9 Twohig KA, Nyberg T, Zaidi A, et al. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. *Lancet Infect Dis*. 2022;22(1):35–42.
10 Butt AA, Dargham SR, Chemaitelly H, et al. Severity of illness in persons infected with the SARS-CoV-2 delta variant vs Beta variant in Qatar. *JAMA Intern Med*. 2022;182(2):197–205.
11 Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and outcomes of hospitalized patients in South Africa during the COVID-19 Omicron wave compared with previous waves. *JAMA*. 2022;327(6):583–584.
12 Ulloa AC, Buchan SA, Daneman N, Brown KA. Estimates of SARS-CoV-2 omicron variant severity in Ontario, Canada. *JAMA*. 2022;327(13):1286–1288.
13 Jassat W, Abdool Karim SS, Mudara C, et al. Clinical severity of COVID-19 in patients admitted to hospital during the omicron wave in South Africa: a retrospective observational study. *Lancet Global Health*. 2022;10(7):e961–e969.
14 Abu-Raddad LJ, Chemaitelly H, Bertollini R. Severity of SARS-CoV-2 reinfections as compared with primary infections. *N Engl J Med*. 2021;385(26):2487–2489.
15 Adhikari EH, SoRelle JA, McIntire DD, Spong CY. Increasing severity of COVID-19 in pregnancy with Delta (B.1.617.2) variant surge. *Am J Obstet Gynecol*. 2022;226(1):149–151.
16 Birol Ilter P, Prasad S, Mutlu MA, et al. Maternal and perinatal outcomes of SARS-CoV-2 infection in unvaccinated pregnancies

during Delta and Omicron waves. *Ultrasound Obstet Gynecol*. 2022;60(1):96–102.
17 Stock SJ, Moore E, Calvert C, et al. Pregnancy outcomes after SARS-CoV-2 infection in periods dominated by delta and omicron variants in Scotland: a population-based cohort study. *Lancet Respir Med*. 2022;S2213–2600(22):360–365.
18 Stuckelberger S, Favre G, Ceulemans M, et al. SARS-CoV-2 vaccine willingness among pregnant and breastfeeding women during the first pandemic wave: a cross-sectional study in Switzerland. *Viruses*. 2021;13(7):1199.
19 Favre G, Maisonneuve E, Pomar L, et al. COVID-19 mRNA vaccine in pregnancy: results of the Swiss COVI-PREG registry, an observational prospective cohort study. *Lancet Reg Health Eur*. 2022;18:100410.
20 Prasad S, Kalafat E, Blakeway H, et al. Systematic review and meta-analysis of the effectiveness and perinatal outcomes of COVID-19 vaccination in pregnancy. *Nat Commun*. 2022;13(1):2414.
21 Panchaud A, Favre G, Pomar L, et al. An international registry for emergent pathogens and pregnancy. *Lancet*. 2020;395(10235):1483–1484.
22 Khare S, Gurry C, Freitas L, et al. GISAID's role in pandemic response. *China CDC Wkly*. 2021;3(49):1049–1051.
23 Villar J, Giuliani F, Bhutta ZA, et al. Postnatal growth standards for preterm infants: the preterm postnatal follow-up study of the INTERGROWTH-21st project. *Lancet Global Health*. 2015;3(11):e681–e691.
24 Bast E, Tang F, Dahn J, Palacio A. Increased risk of hospitalisation and death with the delta variant in the USA. *Lancet Infect Dis*. 2021;21(12):1629–1630.
25 Wolter N, Jassat W, Walaza S, et al. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. *Lancet*. 2022;399(10323):437–446.
26 Prématurité : une légère baisse pendant le premier confinement de 2020 dans les départements de moindre circulation du virus. Direction de la recherche, des études, de l'évaluation et des statistiques; 2022 [Internet]. [cited 2022 Sep 30]. Available from: https://drees.solidarites-sante.gouv.fr/publications-communique-de-presse/etudes-et-resultats/prematurite-une-legere-baisse-pendant-le.
27 Office Fédérale de la Statistique Suisse (Swiss Federal Statistical Office). Santé des nouveau-nés [Internet]. [cited 2022 Feb 25]; Available from: https://www.bfs.admin.ch/bfs/fr/home/statistiken/gesundheit/gesundheitszustand/gesundheit-neugeborene.html.
28 Silasi M, Cardenas I, Racicot K, Kwon J-Y, Aldo P, Mor G. Viral infections during pregnancy. *Am J Reprod Immunol*. 2015;73(3):199–213.
29 Hatfield KM, Baggs J, Wolford H, et al. Effectiveness of coronavirus disease 2019 (COVID-19) vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among residents of US nursing homes before and during the delta variant predominance, December 2020–November 2021. *Clin Infect Dis*. 2022;75(Supplement_2):S147–S154.
30 Grannis SJ, Rowley EA, Ong TC, et al. Interim estimates of COVID-19 vaccine effectiveness against COVID-19–associated emergency department or urgent care clinic encounters and hospitalizations among adults during SARS-CoV-2 B.1.617.2 (delta) variant predominance — nine states, June–August 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(37):1291–1293.
31 Thompson MG. Effectiveness of a third dose of mRNA vaccines against COVID-19–associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance — VISION network, 10 states, August 2021–January 2022. *MMWR Morb Mortal Wkly Rep [Internet]*. 2022;71 [cited 2022 Nov 3]. Available from: https://www.cdc.gov/mmwr/volumes/71/wr/mm7104e3.htm.
32 Medić S, Anastassopoulou C, Lozanov-Crvenković Z, et al. Risk and severity of SARS-CoV-2 reinfections during 2020–2022 in Vojvodina, Serbia: a population-level observational study. *The Lancet Reg Health Eur [Internet]*. 2022;20 [cited 2022 Nov 8]. Available from: https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(22)00147-8/fulltext.
33 Michlmayr D, Hansen CH, Gubbels SM, et al. Observed protection against SARS-CoV-2 reinfection following a primary infection: a Danish cohort study among unvaccinated using two years of nationwide PCR-test data. *The Lancet Regional Health – Europe [Internet]*. 2022;20 [cited 2022 Nov 8]. Available from: https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(22)00146-6/fulltext.
34 Nealon J, Cowling BJ. Omicron severity: milder but not mild. *Lancet*. 2022;399(10323):412–413.
35 Abbas-Hanif A, Modi N, Majeed A. Long term implications of covid-19 in pregnancy. *BMJ*. 2022;377:e071296.

Received: 12 July 2022 | Revised: 23 September 2022 | Accepted: 6 November 2022

DOI: 10.1111/bcp.15611

ORIGINAL ARTICLE

COVID-19-related medicine utilization study in pregnancy: The COVI-PREG cohort

Guillaume Favre[1] | Eva Gerbier[1,2] | Emeline Maisonneuve[1,2] | Léo Pomar[1,3] | Ursula Winterfeld[4] | Karine Lepigeon[1] | Kitty W. M. Bloemenkamp[5] | Odette de Bruin[5,6] | Hurley Eimir[7] | Hedvig Nordeng[7] | Satu J. Siiskonen[8] | Miriam C. J. M. Sturkenboom[6] | David Baud[1] | Alice Panchaud[2,9] | the COVI-PREG and CONSIGN group

[1]Materno-fetal and Obstetrics Research Unit, Department "Femme-Mère-Enfant", University Hospital, Lausanne, Switzerland

[2]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

[3]School of Health Sciences (HESAV), University of Applied Sciences and Arts Western Switzerland, Lausanne, Switzerland

[4]Swiss Teratogen Information Service, Clinical pharmacology service, Lausanne University Hospital and University of Lausanne, Switzerland

[5]Department of Obstetrics, WKZ Birth Centre, Division Woman and Baby, UMC Utrecht, Utrecht, the Netherlands

[6]Julius Global Health, University Medical Center Utrecht, Utrecht, Netherlands

[7]PharmacoEpidemiology and Drug Safety Research Group, Department of Pharmacy, and PharmaTox Strategic Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway

[8]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands

[9]Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

Correspondence
Alice Panchaud, Institute of Primary Health Care (BIHAM), University of Bern, Bern 3012, Switzerland.
Email: alice.panchaudmonnat@biham.unibe.ch

Funding information
This research was funded by a grant from the Swiss Federal Office of Public Health. The research leading to these results was conducted as part of the activities of the EU PE&PV (Pharmacoepidemiology and Pharmacovigilance) Research Network which is a public academic partnership coordinated by the Utrecht University, The Netherlands. The project named CONSIGN has received support from the European Medicines Agency under the Framework service contract No. EMA/2018/28/PE. The content of this paper expresses the opinion of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Aim: The objective of this study was to describe the use of COVID-19-related medicines during pregnancy and their evolution between the early/late periods of the pandemic.

Methods: Pregnant women who tested positive for SARS-CoV-2 from March 2020 to July 2021 were included using the COVI-PREG registry. Exposure to the following COVID-19-related medicines was recorded: antibiotics, antivirals, hydroxychloroquine, corticosteroids, anti-interleukin-6 and immunoglobulins. We described the prevalence of medicines used, by trimester of pregnancy, maternal COVID-19 severity level and early/late period of the pandemic (before and after 1 July 2020).

Findings: We included 1964 pregnant patients who tested positive for SARS-CoV-2. Overall, 10.4% (205/1964) received at least one COVID-19-related medicine including antibiotics (8.6%; 169/1694), corticosteroids (3.2%; 62/1964), antivirals (2.0%; 39/1964), hydroxychloroquine (1.4%; 27/1964) and anti-interleukin-6 (0.3%; 5/1964). The use of at least one COVID-19-related medicine was 3.1% (12/381) in asymptomatic individuals, 4.2% (52/1233) in outpatients, 19.7% (46/233) in inpatients without oxygen, 72.1% (44/61) in those requiring standard oxygen, 95.7% (22/23) in those requiring high flow oxygen, 96.2% (25/26) in patients who required intubation and 57.1% (4/7) among patients who died. The proportion who received medicines to treat COVID-19 was higher before than after July 2020 (16.7% *vs.*

7.7%). Antibiotics, antivirals and hydroxychloroquine had lower rates of use during the late period.

Conclusion: Medicine use in pregnancy increased with disease severity. The trend towards increased use of corticosteroids seems to be aligned with changing guidelines. Evidence is still needed regarding the effectiveness and safety of COVID-19-related medicines in pregnancy.

KEYWORDS

COVID-19, COVID-19-related medicine, drug use, medicine use, pharmaco-epidemiology, pregnancy, SARS-CoV-2

1 | INTRODUCTION

During this unprecedented COVID-19 crisis, pregnant women were particularly at risk of severe disease compared to non-pregnant women of the same age, with up to 9% requiring intensive care unit admission.[1–3] Pregnant women were also at higher risk of preterm birth, mostly induced.[2,4] Newborn transmission ranged from 1 to 4% among SARS-CoV-2 positive pregnant women close to delivery, mainly after birth, with exceptional severe adverse neonatal outcome directly caused by the virus.[5–7]

Repurposed medicines have been proposed to treat COVID-19. Corticosteroids, remdesivir, anakinra, tocilizumab and other anti-SARS-CoV2 monoclonal antibodies are currently authorized to treat COVID-19 in the European Union.[8] Other medicines have been used off-label, including lopinavir-ritonavir, and high doses of hydroxychloroquine.

Since the beginning of the pandemic, guidelines have drastically changed, as new treatments and data have emerged over time.[9] Additionally, clinical guidelines specifically dedicated to the pregnant women population were drawn from information collected in the general population as most studies excluded pregnant women.[10] Information on the safety of several repurposed medicines to treat COVID-19 in pregnancy is scarce and insufficient to draw conclusions about potential risks.

The use of the anti-interleukin 6 (anti-IL6), tocilizumab and the antiviral remdesivir remains reassuring but extremely limited in pregnant women.[11,12] Corticosteroids have been well studied during the late pregnancy period[13] but first trimester administration raised questions about the potential increased risk of cleft lips and gestational diabetes incidence, but no evidence exists to rule this out.[14] Recommendations for COVID-19 have been drawn from the RECOVERY trial reporting a decreased mortality in the general population requiring oxygen and was first reported on 16 June 2020.[15,16] The use of lopinavir/ritonavir has been studied in pregnant patients outside COVID-19 (e.g., Human Immunodeficiency Viruses or Hepatitis B virus), and no concerns have been raised to date.[17] Chloroquine/hydroxychloroquine has been used during pregnancy for treating lupus or rheumatoid arthritis with contradictory results regarding birth defects.[18,19] There is insufficient evidence on the safety of the use of ivermectin for treating parasitosis during pregnancy.[20] The majority of observational studies regarding azithromycin use in pregnancy have not found an increased risk of major congenital anomalies.[21] However, due to their lack of efficacy and potential side effects, chloroquine/hydroxychloroquine alone or combined with azithromycin, or ivermectin are no longer recommended for the treatment of COVID-19.[22,23]

It is therefore important to assess how pregnant women were exposed to COVID-19-related medicines given the complexity and the evolving evidence and recommendations during this pandemic. In this study, we aimed to describe the use of COVID-19-related medicines during pregnancy from March 2020 until July 2021 using the COVI-PREG international registry.[24]

What is already known about this subject

- Pregnant women are at high risk of severe forms of COVID-19 leading to higher risks of preterm birth.
- Repurposed drugs have been used to treat COVID-19 even with scarce safety information.
- Pregnant women have been excluded from the majority of COVID-19 clinical trials.

What this study adds

- COVID-19 medicine use in pregnancy increased with disease severity.
- The management of COVID-19 in pregnancy has changed over time, with a decrease in the use of medicines which are no longer recommended, and an increase in the use of corticosteroids, especially for cases requiring oxygen, which is recommended.
- Further studies are urgently needed to assess the effectiveness and safety of COVID-19 medicines in pregnancy.

2 | METHODS

2.1 | Design and settings

This study used the data collected from 24 March 2020 to 1 July 2021 in the COVI-PREG registry database which is a prospective cohort study aiming to assess the impact of SARS-CoV-2 infection in pregnant women and their fetuses/newborns.[24] Pregnant women tested for SARS-CoV-2 during pregnancy, with the exception of those under 18 or declining/not able to consent, were eligible in this multicentre international study. Any health facility with an antenatal clinic or labour ward worldwide was able to contribute to the registry. The study was approved by both the Swiss Ethical Board (CER-VD-2020-00548) and the local ethics boards at each participating centre.

2.2 | Data collection

At the time of a positive SARS-CoV-2 test, patients were included in the study if they agreed to participate. The local investigator completed the enrolment form regarding patient's baseline basic characteristics, medical history (defined as a condition present before pregnancy) and information about SARS-CoV-2 exposure and testing, using the REDCap (Research Electronic Data Capture) secure web application hosted at Lausanne University Hospital data centre. They completed the natural history form regarding the course of COVID-19 at the end of the COVID-19 event or eventually at the end of the pregnancy, using individual medical records. They also completed the pregnancy and neonatal outcome form after the patient was discharged from maternity. Only de-identified data were recorded in the online database. No dedicated clinical visits were planned for the study.

2.3 | Participants, inclusion and exclusion criteria

Pregnant patients who tested positive for SARS-CoV-2 with a history of symptoms, potential virus exposure or universal screening performed depending on local guidelines, who presented to one of the participating health care facilities during pregnancy, were eligible for inclusion in the study. Confirmed infection was defined as a patient presenting a positive test at any time during pregnancy regardless of its indication. Patients who were not tested or had a negative or unknown test result were excluded from the analysis. Confirmed positive SARS-CoV-2 diagnosis was defined as a positive nasopharyngeal reverse transcriptase polymerase chain reaction (RT-PCR) or antigen test during pregnancy. Patients with a positive serology but no positive nasopharyngeal RT-PCR or antigen test were not included in the study. History of COVID-19 before pregnancy and COVID-19 vaccination details were not requested in the COVI-PREG registry for patients infected with COVID-19 during the study period.

2.4 | Exposure to COVID-19-related medicines

The exposure of interest was defined as any of the medicines reported to treat a COVID-19 event during pregnancy, without a dose or duration threshold. Information about medicine exposure was collected by local investigators based on individual medical records (either extracted from pregnancy follow-up visit documents, hospital discharge letters and/or maternity discharge letters). The following medicine categories were collected: antibiotics, antivirals, hydroxychloroquine (HCQ), corticosteroids (for maternal indication), anti-IL6 and immunoglobulins (an exhaustive list of substance names is included in Table S1). Symptomatic treatments defined as any medicine not intended to treat directly COVID-19, such as antipyretic and antithrombotic treatments, were not recorded. No information was available on the timing of COVID-19-related medicine intake.

2.5 | Co-variables

Sociodemographic characteristics of patients such as marital status, ethnicity, region of the world and educational level were collected. Maternal age was divided into five categories ≤25, 26–30, 31–35, 36–40 and >40 years. Medical information such as medical history, maternal body mass index (BMI) at inclusion, maternal alcohol or tobacco consumption, obstetrical history, previous pregnancy complications and ongoing pregnancy complications before exposure to SARS-CoV-2 was also collected. Trimesters of pregnancy were defined as trimester 1: the period between the last menstrual period (LMP) and gestational week (GW) 13 plus 6 days; trimester 2: the period between GW 14 and 27 plus 6 days; and trimester 3: the period starting at GW 28.

2.5.1 | Maternal COVID-19 severity

Severity of COVID-19 disease was divided into severity levels based on the National Institute of Health (NIH) treatments guidelines: level (0) asymptomatic patients, (1) mild to moderate illness, not hospitalized, (2) hospitalized patient without oxygen support, (3) hospitalized patient requiring standard oxygen support, (4) high flow oxygen support requirement (including high flow cannula and non-invasive ventilation), (5) mechanical ventilation requirement and (6) maternal death.[22]

2.5.2 | Early and later pandemic period

The pandemic period was divided into two periods corresponding to the early (24 March 2020 to 30 June 2020) and later (1 July 2020 to 1 July 2021) pandemic periods. June 2020 corresponds to the end of the first infection wave in Europe, and coincides with a key change in the NIH clinical guidelines against the use of hydroxychloroquine for COVID-19 patients, and recommendation for the use of

dexamethasone in the light of RECOVERY trial preliminary results.[16,25] Patients were stratified into early and late period according to the recorded date of the onset of their COVID-19-related symptoms. For asymptomatic patients and those missing dates of onset of symptoms, the date of their SARS-CoV-2 positive test was used instead.

2.6 | Statistical analysis

Descriptive statistics were used to present baseline demographics and characteristics of the study population. Prevalence of reported medicine use for the COVID-19 event overall and stratified by pregnancy trimesters was categorized by early or late pandemic period, and by severity level of maternal COVID-19. Prevalence of medicine use was defined as the proportion of patients exposed to at least one medication, divided by the total number of included pregnancies. The 95% confidence intervals (95% CI) were calculated for each reported prevalence using the exact Clopper-Pearson method. Statistical analyses were performed using Stata 16 (StataCorp., College Station, TX, USA).

3 | RESULTS

3.1 | Demographics

The study population included 1964 pregnant patients who had a confirmed SARS-CoV-2 diagnosis during pregnancy. A description of cases included by country is presented in Table S2. The median age was 32 years, with 53.0% ($n = 1040$) of positive diagnoses in trimester 3, 31.9% ($n = 627$) in trimester 2 and 13.8% ($n = 272$) in trimester 1. White ethnicity represented 53.5% ($n = 1050$) of patients and 21.3% ($n = 418$) had a BMI greater than 30 kg/m^2. A total of 32.6% ($n = 640$) patients were nulliparous. Thyroid imbalance (5.1%, $n = 100$), pulmonary disease (3.1%, $n = 60$) and hypertensive disorder (2.7%, $n = 53$) were the most frequent comorbidities. Gestational diabetes and pre-eclampsia were respectively diagnosed before positive SARS-CoV-2 tests in 9.6% ($n = 189$) and in 1.9% ($n = 37$) of women (Table 1).

3.2 | Exposure to COVID-19-related medicines

A description of patient characteristics with and without exposure to COVID-19-related medicines is presented in Table S3. The complete description of COVID-19-related medication use among pregnant women who tested positive for SARS-CoV-2 during the whole study period is presented in Table 2. Overall, 10.4% ($n = 205/1964$) of pregnant women received at least one COVID-19-related medicine. Antibiotics (8.6%, $n = 169$) were the most frequently used medicine category, mostly represented by azithromycin (40.2%; 68/169), amoxicillin clavulanic acid (31.4%; 53/169), ceftriaxone (17.2%; 29/169) and amoxicillin (10.7%; 18/169), followed by corticosteroids (3.2%; 62/1964), mostly dexamethasone (62.9%; 39/62) and methylprednisolone (19.4%; 12/62). Antivirals were used by 2.0% (39/1964) of pregnant women, mostly lopinavir associated with ritonavir (33.3%; 13/39), oseltamivir (33.3%; 13/39) and remdesivir (25.6%; 10/39). Finally, HCQ was used by 1.4% (27/1964) of patients, anti-IL6 (tocilizumab) by 0.3% (5/1964) and no one was exposed to immunoglobulins. Among all medicine categories, antibiotics represented 56.0% (169/302), corticosteroids 20.5% (62/302), antivirals 12.9% (39/302), hydroxychloroquine 8.9% (27/302) and anti-IL-6 1.7% (5/302) (Figure 1).

The prevalence of exposure to COVID-19-related medicines by pregnancy trimester is reported in Table S4. The proportion of patients who received a COVID-19-related medicine was 6.6% (18/72), 11.2% (70/627) and 10.8% (112/1040) in trimesters 1, 2 and 3, respectively. The prevalence of exposure to COVID-19-related medicines by world regions is presented in Table S5.

3.3 | Medicine use by COVID-19 severity

Stratified by severity, the use of at least one COVID-19-related medicine was 3.1% (12/381) in asymptomatic patients, 4.2% (52/1233) in level 1 patients, 19.7% (46/233) in level 2 patients, 72.1% (44/61) in level 3 patients, 95.7% (22/23) in level 4 patients, 96.2% (25/26) in level 5 patients and 57.1% (4/7) among patients who died. The use of corticosteroids was 0.2% (2/1233) for level 1 patients, 3.9% (9/233) for level 2 patients, 34.4% (21/61) for level 3 patients, 56.5% (13/23) for level 4 patients, 57.7% (15/26) for level 5 patients and 14.3% (1/7) in patients who died. No corticosteroids were recorded for asymptomatic patients. The description of other medicine categories by level of severity is presented in Table 3. Individual medicine names are presented in Table S6. When stratified by trimester of infection, 1.5% (4/272) of patients infected in the first trimester required standard oxygen (level 3 or more). This figure increased to 6.9% (43/627) and 6.5% (67/1040) patients in second and third trimester infections, respectively.

3.4 | Early *vs.* late pandemic period

A total of 592 pregnant women tested positive in the early pandemic period and 1358 in the late pandemic period. Patients with no information about the period of exposure were excluded ($n = 14$). Patient characteristics according to the period of the pandemic are described in Table S7. A description of pregnant patients who tested positive for SARS-CoV-2 over time is presented in Figure S1. COVID-19-related medicine use over time is presented in Figure S2 and shows a decrease in the recorded use of medicines over time. The proportion of patients who received at least one medicine to treat COVID-19 during the early period was higher (16.7%, 95% CI 13.8–20.0) compared to the late period (7.7%, 95% CI 6.3–9.2) (Table 4). Antibiotics (14.7%, 95% CI 11.9–17.8 *vs.* 5.9%, 95% CI 4.7–7.3), antivirals (4.9%, 95% CI 3.3–7.0 *vs.* 0.7%, 95% CI

TABLE 1 Description of pregnant persons tested positive for SARS-CoV 2

	Pregnant women tested positive $n = 1964$		
	Median		**IQR**
Age (years); median	32		28–35
	n	**%**	95%CI
Age category			
≤ 25 years old (y.o.)	291	**14.9**	13.3-16.5
26–30 y.o.	554	**28.3**	26.3-30.4
31–35 y.o.	661	**33.8**	31.7-35.9
36–40 y.o.	357	**18.2**	16.6-20.0
≥ 41 y.o.	94	**4.8**	3.9-5.8
Trimester of pregnancy at infection			
Trimester 1	272	**13.8**	12.4-15.5
Trimester 2	627	**31.9**	29.9-34.0
Trimester 3	1040	**53.0**	50.7-55.2
Unknown trimester	25	**1.3**	0.8 1.9
Baseline characteristics			
Marital status			
- Married or domestic partnership	1625	**82.7**	81.0-84.4
- Single never married	165	**8.4**	7.2-9.7
- Divorced or separated	14	**0.7**	0.4-1.2
- Widowed	2	**0.1**	0.0-0.4
- Unknown	90	**4.6**	3.7-5.6
Ethnicity			
- White	1050	**53.5**	51.2-55.7
- Hispanic or Latino	316	**16.1**	14.5-17.8
- Black or African American	196	**10.0**	8.7-11.4
- Asian or Pacific islander	98	**5.0**	4.1-6.0
- Other	121	**6.2**	5.1-7.3
- Unknown	96	**4.9**	4.0-5.9
Region of the world			
Europe	1310	**66.7**	64.6-68.8
Asia	262	**13.3**	11.9-14.9
South/Central America	344	**17.5**	15.9-19.3
North America	48	**2.4**	1.8-3.2
Education level			
- University or college or equivalent	489	**24.9**	23.0-26.9
- Intermediate	193	**9.8**	8.5-11.2
- Secondary school	302	**15.4**	13.8-17.0
- Primary school or less	104	**5.3**	4.3-6.4
- Unknown	684	**34.8**	32.7-37.0
Maternal BMI (kg/m^2)			
BMI more than 30	418	**21.3**	19.5-23.2
BMI more than 35	160	**8.1**	7.0-9.4
Maternal addiction	70	**3.6**	2.8-4.5
- Drug	7	**0.4**	0.1-0.7
- Tobacco	64	**3.3**	2.5-4.1
- Alcohol	8	**0.4**	0.2-0.8

TABLE 1 (Continued)

	Pregnant women tested positive $n = 1964$		
	Median		IQR
Obstetrical history			
Nulliparous	640	**32.6**	30.5-34.7
Previous caesarean section	353	**18.0**	16.3-19.7
Medical history			
- Pulmonary	60	**3.1**	2.3-3.9
- Cardiac	28	**1.4**	0.9-2.1
- Hypertensive	53	**2.7**	2.0-3.5
- Diabetes	36	**1.8**	1.3-2.5
- Immunosuppression	12	**0.6**	0.3-1.1
- Neurological	17	**0.9**	0.5-1.4
- Digestive	23	**1.2**	0.7-1.8
- Renal	14	**0.7**	0.4-1.2
- Urological	5	**0.3**	0.1-0.6
- Oncological	12	**0.6**	0.3-1.1
- Thyroid imbalance	100	**5.1**	4.2-6.2
- Other	229	**11.7**	10.3-13.2
Previous pregnancy complications			
- Preeclampsia	39	**2.0**	1.4-2.7
- Intra uterine growth restriction	33	**1.7**	1.2-2.4
- Fetal malformation	16	**0.8**	0.5-1.3
- Preterm birth	34	**1.7**	1.2-2.4
- Postpartum haemorrhage	37	**1.9**	1.3-2.6
- Other	121	**6.2**	5.1-7.3
Ongoing pregnancy			
- Singletons	1902	**96.8**	96.0-97.6
Pregnancy condition (before exposure to the virus)			
- Preeclampsia	37	**1.9**	1.3-2.6
- Gestational diabetes	189	**9.6**	8.4-11.0
- Intra-uterine growth restriction	40	**2.0**	1.5-2.8
- Abnormal fetal Doppler	12	**0.6**	0.3-1.1
- Macrosomia	17	**0.9**	0.5-1.4
- Threatened preterm labour	32	**1.6**	1.1-2.3
- Placenta praevia	9	**0.5**	0.2-0.9
- PPROM	20	**1.0**	0.6-
- Other	174	**8.9**	7.6-10.2

Abbreviations: BMI, body mass index; IQR, interquartile range; PPROM, preterm premature rupture of membranes.

0.4–1.4) and HCQ (4.1%, 95% CI 2.6–6.0 *vs*. 0.1%, 95% CI 0.0–0.5) had a lower rate of reported use in the later period compared to the early one. The use of corticosteroids increased from 2.4% (95% CI 1.3–3.9) to 3.5% (95% CI 2.6–4.7) whereas anti-IL6 use was 0.5% (95% CI 0.1–1.5) *vs*. 0.1% (95% CI 0.0–0.5) during the early and late periods, respectively (Table 4).

A stratified analysis by severity of the disease is also reported in Table 4.

Corticosteroid use increased in the late pandemic period compared to the early period in level 2 (8/143; 5.6%; 95% CI 2.4–10.7 *vs*. 4/90; 1.1%; 95% CI 0.0–0.60), level 3 (19/37; 51.4%; 95% CI 34.4–68.1 *vs*. 2/24; 8.3%; 95% CI 1.0–27.0), level 4 (9/11; 81.8%; 95% CI 48.2–97.7 *vs*. 4/90; 1.1%; 95% CI 0.0–0.60), level 5 (10/17; 58.8%; 95% CI 32.9–81.6 *vs*. 5/9; 55.6%; 95% CI 21.2–86.3) and level 6 (1/3; 33.3%; 95% CI 0.8–90.6 *vs*. 1/4; 25.0%; 95% CI 0.6–80.6).

TABLE 2 COVID-19 medicines use in pregnant women tested positive for SARS-CoV-2

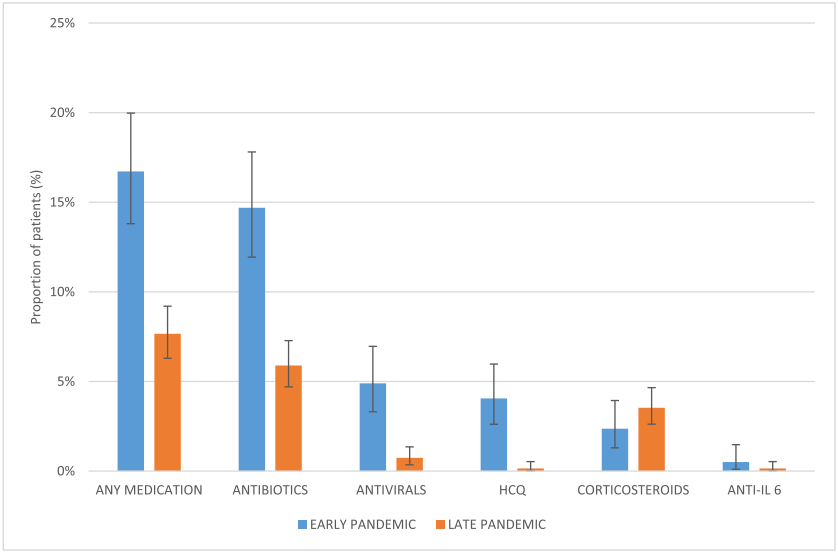
	Overall population *n* = 1964		
	n	**%**	**95% CI**
ANY MEDICATION	**205/1964**	**10.4**	**9.1–11.9**
ANTIBIOTICS	**169/1964**	**8.6**	**7.4–9.9**
Amoxicillin	18/169	10.7	6.4–16.3
Amoxicillin clavulanic acid	53/169	31.4	24.5–38.9
Ampicillin	11/169	6.5	3.3–11.3
Ampicillin sulbactam	2/169	1.2	0.1–4.2
Azithromycin	68/169	40.2	32.8–48.0
Cefalexin	1/169	0.6	0.0–3.3
Cefalotin	2/169	1.2	0.1–4.2
Cefazolin	5/169	3.0	1.0–6.8
Cefepime	11/169	6.5	3.3–11.3
Cefotaxime	13/169	7.7	4.2–12.8
Ceftazidime	3/169	1.8	0.4–5.1
Ceftriaxone	29/169	17.2	11.8–23.7
Cefuroxime	4/169	2.4	0.6–5.9
Ciprofloxacin	3/169	1.8	0.4–5.1
Clarithromycin	8/169	4.7	2.1–9.1
Clindamycin	6/169	3.6	1.3–7.6
Cloxacillin	1/169	0.6	0.0–3.3
Gentamicin	8/169	4.7	2.1–9.1
Imipenem cilastatin	2/169	1.2	0.1–4.2
Meropenem	5/169	3.0	1.0–6.8
Metronidazole	7/169	4.1	1.7–8.3
Moxifloxacin	1/169	0.6	0.0–3.3
Nitrofurantoïn	1/169	0.6	0.0–3.3
Piperacillin tazobactam	9/169	5.3	2.5–9.9
Pristinamycin	1/169	0.6	0.0–3.3
Rifamycin	1/169	0.6	0.0–3.3
Roxithromycin	2/169	1.2	0.1–4.2
Spiramycin	3/169	1.8	0.4–5.1
Teicoplanin	1/169	0.6	0.0–3.3
Vancomycin	8/169	4.7	2.1–9.1
ANTIVIRALS	**39/1964**	**2.0**	**1.4–2.7**
Atazanavir	1/39	2.6	0.1–13.5
Darunavir	1/39	2.6	0.1–13.5
Gancicolovir	1/39	2.6	0.1–13.5
Lopinavir	1/39	2.6	0.1–13.5
Lopinavir + ritonavir	13/39	33.3	19.1–50.2
Oseltamivir	13/39	33.3	19.1–50.2
Remdesivir	10/39	25.6	13.0–42.1
Ribavirin	1/39	2.6	0.1–13.5
Ritonavir	1/39	2.6	0.1–13.5
HCQ	**27/1964**	**1.4**	**0.9–2.0**
CORTICOSTEROIDS	**62/1964**	**3.2**	**2.4–4.0**
Dexamethasone	39/62	62.9	49.7–74.8

TABLE 2 (Continued)

	Overall population $n = 1964$		
	n	**%**	**95% CI**
Hydrocortisone	2/62	3.2	0.4–11.2
Methylprednisolone	12/62	19.4	10.4–31.4
Prednisolone	2/62	3.2	0.4–11.2
Prednisone	4/62	6.5	1.8–15.7
ANTI-IL6	**5/1964**	**0.3**	**0.1–0.6**
Tocilizumab	5/5	100.0	47.8–100
IMMUNIOGLOBULIN	**0/1964**	**0.0**	**0.0–0.2**

Abbreviations: ANTI-IL6, anti-interleukin 6; HCQ, hydroxychloroquine.

FIGURE 1 Medicine categories use between early and later pandemic period



4 | DISCUSSION

To our knowledge, this is one of the first studies to report use of COVID-19-related medicines among pregnant women who tested positive for SARS-CoV-2.[26] More than 10% of pregnant women in our study population used at least one COVID-19-related medicine. Antibiotics were the most prescribed medicine category (8.6%) followed by corticosteroids (3.2%), antivirals (2.0%), HCQ (1.4%) anti-IL6 (0.3%).

Despite the lack of robust safety and efficacy information for antivirals in pregnancy, 39 patients (2%) were exposed to this medicine category. Remdesivir, the only antiviral treatment recommended to be used for COVID-19 on a 'case by case' basis according to the NIH[22] and not recommended by the WHO,[23] was the third most frequently used antiviral, accounting for 25.6% (10/39) of antiviral use in our study. Lopinavir/ritonavir and oseltamivir, neither of which are recommended in the treatment of COVID-19 due to the lack of evidence of efficacy, were more frequently used. HCQ was initially suggested then no longer recommended for the treatment of COVID-19 due to the lack of benefit in severe COVID-19 and its potential cardiac toxicity in the general population. Still, 1.4% (27/1964) of patients received this medicine but mostly at the beginning of the pandemic (24/27) when the RECOVERY data were not yet known.[15]

COVID-19-related medicine use was similar among second and third trimester infections, with approximately 11% of women using at least one COVID-19-related medicine in each of these trimester infections. Medication use was lower in the first trimester infections, with 6.6% of patients using at least one COVID-19-related medicine. The first trimester is a challenging period as it is the period at risk of potential teratogenicity as this is the fetal organogenesis period, especially considering medications with scarce safety data (e.g., COVID-19 medicine). However, the disease severity level for first trimester infections was lower, and thus may not have required COVID-19 medicine use. Our results are limited to a small group of first trimester infections.

Recorded medicine use decreased over time. The recorded use of at least one COVID-19-related medicine overall, as well as antibiotics and antivirals, were significantly lower in the late period (July 2020–June 2021) compared to the early period of COVID-19. Use of corticosteroids increased in the late period (2.8%, 95% CI; 1.9–3.1 *vs.*

TABLE 3 COVID-19 related medicine use stratified by level of severity

	Asymptomatic $n = 381$			LEVEL 1 Outpatient management $n = 1233$			LEVEL 2 Hospitalized without O2 $n = 233$			LEVEL 3 Hospitalized with standard O2 $n = 61$		
	n	%	95% CI	*n*	%	95% CI	*n*	%	95% CI	*n*	%	95% CI
Any medication	12/381	3.1	1.6–5.4	52/1233	4.2	3.2–5.5	46/233	19.7	14.8–25.4	44/61	72.1	59.2–82.9
Antibiotics	11/381	2.9	1.4–5.1	47/1233	3.8	2.8–5.0	41/233	17.6	12.9–23.1	29/61	47.5	34.6–60.7
Antivirals	0/381	0.0	-	6/1233	0.5	0.2–1.1	9/233	3.9	1.8–7.2	8/61	13.1	5.8–24.2
HCQ	1/381	0.3	0.0–1.5	7/1233	0.6	0.2–1.2	6/233	2.6	1.0–5.5	5/61	8.2	2.7–18.1
Corticoids	0/381	0.0	-	2/1233	0.2	0.0–0.6	9/233	3.9	1.8–7.2	21/61	34.4	22.7–47.7
Anti-IL6	0/381	0.0	-	0/1233	0.0	-	0/233	0.0	-	0/61	0.0	-
Immunoglobulins	0/381	0.0	-	0/1233	0.0	-	0/233	0.0	-	0/61	0.0	-

Abbreviations: ANTI-IL6, anti-interleukin 6; O2, oxygen; High Flow O2, high flow oxygen canula and/or non-invasive ventilation; HCQ: hydroxychloroquine.
[a]Two patients died before ICU admission and one refused hospital admission.

TABLE 3 (Continued)

	LEVEL 4 High flow O2 $n = 23$			LEVEL 5 Mechanical ventilation $n = 26$			LEVEL 6 Maternal death[a] $n = 7$[a]		
	n	%	95% CI	*n*	%	95% CI	*n*	%	95% CI
Any medication	22/23	95.7	78.1–99.9	25/26	96.2	80.4–99.9	4/7	57.1	18.4–90.1
Antibiotics	14/23	60.9	38.5–e80.3	24/26	92.3	74.9–99.1	3/7	42.9	9.9–81.6
Antivirals	7/23	30.4	13.2–52.9	6/26	23.1	9.0–43.6	3/7	42.9	9.9–81.6
HCQ	4/23	17.4	5.0–38.8	3/26	11.5	2.4–30.2	1/7	14.3	0.4–57.9
Corticoids	13/23	56.5	34.5–76.8	15/26	57.7	36.9–76.6	2/7	28.6	3.7–71.0
Anti-IL6	2/23	8.7	1.1–28.0	2/26	7.7	0.9–25.1	1/7	14.3	0.4–57.9
Immunoglobulins	0/23	0.0	-	0/26	0.0	-	0/7	0.0	-

Abbreviations: ANTI-IL6, anti-interleukin 6; O2, oxygen; High Flow O2, high flow oxygen canula and/or non-invasive ventilation; HCQ: hydroxychloroquine.
[a]Two patients died before ICU admission and one refused hospital admission.

TABLE 4 Medicine use comparing early to later period after beginning of the COVID-19 pandemic

		EARLY PANDEMIC $n = 592$			LATE PANDEMIC $n = 1358$		
		n	Proportion	95% CI	*n*	Proportion	95% CI
TOTAL		**592**	**100.0%**		**1358**	**100.0%**	
	Any medication	99/592	16.7%	13.8–20.0	104/1358	7.7%	6.3–9.2
	Antibiotics	87/592	14.7%	11.9–17.8	80/1358	5.9%	4.7–7.3
	Antivirals	29/592	4.9%	3.3–7.0	10/1358	0.7%	0.4–1.4
	HCQ	24/592	4.1%	2.6–6.0	2/1358	0.1%	0.0–0.5
	Corticoids	14/592	2.4%	1.3–3.9	48/1358	3.5%	2.6–4.7
	Anti-IL6	3/592	0.5%	0.1–1.5	2/1358	0.1%	0.0–0.5
	Immunoglobulin	0/592	0.0%	-	0/1358	0.0%	-
LEVEL 0		**87**	**14.7%**		**293**	**21.6%**	
	Any medication	5/87	5.7%	1.9–12.9	7/293	2.4%	1.0–4.9
	Antibiotics	4/87	4.6%	1.3–11.4	7/293	2.4%	1.0–4.9
	Antivirals	0/87	0.0%	-	0/293	0.0%	-
	HCQ	1/87	1.1%	0.0–6.2	0/293	0.0%	-
	Corticoids	0/87	0.0%	-	0/293	0.0%	-
	Anti-IL6	0/87	0.0%	-	0/293	0.0%	-
	Immunoglobulin	0/87	0.0%	-	0/293	0.0%	-
LEVEL 1		**367**	**62.0%**		**853**	**62.8%**	
	Any medication	27/367	7.4%	4.9–10.5	23/853	2.7%	1.7–4.0
	Antibiotics	25/367	6.8%	4.5–9.9	20/853	2.3%	1.4–3.6
	Antivirals	4/367	1.1%	0.3–2.8	2/853	0.2%	0.0–0.8
	HCQ	4/367	1.1%	0.3–2.8	2/853	0.2%	0.0–0.8
	Corticoids	1/367	0.3%	0.0–1.5	1/853	0.1%	0.0–0.7
	Anti-IL6	0/367	0.0%	-	0/853	0.0%	-
	Immunoglobulin	0/367	0.0%	-	0/853	0.0%	-
LEVEL 2		**90**	**15.2%**		**143**	**10.5%**	
	Any medication	25/90	27.8%	18.9–38.2	21/143	14.7%	9.3–21.6
	Antibiotics	23/90	25.6%	16.9–35.8	18/143	12.6%	7.6–19.2
	Antivirals	8/90	8.9%	3.9–16.8	1/143	0.7%	0.0–3.8
	HCQ	6/90	6.7%	2.5–13.9	0/143	0.0%	-
	Corticoids	1/90	1.1%	0.0–6.0	8/143	5.6%	2.4–10.7
	Anti-IL6	0/90	0.0%	-	0/143	0.0%	-
	Immunoglobulin	0/90	0.0%	-	0/143	0.0%	-
LEVEL 3		**24**	**4.1%**		**37**	**2.7%**	
	Any medication	19/24	79.2%	57.8–92.9	25/37	67.6%	50.2–82.0
	Antibiotics	15/24	62.5%	40.6–81.2	14/37	37.8%	22.5–55.2
	Antivirals	5/24	20.8%	7.1–42.2	3/37	8.1%	1.7–21.9
	HCQ	5/24	20.8%	7.1–42.2	0/37	0.0%	-
	Corticoids	2/24	8.3%	1.0–27.0	19/37	51.4%	34.4–68.1
	Anti-IL6	0/24	0.0%	-	0/37	0.0%	-
	Immunoglobulin	0/24	0.0%	-	0/37	0.0%	-
LEVEL 4		**12**	**2.0%**		**11**	**0.8%**	
	Any medication	12/12	100.0%	73.5–100.0	10/11	90.9%	58.7–99.8
	Antibiotics	10/12	83.3%	51.6–97.9	4/11	36.4%	10.9–69.2
	Antivirals	6/12	50.0%	21.1–78.9	1/11	9.1%	0.2–41.3
	HCQ	4/12	33.3%	9.9–65.1	0/11	0.0%	-

(Continues)

TABLE 4 (Continued)

		EARLY PANDEMIC $n = 592$			LATE PANDEMIC $n = 1358$		
		n	Proportion	95% CI	*n*	Proportion	95% CI
	Corticoids	4/12	33.3%	9.9–65.1	9/11	81.8%	48.2–97.7
	Anti-IL6	2/12	16.7%	2.1–48.4	0/11	0.0%	-
	Immunoglobulin	0/12	0.0%	-	0/11	0.0%	-
LEVEL 5		**9**	**1.5%**		**17**	**1.3%**	
	Any medication	8/9	88.9%	51.8–99.7	17/17	100.0%	80.5–100.0
	Antibiotics	8/9	88.9%	51.8–99.7	16/17	94.1%	71.3–99.9
	Antivirals	3/9	33.3%	7.5–70.1	3/17	17.6%	3.8–43.4
	HCQ	3/9	33.3%	7.5–70.1	0/17	0.0%	-
	Corticoids	5/9	55.6%	21.2–86.3	10/17	58.8%	32.9–81.6
	Anti-IL6	0/9	0.0%	-	2/17	11.8%	1.5–36.4
	Immunoglobulin	0/9	0.0%	-	0/17	0.0%	-
LEVEL 6		**4**	**0.7%**		**3**	**0.2%**	
	Any medication	3/4	75.0%	19.4–99.4	1/3	33.3%	0.8–90.6
	Antibiotics	2/4	50.0%	6.8–93.2	1/3	33.3%	0.8–90.6
	Antivirals	3/4	75.0%	19.4–99.4	0/3	0.0%	-
	HCQ	1/4	25.0%	0.6–80.6	0/3	0.0%	-
	Corticoids	1/4	25.0%	0.6–80.6	1/3	33.3%	0.8–90.6
	Anti-IL6	1/4	25.0%	0.6–80.6	0/3	0.0%	-
	Immunoglobulin	0/4	0.0%	-	0/3	0.0%	-

Note: Severity levels are defined as: Level (0) Asymptomatic patients, (1) Mild to moderate illness, not hospitalized, (2) Hospitalized patient without oxygen support, (3) Hospitalized patient requiring standard oxygen support, (4) High flow oxygen support requirement (including high flow cannula and non-invasive ventilation), (5) Mechanical ventilation requirement and (6) Maternal death.
Abbreviations: HCQ, hydroxychloroquine; ANTI-IL6, anti-interleukin 6.

3.9%, 95% CI; 2.6–5.5) especially in the level 2 and more severe cases (Table 4). These results are consistent with data from the hospitalized general population in the United States, where hydroxychloroquine use decreased and corticosteroid use increased over time.[27] This reflects the accumulating evidence supporting corticosteroids, especially dexamethasone, as a beneficial and safe treatment for second phase COVID-19, which is now clearly recommended in official guidelines for patients requiring oxygen support.[22,28] In our study, corticosteroid use was reported in the majority of patients who required oxygen support, which is consistent with current guidelines.[22,28] Use of medicines stratified by maternal infection severity level shows that medicine use increased with the severity of the disease, from 3.1% in asymptomatic patients to 96.4% of patients requiring mechanical ventilation exposed to at least one COVID-19-related medicine. The SARS-CoV-2 delta variant has been reported to increase severity in pregnant women.[29] However, it is unlikely that this factor influenced COVID-19-related medicine use over time as no patient was tested positive during the delta variant predominant period in our study (data extracted from GISAID).[30]

Some limitations of our study should be considered. First, we did not report on other medicines administered to prevent COVID-19 complications, such as antithrombotic medicines, as these were not indicated at the beginning of the pandemic and therefore not systematically recorded in the registry. Prophylactic anticoagulation is recommended in pregnant women hospitalized for COVID-19 but with a low evidence rating.[31] The CONSIGN work package 1 is currently analysing antithrombotic treatment for COVID-19 in pregnancy.[32]

Second, a selection bias towards symptomatic patients cannot be excluded as different strategies have been adopted by centres such as universal screening at admission, symptom-based testing or contact to a positive case history testing. These different strategies have also changed over time as available resources and sanitary situation have changed, which possibly affects the recruitment of patients. Routine systematic screening was not always possible, thereby preventing the recruitment of all asymptomatic positive patients and leading to a possible overestimation of symptomatic patients, more likely to receive a COVID-19-related medicine. Unfortunately, we did not have access to the different testing strategies adopted in every institution participating in the study. Mild to moderate COVID-19 patients were also more likely to be managed in the outpatient setting without reaching a hospital participating in the study. This selection bias might have overestimated the use of COVID-19 medicines. Similarly, severely affected patients were very likely to be tested for SARS-CoV-2 and included in the study. Additionally, COVID-19-related medicine use

differed across geographical regions, potentially due to different local protocols for screening and/or patient management. Third, due to its design, this study cannot estimate the safety and efficacy of COVID-19-related medicines among pregnant women and this needs to be urgently assessed in this population at high risk from severe COVID-19.

This study brought evidence that pregnant women were not spared from the COVID-19 pandemic and specific recommendations regarding pregnancy were crucial in this public health crisis situation. Lessons learned from this pandemic should support the development of rapid clinical practice guidelines specific to this special population in the future.[33]

5 | CONCLUSION

Medicine use in pregnant women was low but increased with the levels of severity of symptoms. The observed decrease in use of medicines that were not recommended for the treatment of COVID-19 after the publication of the first scientific evidence (e.g., antivirals, hydroxychloroquine) and the tendency for an increased use of corticosteroids seem to be aligned with the evolution of guidelines. Finally, there is a large lack of evidence regarding the effectiveness and safety of COVID-19-related medicines in pregnant women, which calls for further and large studies in different settings that are able to stratify by severity.

COVIPREG group

Eran Hadar, Rabin Medical Center, Helen Schneider Hospital for Women and the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; Anna Goncé, Karen Castillo and Eduard Gratacós, Maternal-Fetal Medicine Department. BCNatal—Fetal Medicine Research Center (Hospital Clínic and Hospital Sant Joan de Déu), Universitat de Barcelona, Barcelona, Spain; Christophe Poncelet, Service de Gynécologie-Obstétrique, Centre Hospitalier René Dubos, Pontoise, France; Fernanda Surita, Amanda Dantas-Silva, Adriana Luz, Carolina Ribeiro-do-Valle and Carolina Borrelli, Department of Obstetrics and Gynecology, State University of Campinas, Campinas, Brazil; Thibaud Quibel, Department of Obstetrics, Maternité Poissy Saint Germain, Poissy, France; Begoña Martinez de Tejada, Sonia Campelo and Véronique Othenin-Girard, Obstetrics Division, Department of Pediatrics, Gynecology, and Obstetrics, Geneva University Hospitals, Geneva, Switzerland; Najeh Hcini and Veronique Lambert, West French Guiana Hospital Center, University of French Guiana, Saint Laurent du Maroni, French Guiana; Leonhard Schäffer and Anett Hernadi, Division of Obstetrics, Baden Cantonal Hospital, Baden, Switzerland; Albaro José Nieto-Calvache, Stiven Ernesto Sinisterra-Díaz, Juliana Maya, Paola Marsela Pérez and Adriana Messa Bryon, Fundación Valle del Lili, Cali, Colombia; Marco de Santis and Carmen de Luca, Telefono Rosso, Teratology Information Service, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; Adolfo Etchegaray and Juliana Moren, Fetal Medicine Unit, Hospital Universitario Austral, Pilar, Buenos Aires, Argentina; Sayed Hamid Mousavi, Shohra Qaderi and Mohammad Delsoz, Department of Research, Afghanistan National Charity Organization for Special Diseases (ANCOSD), Kabul, Afghanistan; Beatrice Eggel, Obstetrics and Gynecology Unit, Sion Hospital, Sion, Switzerland; Michael Geary, Jennifer Donnelly, Maria Kennelly, Fadi-Tamas Salameh, Claire McCarthy and Brian Cleary, Department of Obstetrics and Gynaecology, Rotunda Hospital, Dublin, Ireland and Department of Pharmacy, Rotunda Hospital, Dublin, Ireland; Romina Capoccia Brugger, Département de gynécologie-obstétrique, RHNE, Neuchâtel, Switzerland; Albert Ko, Uma Reddy and Olga Grechukhina, Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, United States; Javiera Fuenzalida and Jorge Carvajal, Maternal-Fetal Medicine, Department of Obstetrics, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile; Johann Silke, Department of Gynecology and Obstetrics, Hospital of the Upper Valais, Visp, Switzerland; Daniel Surbek, Anda-Petronela Radan and Luigi Raio, Department of Obstetrics and Feto-maternal Medicine, University Hospital of Bern, University of Bern, Bern, Switzerland; Monya Todesco Bernasconi and Mirjam Moser, Department of Obstetrics, Cantonal Hospital Aarau, Aarau, Switzerland; Jan Deprest and Jute Richter, Department of Obstetrics and Gynecology, University Hospitals Leuven, Leuven, Belgium; Pedro Viana Pinto and Marina Moucho, Department of Obstetrics, S. João University Hospitalar Center, Porto, Portugal; Johana Sichitiu, Yves Ville, Laurent Salomon and Julien Stirnemann, Necker-Enfants Malades Hospitals, Department of Obstetrics, Paris, France; Augusto Rojas Martinez, Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, Mexico; Karina Krajden Haratz, Division of Ultrasound in Obstetrics and Gynecology, Lis Maternity Hospital, Tel Aviv, Israel; Gustavo Malinger, Division of Ultrasound in Obstetrics and Gynecology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; Ann-Christin Tallarek and Kurt Hecher, Department of Obstetrics and Prenatal Medicine, University Hospital Hamburg Eppendorf, Hamburg, Germany; Lavinia Schuler-Faccini, Maria Teresa Vieira Sanseverino and Mariana Horn Scherer, Departamento de Genética, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; Maria Celeste Osorio Wender and Maria Lucia Da Rocha Oppermann, Maternity Ward, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; Betania Bohrer, and Luciana Friedrich, Pediatra e Neonatologista, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; Camilia Giuliani, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; Mary F. Higgins, UCD Perinatal Research Centre, Obstetrics and Gynaecology, National Maternity Hospital, Dublin, Ireland; Andrea Papadia, Maria Luisa Gasparri, Antonilli Morena, Christian Polli and Edoardo Taddei, Department of Gynecology and Obstetrics Ente Ospedaliero Cantonale, Lugano, Switzerland; Karin Nielsen-Saines, Mary Catherine Cambou, Rashmi Rao, Thalia Mok and Viviana Fajardo, Department of Pediatrics, Division of Infectious Diseases, David Geffen UCLA School of Medicine, Los Angeles, United States;

Nicolas Mottet, Department of Obstetrics and Gynecology, Besançon University Hospital, Besançon, France; Charles Garabedian and Louise Ghesquiere, CHU Lille, Department of Obstetrics, Lille, France; Christian R. Kahlert and Tina Fischer, Infectious Diseases and Hospital Epidemiology, Children's Hospital of Eastern Switzerland, St. Gallen, Switzerland; Claudia Grawe, Department of Obstetrics, Gynecology Stadtspital Triemli Zürich, Zurich, Switzerland; Cora Alexandra Voekt, Department of Obstetrics, Grabs Hospital, Grabs, Switzerland; Sophie Defert and Jérôme Dimet, Department of Gynecology, Mont-de-Marsan Hospital, Mont-de-Marsan, France; Paul Böckenhoff and Brigitte Strizek, Department of Obstetrics and Prenatal Medicine, University Hospital Bonn, Bonn, Germany; Loïc Sentilhes, Amaury Brot, Aurélien Mattuizzi and Clémence Houssin, Department of Obstetrics and Gynecology, Bordeaux University Hospital, Bordeaux, France; Dirk Bassler, Department of Obstetrics, University Hospital Zurich and Neonatal Department, University of Zurich, Zurich, Switzerland; Brigitte Weber, Department of Obstetrics and Gynecology, Obwald Cantonal Hospital, Sarnen, Switzerland; Marie-Claude Rossier, Department of Obstetrics and Gynecology, Hospital Riviera Chablais, Rennaz, Switzerland; Jérôme Mathis, Edouard Ha and Caroline Eggemann, Department of Obstetrics and Gynecology, Centre hospitalier Bienne, Bienne, Switzerland; Andrea Bloch, Obstetrics and Gynecology Unit, Hopital du Jura, Delemont, Switzerland; Roberta Netto, Department of Anesthesia, Intensive Care, and Out-of-Hospital Emergency, AUSL Aosta, Aosta, Italy; Martin Kaufmann, Department of Obstetrics, Spital Bülach, Bülach, Switzerland; Otto Henrique May Feuerschuette, Departamento de Ginecologia e Obstetrícia, Hospital Universitário Polydoro Ernani de São Thiago, HU-UFSC, Florianópolis, Brazil; Bénédicte Breton, Department of Obstetrics and Gynecology, Annecy Genevois Hospital Centre, Annecy, France; Arnaud Toussaint, Department of Gynecology and Obstetrics, Intercantonal Hospital of Broye, Payerne, Switzerland; Renato Augusto Moreira de Sa, Maternal and Infant Department, Federal Fluminense University, Clinical Research Department, Fernandes Figueira Institut - FIOCRUZ, Perinatal Rede D'or, Rio de Janeiro, Brazil; Mohamed Elbahnasawy and Sherief Abd-Elsalam, Emergency Medicine and Traumatology Department, Tanta University Faculty of Medicine, Tanta, Egypt; Guillaume Ducarme, Department of Obstetrics and Gynecology, Centre Hospitalier Departemental de Vendée, La-Roche-sur-Yon, France; Hélène Pelerin, Clinical Research Department, Centre Hospitalier Départemental de Vendée, La-Roche-sur-Yon, France; Ahmed Nafea, Shatby Hospital for Gynecology and Obstetrics, Alexandria, Egypt; Gaetan Plantefeve, Cecile Le Parco and Mohamed Derouich, Victor Dupouy Hospital, Argenteuil, France; Anis Feki and Gaston Grant, Département de gynécologie et obstétrique-HFR, Fribourg, Switzerland; Ina Hoffmann, Department of Obstetrics and Gynecology, Olten Cantonal Hospital, Olten, Switzerland; Kathryn Denize, Ottawa Hospital Research Institute, Ottawa, Canada; Manuel Guerra Canales, Medicina Materno Fetal, Hospital San José, Santiago, Chile; Carina Britschgi and Panagiotis Kanellos, Department of Gynecology and Obstetrics, Kantonal Hospital of Uri, Altdorf, Switzerland; Elke Barbara Prentl and Jessica Maisel, Department of Obstetrics and Gynecology, Winterthur Cantonal Hospital, Winterthur, Switzerland; Irene Hoesli and Cécile Monod, Department of Obstetrics, Basel, University Hospital, Basel, Switzerland; Grit Vetter and Brigitte Frey Tirri, Department of Obstetrics, Kantonsspital Baselland, Liestal, Switzerland; Carolin Blume and Stylianos Kalimeris, Kantonsspital Graubünden, Frauenklinik Fontana, Chur, Switzerland; Anne-Claude Muller Brochut, GynEcho private practice, Fribourg, Switzerland; Lucie Sedille, Department of Obstetrics and Gynecology, La Rochelle Hospital, La Rochelle, France; Inês Martins and Diogo Ayres dos Camps, Department of Obstetrics, Gynecology and Reproductive Medicine, Santa Maria University Hospital, Lisbon, Portugal; Michel Boulvain, Pôle Department of Gynecology and Obstetrics, GHOL Hôpital de Nyon, Nyon, Switzerland; Steffi Leu, Department of Obstetrics and Gynecology, Nidwald Cantonal Hospital, Stans, Switzerland; Kathrin Bütikofer, Department of Obstetrics and Gynecology, Olten Cantonal Hospital, Olten, Switzerland; Lisandra Stein Bernardes, Cristina Nunes dos Santos, Bruna Hipólito Micheletti, Jéssica Mosello, and Natálya Gonçalves Pereira, Department of Obstetrics and Neonatology, São Paulo University, São Paulo, Brazil; Stefanie Sturm, Frauenpraxis Schaffhausen, Schaffhausen, Switzerland; Manggala Pasca Wardhana, Obstetrics and Gynecology Department, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo Academic General Hospital, Surabaya, Indonesia; Irida Dajti, Department of Obstetrics Gynecology "Koco Gliozheni" University Hospital, Tirana, Albania; Feras Al Kharouf, Department of Obstetrics and Gynecology, King Abdulaziz Medical City, Ministry of National Guard-health Affairs, Riyad, Saudi Arabia; Chloé Moreau, Clinical Research Department, Centre Hospitalier Départemental de Vendée, La-Roche-sur-Yon, France; Mingzhu Yin, Hunan Engineering Research Center of Gynecology and Obstetrics Disease, Xiangya Hospital, Chansha, China; Annina Haessig, Department of Obstetrics and Gynecology, Zuger Kantonsspital, Zug, Switzerland; Sandrine Ackermann, Masset & Ackermann private practice, Prilly, Switzerland; Olivia Hernandez, Hospital Felix Bulnes Cerda, Santiago, Chile; Karoline Aebi-Popp, Department of Infectious Diseases, University Hospital Bern, Bern, Switzerland; Sophie Masmejan and Karine Lepigeon, Materno-fetal and Obstetrics Research Unit, Department "Femme-Mère-Enfant", University Hospital, Lausanne, Switzerland; Eric Giannoni, Clinic of Neonatology, Department Mother-Woman-Child, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

ACKNOWLEDGEMENTS

We greatly thank Dr. Hilde Engjom from the Department of Mental and Physical Health, Norwegian Institute of Public Health, Bergen, Norway, for her contribution in the discussions within the CONSIGN group. We thank every patient who agreed to participate in this study.

COMPETING INTERESTS

The authors declare no conflict of interest.

CONTRIBUTORS

G.F., L.P., D.B. and A.P. conceived and designed the study. G.F., E.M., M.S. and A.P. analysed the data. All authors interpreted the data.

G.F. and E.G. drafted the manuscript. E.M., M.S. and A.P. critically revised the manuscript. A.P. provided supervision and mentorship. The COVI-PREG group contributed to data collection. Each author made a contribution in reviewing the manuscript drafting or revision and accepts accountability for the overall work. All authors approved the final version of the report.

DATA AVAILABILITY STATEMENT

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

ORCID

Guillaume Favre https://orcid.org/0000-0001-6181-3126
Alice Panchaud https://orcid.org/0000-0001-6086-2401

REFERENCES

1. Favre G, Pomar L, Baud D. Coronavirus disease 2019 during pregnancy: do not underestimate the risk of maternal adverse outcomes. *Am J Obstet Gynecol MFM*. 2020;2(3):100160. doi:10.1016/j.ajogmf.2020.100160
2. Vouga M, Favre G, Martinez-Perez O, et al. Maternal outcomes and risk factors for COVID-19 severity among pregnant women. *Sci Rep*. 2021;11(1):13898. doi:10.1038/s41598-021-92357-y
3. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. 2020;370:m3320. doi:10.1136/bmj.m3320
4. Villar J, Ariff S, Gunier RB, et al. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: the INTERCOVID Multinational Cohort Study. *JAMA Pediatr*. 2021;175(8):817-826. doi:10.1001/jamapediatrics.2021.1050
5. Sankaran D, Nakra N, Cheema R, Blumberg D, Lakshminrusimha S. Perinatal SARS-CoV-2 infection and neonatal COVID-19: a 2021 update. *Neoreviews*. 2021;22(5):e284-e295. doi:10.1542/neo.22-5-e1001
6. Favre G, Mazzetti S, Gengler C, et al. Decreased fetal movements: a sign of placental SARS-CoV-2 infection with perinatal brain injury. *Viruses*. 2021;13(12):2517. doi:10.3390/v13122517
7. Baud D, Greub G, Favre G, et al. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. *JAMA*. 2020;323(21):2198-2200. doi:10.1001/jama.2020.7233
8. European Medicines Agency. COVID-19 treatments: authorised. 2021. ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-covid-19/covid-19-treatments-authorised. Accessed July 1, 2021.
9. Favre G, Pomar L, Qi X, Nielsen-Saines K, Musso D, Baud D. Guidelines for pregnant women with suspected SARS-CoV-2 infection. *Lancet Infect Dis*. 2020;20(6):652-653. doi:10.1016/S1473-3099(20)30157-2
10. Dashraath P, Nielsen-Saines K, Madhi SA, Baud D. COVID-19 vaccines and neglected pregnancy. *Lancet*. 2020;396(10252):e22. doi:10.1016/S0140-6736(20)31822-5
11. Jiménez-Lozano I, Caro-Teller JM, Fernández-Hidalgo N, et al. Safety of tocilizumab in COVID-19 pregnant women and their newborn: a retrospective study. *J Clin Pharm Ther*. 2021;46(4):1062-1070. doi:10.1111/jcpt.13394
12. Burwick RM, Yawetz S, Stephenson KE, et al. Compassionate use of remdesivir in pregnant women with severe Covid-19. *Clin Infect Dis*. 73(11):e3996-e4004. doi:10.1093/cid/ciaa1466
13. Committee on Obstetric Practice. Committee Opinion No. 713: antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol*. 2017;130(2):e102-e109. doi:10.1097/AOG.0000000000002237
14. Bandoli G, Palmsten K, Forbess Smith CJ, Chambers CD. A review of systemic corticosteroid use in pregnancy and the risk of select pregnancy and birth outcomes. *Rheum Dis Clin North Am*. 2017;43(3):489-502. doi:10.1016/j.rdc.2017.04.013
15. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704. doi:10.1056/NEJMoa2021436
16. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19—RECOVERY Trial. recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19. Accessed February 17, 2022.
17. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French Perinatal Cohort Study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. doi:10.1371/journal.pmed.1001635
18. Andersson NW, Skov L, Andersen JT. Fetal safety of chloroquine and hydroxychloroquine use during pregnancy: a nationwide cohort study. *Rheumatology*. 2021;60(5):2317-2326. doi:10.1093/rheumatology/keaa592
19. Huybrechts KF, Bateman BT, Zhu Y, et al. Hydroxychloroquine early in pregnancy and risk of birth defects. *Am J Obstet Gynecol*. 2021;224(3):290.e1-290.e22. doi:10.1016/j.ajog.2020.09.007
20. Nicolas P, Maia MF, Bassat Q, et al. Safety of oral ivermectin during pregnancy: a systematic review and meta-analysis. *Lancet Glob Health*. 2020;8(1):e92-e100. doi:10.1016/S2214-109X(19)30453-X
21. Taylor-Cousar JL, Jain R, Kazmerski TM, et al. Concerns regarding the safety of azithromycin in pregnancy—relevance for women with cystic fibrosis. *J Cyst Fibros*. 2021;20(3):395-396. doi:10.1016/j.jcf.2020.08.003
22. Clinical Management Summary. COVID-19 Treatment Guidelines. covid19treatmentguidelines.nih.gov/management/clinical-management/clinical-management-summary/. Accessed September 22, 2021.
23. Therapeutics and COVID-19: living guideline. who.int/publications-detail-redirect/WHO-2019-nCoV-therapeutics-2022.1. Accessed January 18, 2022.
24. Panchaud A, Favre G, Pomar L, et al. An international registry for emergent pathogens and pregnancy. *Lancet*. 2020;395(10235):1483-1484. doi:10.1016/S0140-6736(20)30981-8
25. Guidelines Archive. COVID-19 Treatment Guidelines. covid19treatmentguidelines.nih.gov/about-the-guidelines/guidelines-archive/. Accessed January 18, 2022.
26. Giesbers S, Goh E, Kew T, et al. Treatment of COVID-19 in pregnant women: a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2021;267:120-128. doi:10.1016/j.ejogrb.2021.10.007
27. Best JH, Kong AM, Kaplan-Lewis E, et al. Treatment patterns in US patients hospitalized with COVID-19 and pulmonary involvement. *J Med Virol*. 2021;93(9):5367-5375. doi:10.1002/jmv.27049
28. WHO. Corticosteroids for COVID-19. 2020. who.int/publications-detail-redirect/WHO-2019-nCoV-Corticosteroids-2020.1. Accessed November 4, 2021.
29. Adhikari EH, MacDonald L, SoRelle JA, Morse J, Pruszynski J, Spong CY. COVID-19 cases and disease severity in pregnancy and neonatal positivity associated with delta (B.1.617.2) and omicron (B.1.1.529) variant predominance. *JAMA*. 2022;327(15):1500-1502. doi:10.1001/jama.2022.4356
30. Khare S, Gurry C, Freitas L, et al. GISAID's role in pandemic response. *China CDC Wkly*. 2021;3(49):1049-1051. doi:10.46234/ccdcw2021.255

31. Antithrombotic Therapy. COVID-19 treatment guidelines. covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy/. Accessed September 23, 2021.
32. Sturkenboom M, Nordeng H, Klungel O, et al. Description of international collaboration in the area of medicines use and effects in COVID-19 affected pregnancies. Published online August 17, 2021. 10.5281/zenodo.5211395
33. Kowalski SC, Morgan RL, Falavigna M, et al. Development of rapid guidelines: 1. Systematic survey of current practices and methods. *Health Res Policy Syst*. 2018;16(1):61. doi:10.1186/s12961-018-0327-8

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Favre G, Gerbier E, Maisonneuve E, et al. COVID-19-related medicine utilization study in pregnancy: The COVI-PREG cohort. *Br J Clin Pharmacol*. 2023; 89(5):1560-1574. doi:10.1111/bcp.15611

Improving data collection in pregnancy safety studies: Towards standardisation of data elements in pregnancy reports from public and private partners, a contribution from the ConcePTION project.

Favre G[1&2]., Richardson J.L.[3&4], Moore A[5]., Geissbühler Y.[5], Jehl V.[5], Oliver A.[3], Shechtman S.[6], Diav-Citrin O[6]., Berlin M[7]., De Haan T[7]., Baud D[2], Panchaud A[8&9], Mor A.[10], Sabidó M.[11], de Souza S.[11], Chambers C.[12], van Rijt-Weetink, Y.R.J.[13], van Puijenbroek E.P.[13], Yates L.M.[14&15], Stellfeld M.[16**], Winterfeld U.[1**]

1. Swiss Teratology Information Service and Clinical Pharmacology Service, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
2. Materno-fetal and Obstetrics Research Unit, Department "Femme-Mère-Enfant", Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
3. UK Teratology Information Service, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom.
4. Institute of Health and Society, Newcastle upon Tyne, United Kingdom.
5. Novartis Pharma AG, Basel, Switzerland.
6. The Israeli Teratology Information Service, Ministry of Health, Jerusalem, Israel.
7. Clinical Pharmacology and Toxicology Unit, Drug Consultation Center, Shamir Medical Center (Assaf Harofeh), Zerifin TIS, affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.
8. Institute of Primary Health Care (BIHAM), University of Bern, Switzerland
9. Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
10. Epidemiology and Benefit Risk, Sanofi, North York, Ontario, Canada.
11. Merck Healthcare KGaA, Darmstadt, Germany.
12. University of California San Diego, and Organization of Teratology Information Specialists (OTIS)
13. Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands.
14. Northern Genetics Service, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK
15. KRISP, University of KwaZulu-Natal, South Africa
16. Novo Nordisk A/S, Søborg, Denmark.

** contributed equally

Abstract

Introduction:

The ConcePTION project aims to improve the way medication use during pregnancy is currently studied. This includes exploring the possibility of developing a distributed data processing and analysis infrastructure using a Common Data Model which could form a foundational platform for future surveillance and research. A prerequisite would be that data from various Data Access Providers (DAPs) can be harmonized according to an agreed set of standard rules concerning the structure and content of the data. To do so, a reference framework of Core Data Elements (CDEs) recommended for primary data studies on drug safety during pregnancy was previously developed. The aim of this study was to assess the ability of different public and private DAPs using different types of primary data sources focusing on multiple sclerosis, as a pilot, to align their data collection variables and definitions with the CDE recommendations framework.

Methods:

Four pregnancy registries (Gilenya, Novartis; Aubagio, Sanofi; the Organization of Teratology Information Specialists, OTIS; Aubagio, Sanofi; the Dutch Pregnancy Drug Register, Lareb), two enhanced pharmacovigilance programs (Gilenya PRIM, Novartis; MAPLE-MS, Merck Healthcare KGaA) and four Teratology Information Services (UK TIS, Jerusalem TIS, Zerifin TIS, Swiss TIS) participated in the study. The ConcePTION primary data source CDE includes 51 items covering administrative functions, the description of pregnancy, medical history, maternal illnesses arising in pregnancy, delivery details, pregnancy and infant outcomes. For each variable in the CDE, the DAPs identified whether their variables were: identical to the one mentioned in the CDE; derived; similar but with divergent definition; not available.

Results:

The majority of the DAP's data variables were either directly taken (85%, n=305/357, ranging from 73 to 94% between DAPs) or derived by combining different variables (12%, n= 42/357, ranging from 0 to 24% between DAPs) to conform to the CDE variables and definitions. For very few of the DAPs variables, alignment with the CDE items was not possible, either because of divergent definitions (1%, n=3/357, ranging from 0 to 2% between DAPs), or because the variables were not available (2%, n=7/357, ranging from 0 to 4% between DAPs).

Conclusion:

DAPs participating in this study presented a very high proportion of variables matching the CDE items, indicating that alignment of definitions and harmonisation of data analysis by different stakeholders to accelerate and strengthen pregnancy pharmacovigilance safety data analyses could be feasible.

Introduction

More than 5 million women become pregnant in the European union every year and the majority take at least one medication during pregnancy.[1] However, few medications have been adequately monitored for safety and labelled for use in pregnant women and it takes an estimated mean time of 27 years after commercialisation to determine the reproductive risk profile of a medication[2].

Clinical evidence on the efficacy and safety of medications for the general population is generally provided by randomized clinical trials. Since pregnant women are usually not included in clinical trials, these rarely provide information on the benefit/risk of medication use during pregnancy.[3] As such, data from post-marketing observational studies are generally required to fill the evidence gap. Primary source data collection methods are commonly used where information about medication exposure and pregnancy outcome is collected directly from pregnant women and/or their healthcare providers. Whilst numerous longstanding datasets from both public and private partners exist, these activities have operated in silos, with considerable perceived heterogeneity in data collection methods. Combining and/or comparing research results on medication safety in pregnancy - whether comparing between studies of the same medication, or between medications for the same disease - is also complicated by heterogeneity in the identification and the definitions of key data elements.[4] This heterogeneity impedes the ability to rapidly combine raw data and/or to assimilate the evidence generated from different studies in order to decrease the time taken to provide reliable conclusions about the safety of medication in pregnancy.[5] These challenges have been identified since the 90s and remain unresolved.[6]

The ConcePTION project aims to challenge and improve the way drug use during pregnancy is studied. This includes exploring the possibility of developing a distributed data processing and analysis infrastructure using a Common Data Model (CDM) which could form a foundational platform for future surveillance and research. A prerequisite would be that data from the various Data Access Providers (DAPs) can be harmonised according to an agreed set of standard rules concerning the structure and content of the data. A reference framework of Core Data Elements (CDEs) recommended for collection of primary data in pregnancy pharmacovigilance or studies investigating foetal safety following maternal medication use during pregnancy, was recently developed in the ConcePTION project as a first step in this process.[5] The aim of the CDE framework is to help optimise and standardise data collection procedures in primary source pregnancy pharmacovigilance studies to improve data harmonisation and evidence synthesis capabilities.

Use of standardised data elements, optimised specifically for pregnancy drug safety studies, by different stakeholders would allow for standardisation of data collection in future studies, which may greatly enhance the possibilities for combining crude data, pooling datasets and/or undertaking comparative assessments of data from studies within the same therapeutic area. This is particularly relevant in pregnancy pharmacovigilance where both exposures and the outcomes being studied are often rare. Effective use of a CDE is well established and integrated in global drug safety and pharmacovigilance systems (FAERS, Eudravigilance, Vigibase), which is based on the electronic transmission of adverse event reports (referred to as Individual Case Safety Reports or ICSRs), using International Conference on Harmonisation (ICH) E2B standard as the CDE. E2B(R3) is the current version for electronic transmission of ICSRs.[7] This standard defines and standardises data elements for transmission of ICSRs on adverse events and adverse drug reactions in pre and post approval period, and allows for exchange of ICSRs between various parties among which are Marketing Authorisation

holders, regulatory authorities, pharmacovigilance centres and Medical Ethical committees. It is however recognised that the data fields used in this system are not specifically designed for pregnancy pharmacovigilance and therefore lack many essential variables[5] that are necessary, in particular to permit quantitative analysis and estimation of prevalence of certain foetal outcomes in relation to medication use. In order to address this, adoption of the ConcePTION primary data source CDE by existing and new DAPs would be required.

The aim of this study was to assess the ability to align the current data collection variables and definitions used by different public and private DAPs for pregnancy registries or enhanced pregnancy pharmacovigilance systems with the ConcePTION primary data CDE recommendations framework using different types of data sources focusing on or including medications used in the treatment of multiple sclerosis (MS).

Methods

Study design

This methodological study explored the degree to which data collected from various DAPs align with the CDE variables and definitions established in the ConcePTION work package engaged in improving the collection, analysis, and interpretation of primary pregnancy safety data.

Data source

Data access providers (DAPs)

DAPs were public institutions and pharmaceutical companies collecting data from pregnant patients and/or health care providers regarding disease modifying therapies for multiple sclerosis during pregnancy, using one of the three following main types of data collection methods:

A. Pregnancy exposure registries. These registries collect health information on pregnancy and foetal outcomes exposed to medicinal products during pregnancy from patients who agree to participate and who give formal consent. There are national pregnancy exposure registries and registries initiated by pharmaceutical companies, academic groups, or research groups and that focus on a single drug, a drug class or a disease. Usually, the data are collected by a health care professional (HCP) through specifically designed data collection forms. This study included representative registries from the above list.

B. Enhanced pharmacovigilance programs. These programmes collect and process pharmacovigilance data via sets of targeted checklists or questionnaire, structured follow-up, rigorous process of data entry, data quality control, and programmed aggregate analysis. Data are collected initially from Individual Case Safety Reports (ICSRs) but are then supplemented by targeted checklists or questionnaires with dedicated pregnancy related fields. Initial reporting can be by the HCP or directly by the patient. For enhanced pharmacovigilance programs of pharmaceutical companies, the data are entered in their respective safety database.

C. Teratology Information Services (TIS) from the European Network of Teratology Information Services (ENTIS). ENTIS is a collaborative network of services offering expertise on possible risks related to exposure to medications, and other environmental exposures, during pregnancy and breastfeeding at an individual level. TISes collect patient data both during initial contact and after a follow-up period covering pregnancy outcome using a similar methodology based on structured telephone interviews and/or mailed questionnaires.

The exhaustive list of participating DAPs is presented below:

A. Pregnancy registries: Gilenya (Novartis), Aubagio (Sanofi), Aubagio (Sanofi, OTIS), The Dutch Pregnancy Drug Register (Lareb)
B. Enhanced pharmacovigilance programs/PRIM: Gilenya PRIM (Novartis), MAPLE-MS (Merck Healthcare KGaA)
C. Teratogen Information Services: members of ENTIS (Swiss TIS (STIS), UK TIS (UKTIS), Zerfin TIS, Jerusalem TIS)

Data collection

Between May and November 2022 DAPs were requested to answer a questionnaire concerning their general characteristics and method of data collection including the following items: name, short name, institution/MAH, governance, website, initial role, geographical localisation, beginning and end date of data collection, primary reporter, notification, transmission and collection of data, follow-up.

In a second questionnaire, each DAP was requested to answer the following questions separately for every CDE item (questionnaire presented in Table 1 - Appendix):

- Can this item be taken directly from an existing field in the DAP database? (yes/no)

For yes responses, these items were already available in the DAPs' database and met the definition of CDE.

- Can this item be derived by combining data from fields in the DAP database? (yes/no)

For yes response, these items could be derived, using other variables in order to meet the definition of the CDE (e.g.: the pre-pregnancy maternal BMI was not directly available in the DAP's database, but could be derived using the maternal pre-pregnancy weight and height that were available in the database).

- Does the DAP collect data, which is similar to this item, but the CDE definition is different from that used in the DAP database? (yes/no)

For yes responses, these items were considered divergent since they were not directly available and could not be derived, but a similar variable was available (e.g.: the pre-pregnancy maternal BMI was not directly available and could not be derived, but the maternal BMI at inclusion / entry to the registry was available).

- Is the item missing from the DAP database? (yes/no)

Following the above answers each CDE item was classified into one of the four following categories: 1) directly matched, 2) derived, 3) divergent, or 4) not available.

It is important to note that the DAPs answered the questionnaire based on their current primary data collection form. This study only focused on the intended data collection step. Data quality (i.e. data accuracy, data completeness) and data processing issues (i.e. data storage, data formatting, other technical issues) were not considered.

Given the fundamental role of E2B(R3) in the data exchange of global pharmacovigilance data, the degree to which ICH E2B(R3) fields align with the ConcePTION primary data pregnancy exposure CDE was also investigated.

Statistical analysis

A descriptive analysis of the CDE variables collected, classified in 4 categories, was performed for each DAP and overall. Results were presented as absolute numbers (n) and proportions (%).

Results

Four pregnancy registries (Gilenya Novartis, Aubagio Sanofi/OTIS, Aubagio Sanofi, The Dutch Pregnancy Drug Register Lareb), two enhanced pharmacovigilance programs (Gilenya PRIM, MAPLE-MS Merck) and one ENTIS consortium (composed of the STIS, UKTIS, Zerifin TIS, Jerusalem TIS) participated in the study. The description of all DAPs is presented in Table 1.

Table 1: Description of data sources

Description	DAP (1/2)		
Name	**Novartis Gilenya Pregnancy Registry**	**Teriflunomide Pregnancy Registry**	**Teriflunomide OTIS pregnancy registry**
Short name	GPR	TPR	TOPR
Institution/MAH	Novartis	Sanofi	Sanofi
Governance	Private	Private	Private
Website	https://www.gilenyapregnancyregistry.com/	None	None
Initial role of the study/partner	Regulatory requirement	Regulatory requirement	Regulatory requirement
Geographical localisation	Global	Global	United States and Canada
Beginning of data collection	2011	2015	2013
End of data collection	Ongoing	Ongoing	Ongoing
Primary reporter	Pregnant women and HCPs	Pregnant women and HCPs	Pregnant women and HCPs
Case enrolment	Upon signature of informed consent by pregnant woman	Upon signature of informed consent by pregnant woman	Upon verbal informed consent by pregnant woman
Follow-up **How long?**	Pregnant woman at enrolment, mid-second trimester and at end of pregnancy. Infant at 3 and 12 months. Structured telephone interviews or structured questionnaires mailed to HCPs	Pregnant woman at enrolment, mid-pregnancy (around gestational week 20) and at end of pregnancy. Infant at one year of age. Structured telephone interviews or structured questionnaires mailed to HCPs	Pregnant woman at enrolment, around gestational weeks 20, 32-34 plus 0-6 weeks after expected date of delivery. Infant at one year of age. Structured telephone interviews and medical records from HCPs
Type of data	Prospective cases	Prospective and retrospective cases	Prospective and retrospective cases
Exposure type	Fingolimod exposures	Teriflunomide exposures	Teriflunomide exposures

Description	DAP (2/2)			
Name	**The Dutch Pregnancy Drug Register**	**Novartis Gilenya Pregnancy outcomes Intensive Monitoring**	**Worldwide pregnancy surveillance program of oral cladribine**	**European Network of Teratology Information Service consortium**
Short name	Lareb	Gilenya PRIM	MAPLE-MS	ENTIS consortium
Institution/MAH	The Netherlands Pharmacovigilance Centre Lareb	Novartis	Merck Healthcare KGaA	STIS, UKTIS, Jerusalem TIS, Zerifin TIS
Governance	Public	Private	Private	Public
Website	www.moedersvanmorgen.nl	None	None	www.entis-org.eu
Initial role of the study/partner	Pharmacovigilance, research	Enhanced pharmacovigilance activity to supplement pregnancy registry study	Regulatory requirement	Counselling, information, research

Geographical localisation	The Netherlands	Global	Global	Switzerland, UK, Israel
Beginning of data collection	2014	2014	2017	1990
End of data collection	Ongoing	Ongoing	Ongoing	Ongoing
Primary reporter	Pregnant women	Pregnant women and HCPs	Pregnant women and HCPs	Pregnant women and HCPs
Case enrolment	Directly through website	At reporting of Individual Case Safety Report to Novartis	At reporting of Individual Case Safety Report to Merck KGaA	At first contact for counselling
Follow-up **How long?**	Pregnant woman at enrolment, gestational weeks 17, 34 plus 2, 6 and 12 months after expected date of delivery. Structured questionnaires mailed to pregnant woman.	Pregnant woman is followed until end of pregnancy. Infant at 3 and 12 months. Structured checklist questionnaires provided to HCPs.	Pregnant woman at enrolment with follow-up until end of pregnancy. Infants with congenital anomalies until one year of age. Structured questionnaires mailed to pregnant women or HCPs.	At enrolment and after estimated date of delivery through structured telephone interviews and/or mailed questionnaires to pregnant woman or HCP.
Type of data	Prospective cases	Prospective cases	Prospective and retrospective cases	Prospective and retrospective cases
Exposure type	All exposures	Fingolimod exposures	Cladribine exposures	All exposures

DAP: data access providers
MS: multiple sclerosis
MAH: Market authorisation holders
OTIS: organization of teratology information specialists
UK: United Kingdom
HCPs: health care providers

Data collection by market authorisation holders (MAHs) was generally initiated as requirements from regulatory authorities, except for the Gilenya PRIM which was initiated by the sponsor to complement the corresponding Gilenya Pregnancy registry. ENTIS is a non-profit organisation and Lareb is a public institution. The primary role of ENTIS member organisations is to counsel pregnant women and/or HCPs on medication use during pregnancy. Data are collected primarily to provide case specific risk assessments and advice but are used collectively for surveillance and research purposes. The Dutch Pregnancy Drug Register is based on data from pregnant women with the purpose of pharmacovigilance and research activity. For the private pregnancy registries, case enrolment required that written informed consent from the pregnant woman was obtained after the woman herself or her HCP spontaneously contacted the registry. MAPLE-MS and Gilenya PRIM included cases from ICSRs reported by pregnant women and HCPs that were recorded in the MAH's safety database. Data collection is enhanced through a targeted questionnaire directed to primary reporters. For ENTIS, pregnancy and infant follow-up data were collected around delivery due date and for some TIS until 3 years of age for live born infants. The other DAPs performed follow-up until 1 year of life of the infant. For MAPLE-MS this follow-up was performed only for infants with congenital anomalies.

Alignment with the CDE (a) DAP Pregnancy specific data collection systems b) ICH E2B(R3) adverse event reporting form

(a) DAP Pregnancy specific data collection systems

Table 2: Alignment of DAPs variables with CDE items

CDE items	TOTAL - n (%) Directly taken	Derived	Divergent	Not available	Directly taken OR derived
Database Administrative Details					
Mother case identifier	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Baby case identifier	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Mother-Baby case identifier/link	6 (86)	1 (14)	0 (0)	0 (0)	7 (100)
Primary reporter type	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Primary reporter contact details	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Initial report date	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Prospective status	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Maternal Details					
Mother's date of birth	6 (86)	0 (0)	1 (14)	0 (0)	6 (86)
Mother's age at last menstrual period (LMP)	4 (57)	2 (29)	1 (14)	0 (0)	6 (86)
Maternal BMI pre-pregnancy	3 (43)	2 (29)	1 (14)	1 (14)	5 (71)
Pregnancy Details					
Date of LMP	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Expected date of delivery (EDD)	6 (86)	1 (14)	0 (0)	0 (0)	7 (100)
Source of directly-reported EDD	5 (71)	2 (29)	0 (0)	0 (0)	7 (100)
Plurality	6 (86)	1 (14)	0 (0)	0 (0)	7 (100)
Prenatal test(s)	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Maternal Medical History					
Maternal pre-pregnancy medical conditions (history)	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Medication Exposure Details					
Drug name(s)	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Drug start date	5 (71)	2 (29)	0 (0)	0 (0)	7 (100)
Drug stop date	5 (71)	2 (29)	0 (0)	0 (0)	7 (100)
Drug indication(s)	6 (86)	1 (14)	0 (0)	0 (0)	7 (100)
Peri-LMP exposure	5 (71)	2 (29)	0 (0)	0 (0)	7 (100)
Trimester 1 exposure	5 (71)	2 (29)	0 (0)	0 (0)	7 (100)
Trimester 2 exposure	5 (71)	2 (29)	0 (0)	0 (0)	7 (100)
Trimester 3 exposure	5 (71)	2 (29)	0 (0)	0 (0)	7 (100)
Route of exposure	6 (86)	0 (0)	0 (0)	1 (14)	6 (86)
Dose per use	6 (86)	1 (14)	0 (0)	0 (0)	7 (100)
Frequency of use	5 (71)	1 (14)	0 (0)	1 (14)	6 (86)
Maternal Outcome Details					
Maternal medical conditions arising in pregnancy	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Maternal death	6 (86)	0 (0)	0 (0)	1 (14)	6 (86)
Pregnancy Outcome Details					
Pregnancy outcome collection status	6 (86)	1 (14)	0 (0)	0 (0)	7 (100)
Date of end of pregnancy	6 (86)	1 (14)	0 (0)	0 (0)	7 (100)
Gestational age at end of pregnancy	6 (86)	1 (14)	0 (0)	0 (0)	7 (100)
Induced termination	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Ectopic pregnancy	6 (86)	1 (14)	0 (0)	0 (0)	7 (100)
Stillbirth	6 (86)	1 (14)	0 (0)	0 (0)	7 (100)
Spontaneous abortion	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Molar pregnancy	6 (86)	0 (0)	0 (0)	1 (14)	6 (86)
Blighted ovum	6 (86)	0 (0)	0 (0)	1 (14)	6 (86)
Live birth	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Live Stillborn Outcome Details					
Gestational timing of live/stillborn offspring	6 (86)	1 (14)	0 (0)	0 (0)	7 (100)
Infant birth weight	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Infant sex	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Infant head circumference	5 (71)	1 (14)	0 (0)	1 (14)	6 (86)
Infant birth length	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Small for Gestational Age at delivery	4 (57)	3 (43)	0 (0)	0 (0)	7 (100)
Large for Gestational Age at Delivery	4 (57)	3 (43)	0 (0)	0 (0)	7 (100)
Neonatal Infant Outcome Details					
Complications in the first year of life	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Postnatal death of live born infant	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Malformation Details					
Congenital anomaly	7 (100)	0 (0)	0 (0)	0 (0)	7 (100)
Details of all congenital anomaly(ies)	6 (86)	1 (14)	0 (0)	0 (0)	7 (100)
Infant malformation case classification	3 (43)	4 (57)	0 (0)	0 (0)	7 (100)

LMP: last menstrual period
EDD: estimated end of pregnancy
BMI: body mass index

This study assessed 51 specific items from the CDE framework recommendations (Table 2). The majority of the DAPs' data variables aligned with the CDE items and definitions; 85%, (n=305/357 were directly taken from existing fields and 12% (n= 42/357) were derived by combining different variables. For very few of the DAPs variables alignment with the CDE items was not possible, either because the definitions were different from the CDE definition (1%, n=3/357), or because the variables were not collected by the DAPs (2%, n=7/357). No discrepancies were reported between DAPs, regarding divergent and not available variables (Table 2 and Table S2, appendix).

Alignment with the CDE items was similar across type of data collection method with variables directly taken or derived for 96% (n=196/204) of items for the pregnancy registries (Gilenya Novartis, Aubagio Sanofi (OTIS), Aubagio Sanofi, The Dutch Pregnancy Drug Register, Lareb), 99% (n=101/102) for the enhanced pharmacovigilance programs (Gilenya PRIM Novartis, MAPLE-MS Merck) and 98% (n=50/51) for ENTIS.

Each of the not available CDE items was unique to a single DAP; none of them were missing in more than one DAP. The 7 not available CDE items were maternal pre-pregnancy BMI, medication route of administration, medication frequency of use, maternal death outcome (as the reporter is the mother herself and this would therefore appear as a case that is LTFU), molar pregnancy or blighted ovum pregnancy outcome and infant head circumference at birth (Table 3).

DAPs' variables that were divergent (with a different definition than the CDE items) related primarily to maternal age which was not always based on maternal date of birth, but rather mother's age at last menstrual period or maternal age at reporting, and maternal pre-pregnancy BMI (Table 3).

Table 3: Details and comments on not available (A) and divergent (B) core data elements (CDE) items

A. Not available CDE items details

CDE items	DAP(s)	Comments
Maternal Details		
Maternal BMI pre-pregnancy	TPR	Information not collected (neither maternal weight nor height)
Medication Exposure Details		
Route of exposure	GPR	Information not collected
Frequency of use	TPR	Information not collected
Maternal Outcome Details		
Maternal death	Lareb	Information cannot be collected as the reporters are mothers themselves
Pregnancy Outcome Details		
Molar pregnancy	GPR	Information not collected
Blighted ovum	GPR	Information not collected
Live- Stillborn Outcome Details		
Infant head circumference	Lareb	Information not collected

B. Divergent CDE items details

CDE items	DAP(s)	Comments
Maternal Details		
Mother's date of birth	TPR	Maternal age is collected directly at LMP
Mother's age at last menstrual period (LMP)	Gilenya PRIM	Maternal age is collected directly **at reporting**
Maternal BMI pre-pregnancy	ENTIS consortium	Maternal BMI is collected at reporting or at beginning of pregnancy

BMI: body mass index

b) ICH E2B(R3) data structure

ICSR ICHE2B(R3) fields lack a greater number of the ConcePTION primary data CDE variables and definitions than the different but pregnancy specific data collection systems used by DAPs participating in this study (details in Table S3 and S4, Appendix). Eight key CDE items were not available in E2B(R3), including prospective status, source of directly reported EDD, plurality, pregnancy outcome collection

status, date of end of pregnancy, gestational age at end of pregnancy, details of congenital anomalies, and infant malformation case classification.

Discussion

The primary data pregnancy pharmacovigilance CDE items proposed by Richardson et al. 2023 were used as a reference for standardising data reporting in pregnancy pharmacovigilance.[5] This study found that for previously collected data by pregnancy specific data collection systems of both private and public DAPs participating in the study, a very high proportion of variables aligned with the ConcePTION primary data CDE items, with 96% of all variables directly matching existing fields or derived by combining other variables.

Although the DAPs participating in this study showed excellent alignment in terms of data elements collected, all operate differently. The Dutch Pregnancy Drug Register was the only dataset which was based on direct reporting by pregnant women only, whereas all the other DAP datasets were based reporting from both HCPs and/or pregnant woman. Additionally, the DAPs collect data in different contexts and for different reasons (e.g. legal versus clinical) that may also lead to differences in reporting patterns and patient recruitment. These differences in patient recruitment and data collection may influence the results obtained by DAPs and hamper the ability to combine data sources, or to directly compare risk or safety estimates across different datasets. Furthermore, follow-up procedure differed between DAPs. The DAPs perform follow-up until 1 year of life, except for ENTIS (where follow-up even within participating centres ranges from outcome at birth to offspring age of three years) and MAPLE-MS (follow-up until 1 year only for infants with congenital anomalies). Again, these differences in follow-up are to be taken into consideration when comparing neonatal and infant outcomes, as several relevant infant outcomes may manifest or only be detected later in life.

While the not available variables identified in the study might not appear be of major interest by non-experts in the field, they are in some contexts important for accurate analysis of pregnancy and infant safety data and to identify possible confounding by indication for product use. For example, maternal BMI was either not collected or collected at beginning of pregnancy or at pregnancy registration instead of before pregnancy by ENTIS member organisations. Recording of maternal weight at advanced stages of gestation could result in an incorrect BMI calculation. Collecting accurate information on maternal BMI is important since, obesity is associated with a higher risk of various maternal and foetal perinatal complications, and these risks are exacerbated with more severe obesity.[10,11] Possible associated complications include congenital anomalies, gestational hypertension, preeclampsia, gestational diabetes, preterm birth, and having a large for gestational age (LGA) infant.[12,13] However, the difference between pre-pregnancy BMI and BMI at reporting might be of limited clinical relevance, particularly where pregnancies are reported in early gestation. The DAPs that did not collect information on route of exposure or frequency of drug use were MAHs single product registries with specific route/frequency of administration. Thus, these not available variables should not lead to a loss of relevant information. The missing "peri-LMP exposure" could be indirectly drawn from start and stop dates of medication intake, and thus did not constitute a crucial missing point. The infant head circumference not available in the Dutch Pregnancy Drug Register is relevant in clinical practice as an easy screening instrument for paediatricians and has value in teratogen surveillance, but it has been reported to be an inaccurate tool for assessing children's development outcome as up to 85% of children measured with a very small head develop normally.[14] The study found that some pregnancy outcomes such as molar pregnancy and blighted ovum were not recorded by Gilenya registry Nevertheless, it's probable that many of these pregnancies were recorded as miscarriages, implying that the actual impact of this discrepancy on data quality is likely insignificant. Similarly, maternal death was not collected by the Dutch Pregnancy Drug Register as the primary reporters are

mothers themselves, and the data collection design does not allow matching this point to the CDE. It should be technically possible that, where feasible, these limited numbers of not available variables identified in the study could easily be included in current pharmacovigilance data collection systems to match the CDE.

This study highlights the extent to which E2B(R3) fields are deficient in key ConcePTION primary data source CDE variables and definitions in stark comparison to the pregnancy specific data collection systems operated by DAPs participating in this study. As ICH E2B(R3) is the standardized procedure for the electronic transmission of ICSRs in spontaneous adverse event reporting, this may lead to a potential loss of important pregnancy and foeto-maternal information during data exchange between various parties among which MAHs, regulatory authorities and primary reporters, for pregnancy exposure reports. Although only a limited number of variables are not available, some of these variables are of high clinical relevance (i. e. gestational age at end of pregnancy, details of congenital anomalies). Since the data exchange system for ICH-E2B(R3) reporting could represent the basis for a CDM that could be used by stakeholders performing pregnancy safety studies, including the ConcePTION Primary Data CDE pregnancy specific items in the E2B guideline would be of utmost importance.

Our study presents a significant contribution to pharmacovigilance in pregnancy, as it is the first study to explore which variables are collected in different pregnancy pharmacovigilance systems and how they conform to the CDE. This study has the advantage of including both public and private DAPs and providing high-level details on the variables collected. However, this study also has limitations that should be taken into consideration. One of the main limitations is that only DAPs collecting pharmacovigilance data on MS drug exposure during pregnancy were included, which could limit the generalisability of the findings. It is noteworthy that all DAPs involved in this study extensive experience and expertise in the area of pregnancy pharmacovigilance or data collection, which again further could impact generalisability.

The study was conducted in the ConcePTION project as a test to see if data could be collected and combined using novel methodological tools developed (CDE and SAP). This study covers the first step of the project exploring intended data collection, without evaluating data storage and data analysis, which will be addressed in future publications. Finally, our research focused only on the essential CDE items. It is important to note that the CDE could evolve over time in regard to emerging evidence.

Conclusion

DAPs participating in this study presented a very high proportion of variables matching to the ConcePTION Primary Data CDE items, indicating that alignment of definitions and harmonisation of data analysis by different stakeholders could be feasible. Importantly, this insight challenges perceived barriers and theoretical concerns regarding the scientific validity of combining diverse datasets to improve teratogen detection. Furthermore, this study indicates that previously collected data from different data collection systems could potentially be more effectively exploited. The low proportion of divergent items and of items not collected together with the possibility to adapt variables to finally match current standards gives the prospect of standardised high quality pharmacovigilance data collection in the future. This study represents a first step in a process of standardising data collection by different stakeholders collecting data as part of collaborative pregnancy safety studies. This might ultimately allow meta-analyses of datasets and/or comparative assessments of data from studies within the same therapeutic area.

Conflict of interests

Conflict of interest GF, JLR, AO, YRJvRW, BD, AP, EvP, ODC, MB, TDH, and UW declare no conflicts of interest, no other financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years, and no previous or ongoing relationships or activities that could appear to have infuenced the submitted work. A Moore was a Novartis associate whist working on this manuscript and other aspects of the ConcePTION project, and holds shares in Novartis Pharma AG. YG, and VJ are employees of Novartis Pharma AG. M Stellfeld is an employee of Novo Nordisk A/S. M Sabidó and SdS are employees of Merck Healthare KGaA. LMY received honoraria from Sanofi Genzyme South Africa on two occasions in 2021 for 1. an Advisory Board presentation on genetic testing in Gaucher's disease (April 2021), and 2. a conference lecture on Genetic testing in the cardiac clinic' (September 2021). A Mor is an employee of Sanofi and holds shares in Sanofi.

Acknowledgement

The ConcePTION project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 821520. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

The research leading to these Results was conducted as part of the ConcePTION consortium. This paper only reflects personal views of the stated authors.

References

1. Lupattelli A, Spigset O, Twigg MJ, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open 2014;4(2):e004365.

2. Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. Am J Med Genet C Semin Med Genet 2011;157C(3):175–82.

3. Scaffidi J, Mol BW, Keelan JA. The pregnant women as a drug orphan: a global survey of registered clinical trials of pharmacological interventions in pregnancy. BJOG 2017;124(1):132–40.

4. Daw JR, Hanley GE, Greyson DL, Morgan SG. Prescription drug use during pregnancy in developed countries: a systematic review. Pharmacoepidemiol Drug Saf 2011;20(9):895–902.

5. Richardson JL, Moore A, Bromley RL, et al. Core Data Elements for Pregnancy Pharmacovigilance Studies Using Primary Source Data Collection Methods: Recommendations from the IMI ConcePTION Project. Drug Saf 2023;

6. Bonati M, Bortolus R, Marchetti F, Romero M, Tognoni G. Drug use in pregnancy: an overview of epidemiological (drug utilization) studies. Eur J Clin Pharmacol 1990;38(4):325–8.

7. EMA. ICH E2B (R3) Electronic transmission of individual case safety reports (ICSRs) - data elements and message specification implementation guide Scientific guideline [Internet]. European Medicines Agency. 2018 [cited 2023 Feb 22];Available from: https://www.ema.europa.eu/en/ich-e2b-r3-electronic-transmission-individual-case-safety-reports-icsrs-data-elements-message

8. Zuber PLF, Moran AC, Chou D, et al. Mapping the landscape of global programmes to evaluate health interventions in pregnancy: the need for harmonised approaches, standards and tools. BMJ Glob Health 2018;3(5):e001053.

9. Geissbühler Y, Rezaallah B, Moore A. An alternative to product-specific pregnancy registries? PRIM; PRegnancy outcomes Intensive Monitoring. Reprod Toxicol 2020;94:13–21.

10. Torloni MR, Betrán AP, Horta BL, et al. Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. Obes Rev 2009;10(2):194–203.

11. Lisonkova S, Muraca GM, Potts J, et al. Association Between Prepregnancy Body Mass Index and Severe Maternal Morbidity. JAMA 2017;318(18):1777–86.

12. Santos S, Voerman E, Amiano P, et al. Impact of maternal body mass index and gestational weight gain on pregnancy complications: an individual participant data meta-analysis of European, North American and Australian cohorts. BJOG 2019;126(8):984–95.

13. Wu L, Li N, Liu Y. Association Between Maternal Factors and Risk of Congenital Heart Disease in Offspring: A Systematic Review and Meta-Analysis. Matern Child Health J 2023;27(1):29–48.

14. Wright CM, Emond A. Head growth and neurocognitive outcomes. Pediatrics 2015;135(6):e1393-1398.

Appendix

Improving data collection as part of pregnancy safety studies: Towards standardisation of data elements in pregnancy reports from public and private partners, a contribution from the ConcePTION project.

Table S1: Questionnaire to complete for each data access providers (DAPs) - Example of the *Maternal details* items

Data variable	**Definition**	**Notes:** Refer also to the full version of the CDE for details of data format and suggested values of each CDE item	**Question 1:** Can this item be taken directly from an existing field in the DAP database (Y/N - please select)?	**Question 2:** Can this item be derived by combining data from fields in the DAP database (Y/N - please select)?	**Question 3:** Does the DAP collect data which is similar to this item, but the CDE definition is too different from that used in the DAP database (Y/N - please select)?	**Question 4:** If this item is missing from DAP database, please summarise the reasons
Mother's date of birth	Mother's date of birth	Availability depends on local law/data collection and storage permissions				
Mother's age at last menstrual period (LMP)	Mother's age (in years) on the first day of the last menstrual period prior to the pregnancy	Availability depends on local law/data collection and storage permissions				
Maternal BMI pre-pregnancy	Maternal BMI at the time of conception (kg/m2)	Local dataset may code this categorically (e.g. underweight, normal weight, overweight or obese)				

BMI: body mass index
Y/N: Yes or No
DAPs: data access providers

Table S2: Alignment of the data access providers (DAPs) with the core data elements (CDE) items, by DAPs

	GPR				TPR				TOPR				Lareb				Gilenya PRIM				MAPLE-MS				ENTIS consortium			
CDE items	**Directly taken**	**Derived**	**Divergent**	**Not available**	**Directly taken**	**Derived**	**Divergent**	**Not available**	**Directly taken**	**Derived**	**Divergent**	**Not available**	**Directly taken**	**Derived**	**Divergent**	**Not available**	**Directly taken**	**Derived**	**Divergent**	**Not available**	**Directly taken**	**Derived**	**Divergent**	**Not available**	**Directly taken**	**Derived**	**Divergent**	**Not available**
Database Administrative Details																												
Mother case identifier	X				X				X				X				X				X				X			
Baby case identifier	X				X				X				X				X				X				X			
Mother-Baby case identifier/link	X				X				X				X					X			X				X			
Primary reporter type	X				X				X				X				X				X				X			
Primary reporter contact details	X				X				X				X				X				X				X			
Initial report date	X				X				X				X				X				X				X			
Prospective status	X				X				X				X				X				X				X			
Maternal Details																												
Mother's date of birth	X						X		X				X				X				X				X			
Mother's age at last menstrual period (LMP)	X				X					X				X					X		X				X			
Maternal BMI pre-pregnancy	X							X	X					X				X			X						X	
Pregnancy Details																												
Date of LMP	X				X				X				X				X				X				X			
Expected date of delivery (EDD)	X				X				X				X					X			X				X			
Source of directly-reported EDD	X					X			X				X				X				X					X		

Plurality	X		X		X		X		X		X			X				
Prenatal test(s)	X		X		X		X		X		X		X					
Maternal Medical History																		
Maternal pre-pregnancy medical conditions (history)	X		X		X		X		X		X		X					
Medication Exposure Details																		
Drug name(s)	X		X		X		X		X		X		X					
Drug start date	X		X		X			X	X				X			X		
Drug stop date	X		X		X			X	X				X			X		
Drug indication(s)	X		X		X		X		X				X			X		
Peri-LMP exposure	X		X		X			X	X					X		X		
Trimester 1 exposure	X		X			X		X	X				X			X		
Trimester 2 exposure	X		X			X		X	X				X			X		
Trimester 3 exposure	X		X			X		X	X				X			X		
Route of exposure	X	X	X		X		X		X				X			X		
Dose per use	X		X		X		X		X					X		X		
Frequency of use	X			X	X		X		X					X		X		
Pregnancy Outcome Details																		
Maternal medical conditions arising in pregnancy	X		X		X		X		X				X			X		
Maternal death	X		X		X					X	X		X			X		
Pregnancy Outcome Details																		
Pregnancy outcome collection status	X		X		X		X		X					X		X		
Date of end of pregnancy	X			X	X		X		X				X			X		
Gestational age at end of pregnancy	X		X		X		X		X				X				X	
Induced termination	X		X		X		X		X				X			X		
Ectopic pregnancy	X		X		X		X		X					X		X		
Stillbirth	X		X		X		X		X					X		X		
Spontaneous abortion	X		X		X		X		X				X			X		
Molar pregnancy		X	X		X		X		X				X			X		
Blighted ovum		X	X		X		X		X				X			X		
Live birth	X		X		X		X		X				X			X		
Live Stillborn Outcome Details																		
Gestational timing of live/stillborn offspring	X		X		X			X	X				X			X		
Infant birth weight	X		X		X		X		X				X			X		
Infant sex	X		X		X		X		X				X			X		
Infant head circumference	X		X		X				X	X				X		X		
Infant birth length	X		X		X		X		X				X			X		
Small for Gestational Age at delivery	X		X		X			X			X		X				X	
Large for Gestational Age at Delivery	X		X		X			X			X		X				X	
Neonatal Infant Outcome Details																		
Complications in the first year of life	X		X		X		X		X				X			X		
Postnatal death of live born infant	X		X		X		X		X				X			X		
Malformation Details																		
Congenital anomaly	X		X		X		X		X				X			X		
Details of all congenital anomaly(ies)	X		X		X		X		X					X		X		
Infant malformation case classification	X		X		X			X			X			X			X	

GPR: Novartis Gilenya Pregnancy Registry

TPR: Teriflunomide Pregnancy Registry

TOPR: Teriflunomide OTIS pregnancy registry

Lareb: The Dutch Pregnancy Drug Register

Gilenya PRIM: Novartis Gilenya Pregnancy outcomes Intensive Monitoring

MAPLE-MS: Worldwide pregnancy surveillance program of oral cladribine

ENTIS consortium: European Network of Teratology Information Service consortium

Table S3: Alignment of the E2B(R3) standard variables with the core data elements (CDE) items

CDE items	E2B(R3) Directly taken	Derived	Similar	Not available
Database Administrative Details				
Mother case identifier	X			
Baby case identifier	X			
Mother-Baby case identifier/link		X		
Primary reporter type	X			
Primary reporter contact details	X			
Initial report date	X			
Prospective status				X
Maternal Details				
Mother's date of birth		X		
Mother's age at last menstrual period (LMP)		X		
Maternal BMI pre-pregnancy			X	
Pregnancy Details				
Date of LMP		X		
Expected date of delivery (EDD)		X		
Source of directly-reported EDD				X
Plurality				X
Prenatal test(s)		X		
Maternal Medical History				
Maternal pre-pregnancy medical conditions (history)		X		
Medication Exposure Details				
Drug name(s)	X			
Drug start date	X			
Drug stop date	X			
Drug indication(s)	X			
Peri-LMP exposure		X		
Trimester 1 exposure		X		
Trimester 2 exposure		X		
Trimester 3 exposure		X		
Route of exposure	X			
Dose per use	X			
Frequency of use	X			
Maternal Outcome Details				
Maternal medical conditions arising in pregnancy		X		
Maternal death		X		
Pregnancy Outcome Details				
Pregnancy outcome collection status				X
Date of end of pregnancy				X
Gestational age at end of pregnancy				X
Induced termination		X		
Ectopic pregnancy		X		
Stillbirth		X		
Spontaneous abortion		X		
Molar pregnancy		X		
Blighted ovum		X		
Live birth		X		
Live Stillborn Outcome Details				
Gestational timing of live/stillborn offspring		X		
Infant birth weight			X	
Infant sex		X		
Infant head circumference		X		
Infant birth length			X	
Small for Gestational Age at delivery		X		
Large for Gestational Age at Delivery		X		
Neonatal Infant Outcome Details				
Complications in the first year of life		X		
Postnatal death of live born infant		X		
Malformation Details				

Congenital anomaly	X	
Details of all congenital anomaly(ies)		X
Infant malformation case classification		X

Table S4: Details and comments on not available (A) and divergent (B) core data elements (CDE) items for E2B(R3) standard

A. Not available CDE items details

CDE items	Comments
Database Administrative Details	
Prospective status	Information not collected
Pregnancy Details	
Source of directly-reported EDD	Information not collected
Plurality	Information not collected
Pregnancy Outcome Details	
Pregnancy outcome collection status	Information not collected
Date of end of pregnancy	Information not collected
Gestational age at end of pregnancy	Information not collected
Malformation Details	
Details of all congenital anomaly(ies)	Information not collected
Infant malformation case classification	Information not collected

B. Divergent CDE items details

CDE items	Comments
Maternal Details	
Maternal BMI pre-pregnancy	No information about the timing of data collection (pre-pregnancy/during pregnancy/after pregnancy)
Live Stillborn Outcome Details	
Infant birth length	No information about the timing of data collection (at birth or later after birth)