COVI-PREG

International COVID-19 and Pregnancy Registry

Coronavirus in pregnancy (COVI-PREG) international registry

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ABSTRACT

At the beginning of the COVID-19 pandemic, reports demonstrated conflicting evidence regarding the impact of SARS-CoV-2 on pregnant women. Therefore, there was an urgent need to acquire robust data on the effect of emergent pathogens on pregnancy. The COVI-PREG registry, an online platform which enables the collection of information on pregnant women exposed to SARS-CoV-2, has been developed. This tool provided evidence that pregnant women were at higher risk of maternal, pregnancy and neonatal adverse outcomes following the infection.

Vaccine hesitancy has been another major problem during this public health crisis, more importantly in pregnancy. COVI-PREG allowed the monitoring of COVID-19 vaccine exposure during pregnancy as pregnant women were excluded from clinical trials. Essential information collected led to the publication of additional data contributing to the knowledge about vaccine safety.

Data on emergent pathogens in pregnancy is often lacking or available after considerable delay, leaving scientists and clinicians only with their intuition, extrapolation, and observations from case series as they emerge. This tool facilitates the collection of information requested to quickly and efficiently answer these queries.

To conclude, COVI-PREG has been successful to provide scientific evidence using real world data and has demonstrated a strong collaboration between Swiss and international partners.

HIGHLIGHTS

- A total of 22 countries and 29 hospitals in Switzerland participated to COVI-PREG.
- More than 7000 patients are now included in COVI-PREG, with more than 800 variables available for each patient.
- The robustness and high quality of COVI-PREG has been recognized worldwide, and is considered one of the top registries, at the level of those created later by the CDC or UK.
- Pregnant women are at higher risk of severe COVID-19.
- Pulmonary comorbidity, hypertensive disorder and diabetes have been identified as risk factors for severe COVID-19.
- COVID-19 infection during pregnancy is a risk factor of adverse perinatal and neonatal adverse outcomes.
- mRNA COVID-19 vaccine appeared to be safe during pregnancy.
- COVID-19 medicine use in pregnant women has changed and seems to be aligned with current guidelines.
- COVI-PREG demonstrated to be a very successful and robust tool to assess and monitor SARS-CoV-2 and COVID-19 vaccine during pregnancy.
- Additional studies are now in process to assess: 1) the neurodevelopment of infant exposed to SARS-CoV-2 and COVID-19 vaccine in utero, 2) the maternal and perinatal outcomes regarding SARS-CoV-2 variants and 3) the maternal and perinatal outcomes overtime regarding the pandemic periods.
- The COVI-PREG project can be easily updated to any exposure (infectious disease, pollution, …) for future perspectives.

INTRODUCTION

At the beginning of the pandemic, information on the emergent pathogen SARS-CoV-2 was missing. The first available data on adults suggested a very high rate of acute respiratory distress syndrome due to infection, and a high fatality rate.

The first data on infected pregnant women were surprisingly reassuring. Considering an altered immunity, reduced respiratory capacity and hemodynamic changes, pregnant women were potentially at higher risk of severe disease. Since high rates of adverse maternal, pregnancy and neonatal outcomes were observed during previous epidemics due to other coronavirus family subtypes (SARS-CoV-1 and MERS-CoV), collecting data on the effect of this coronavirus during pregnancy appeared as a most pressing matter.

THE 1ST REGISTRY TO ASSESS THE IMPACT OF COVID-19 ON PREGNANCY

Due to the potential vulnerability of pregnant women, we created COVI-PREG, an international registry enabling the collection of data on women exposed to SARS-CoV-2 during pregnancy. COVI-PREG was an online tool allowing collaborators based in hospital and clinics worldwide to include and fill in information on pregnant patients exposed to the virus as shown in figure 1. The COVI-PREG registry's aims were initially to assess the natural history of the virus among pregnant women exposed to the virus and, to evaluate the impact of the infection on maternal, pregnancy and neonatal outcomes.

The tool was a robust data collection system allowing collaborators to fill in patients' information including baseline characteristics, COVID-19 management, the pregnancy course, as well as maternal, pregnancy and neonatal outcome. The COVI-PREG registry highlighted that pregnant women were a specific population at higher risk of severe COVID-19.

Once the COVID-19 vaccine was available, a new module was built in COVI-PREG registry to follow-up vaccine exposure and assess its safety. Since pregnant women were excluded from the clinical trials evaluating the COVID-19 vaccine and because vaccine hesitancy was high, it was crucial to study the safety of the vaccine during pregnancy quickly to improve the vaccination uptake for this special population.

ENROLMENT DATA

As of September 15th 2022, the COVI-PREG consortium was composed of 77 collaborating centers worldwide representing 22 countries.

Since March 2020, the COVI-PREG registry has included a total of 7423 pregnant patients worldwide, including more than 4300 patients infected with SARS-CoV-2 and more than 2900 exposed to COVID-19 vaccine (table 1).

In Switzerland, a total of 3555 patients have been included (1634 infected with the virus and 1921 exposed to the COVID-19 vaccine).

Since the FOPH funding (January 1st 2021), more than 5300 patients have been enrolled, including more than 3000 from Switzerland.

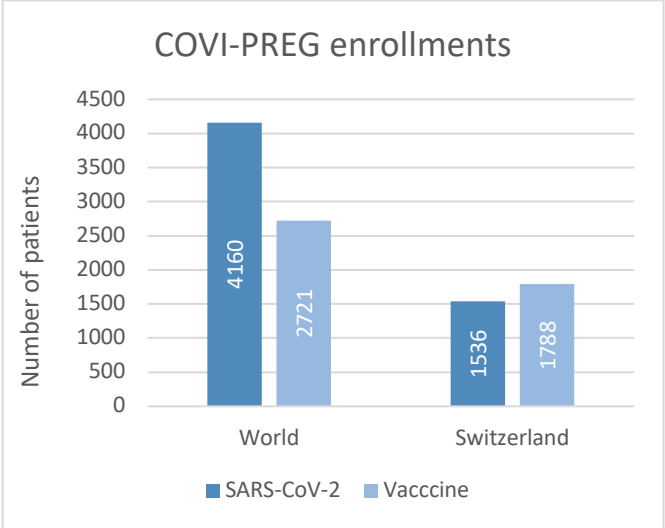

Table 1: COVI-PREG patients' enrollments worldwide and in Switzerland

SARS-COV-2 & PERINATAL OUTCOMES

The COVI-PREG consortium was one of the first to publish data on COVID-19 in pregnancy, assessing the impact of the infection on pregnant women and assessing risk factors associated with severe disease.

We studied 926 pregnant patients tested positive for SARS-CoV-2, among which 9.9% (n = 92) presented a severe disease. A total of 6 (0.6%) maternal deaths were reported. We identified several risk factors associated with severe disease: Pulmonary comorbidities, hypertensive disorders and diabetes. Pregnant patients with severe maternal outcomes were at higher risk of cesarean section, preterm delivery and neonatal intensive care unit admission.

In conclusion, pregnant women, particularly those with comorbidities, were at higher risk of severe COVID-19. Obstetrical as well as neonatal outcomes appear to be influenced by the severity of the maternal disease.

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A TOOL TO ASSESS COVID-19 VACCINE SAFETY IN PREGNANCY

Due to the exclusion of pregnant women from mRNA COVID-19 vaccine trials, the COVI-PREG registry was a useful tool to assess the safety of the vaccine during pregnancy through a observational design.

We recently published a Swiss study describing the adverse effects following COVID-19 vaccine injection during pregnancy, including 1012 pregnant women. A total of 80% of patients reported a local reaction, and up to 42% (Pfizer 1st/2nd dose and Moderna 1st dose) and 80% (Moderna 2nd dose) experienced a systemic reaction following injection, which was similar to the general population. Severe adverse events were rare, including venous thromboembolism, fever requiring hospitalization, and herpes zoster, which can occur following any vaccine injection.

Among more than 500 patients exposed to the vaccine before 37 weeks of gestation with a known pregnancy outcome, the rate of preterm birth was 6.4% (33/513), which was similar to the previous 3 years' national Swiss rates (6.3-7%). The rate of small for gestational age was low (3.9%; 21/530) as well as the rate of neonatal intensive care unit admission (4.7%; 25/530). No stillbirth or neonatal deaths were reported.

To conclude, no red flags were reported in this descriptive analysis of pregnancy and neonatal outcomes. This study brings additional evidence in favor of the safety of the COVID-19 vaccine during pregnancy.

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A TOOL TO ASSESS COVID-19 TREATMENT UTILIZATION IN PREGNANCY

The COVI-PREG registry has been selected to study COVID-19 treatments in pregnancy by the CONSIGN (COVID-19 infectiOn aNd medicineS In pregnancy) consortium, which is a project set up by the European Medicine Agency to guide decision making about treatments options for COVID-19 in pregnant women.

The first aim of this study was to describe the use of COVID-19 related medicines during pregnancy defined as antibiotics, antivirals, hydroxychloroquine corticosteroids, anti-interleukin-6 and immunoglobulins. The secondary aim was to study the evolution of COVID-19 medicine use between the early (before July 1st 2020) and late (after July 1st 2020) period of the pandemic.

We included 1,964 pregnant patients tested positive for SARS-CoV-2 from March 2020, to July 2021. Overall, 10.4% (205/1964) received at least one COVID-19 related medicine including antibiotics (8.6%) corticosteroids (3.2%), antivirals (2.0%), hydroxychloroquine (1.4%), and anti-interleukin-6 (0.3%). The use of at least one COVID-19 related medicine was 3.1% (12/381) in asymptomatic patients, 4.2% (52/1233) in outpatients, 19.7% (46/233) in inpatients without oxygen, 72.1% (44/61) in patients requiring standard oxygen, 95.7% (22/23) in patients requiring high flow oxygen, 96.2% (25/26) in intubated patients and 57.1% (4/7) among patients who died.

The proportion of patients who received at least one medicine to treat COVID-19 was higher before than after July 1st 2020 (16.7% vs. 7.7%). Antibiotics, antivirals, and hydroxychloroquine had lower rates of use in the latter period.

Medicine use in pregnancy was associated with disease severity. The trend toward increased corticosteroids use seems to be aligned with changing guidelines. However, evidence is still needed regarding the effectiveness and safety of COVID-19 related medicines in pregnancy.

A meta-analysis including other international consortium of CONSIGN is currently at the protocol phase. The aim of the meta-analysis is to pool as much data as possible to answer unresolved questions at the single project level, enabling the evaluation of rare events.

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COVI-PREG, WHAT'S NEXT?

NEURODEVLOPMENT OUTCOMES IN CHILDREN EXPOSED IN UTERO TO SARS-COV-2

No data is available regarding the neurodevelopment of children exposed to the SARS-CoV-2 virus or the COVID-19 vaccine during pregnancy.

This children follow-up study aims to assess their neurodevelopment using the Ages and Stages Questionnaire version 3 (ASQ-3), completed by the parents at home. Data collection is currently ongoing.

This is an important concern for patients during pregnancy and we have scarce information on the long-term impact of the disease on the offspring. COVI-PREG will therefore provide major information on long-term follow-up of mother-child pairs.

PRE-DELTA, DELTA AND OMICRON SARS-COV-2 VARIANT INFECTION

An additional analysis is currently in progress to assess maternal outcomes after SARS-CoV-2 infection during pregnancy according to the different SARS-CoV-2 variants: pre-Delta, Delta and Omicron variant period. Several studies have reported more severe effects of the Delta variant compared to the pre-Delta one. On the other hand, few data are available yet regarding the real impact of the Omicron variant. The purpose of this study is to evaluate the impact of this variant on the mother and her unborn child compared to the delta and pre-delta waves.

INTERNATIONAL COLLABORATIONS

The COVI-PREG consortium is participating in an international sequential prospective meta-analysis led by Prof. Emily Smith, Georges Washington University, USA. The research group consists of 41 participating countries, amounting to 76,000 followed-up pregnant patients.

A first study evaluating the risk factors of adverse outcomes among pregnant women with COVID-19 was published. This research included data from 21 participating study groups including almost 22000 cases from 33 countries.

This study confirms that pregnant women with comorbidities including diabetes, hypertension, and cardiovascular disease, were at increased risk for severe COVID-19-related outcomes, maternal morbidities, and adverse birth outcomes. They also identified several less commonly known risk factors, including HIV infection, pre-pregnancy underweight, and anaemia. Although pregnant women are already considered a high-risk population, special priority for prevention and treatment should be given to pregnant women with these additional risk factors.

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PERSPECTIVES

The 2022 monkeypox outbreak, caused by the zoonotic monkeypox virus, has spread across five WHO regions (the Americas, Africa, Europe, Eastern Mediterranean, and Western Pacific) and is a global public health concern. The atypically high rate of person-to-person transmission among cases with no travel or exposure to animals from endemic regions increases the possibility of the virus establishing itself as a human pathogen. As the outbreak expands, groups at heightened risk of severe disease may acquire the infection, including pregnant people. However, data regarding the impact of monkeypox in pregnancy are scarce. We have started a thorough literature review to collect the information available on the impact of monkeypox in pregnancy as well as its available treatment. We are ready to launch a prospective data collection on pregnant women exposed to monkeypox or to vaccines used in pre or post exposure, should the situation become more prevalent.

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CONCLUSION

The COVI-PREG registry was an efficient tool which allowed us to assess several key aspects of this new SARS-CoV-2 virus among pregnant women.

In addition, COVI-PREG was one of the largest pregnancy and COVID-19 research projects worldwide, bringing fast and relevant scientific evidence helping clinicians and stakeholders to better understand and manage this unprecedented health crisis. The COVI-PREG update for the COVID-19 vaccine safety study also confirmed that the tool is easily adaptable to the changing situation and permits to monitor different exposures of interest.

Given the success of the project, a still growing number of collaborators are joining the study, building a strong network of partners, on both Swiss and international levels, for future research perspectives.