COVI-PREG
International COVID-19 and Pregnancy Registery

CHUV Département de gynécologie obstétrique et génétique médicale

Project Title: Registry for pregnant women exposed to SARS-CoV 2

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO) [1].
Type of Research Project:	Research project in which coded health-related personal data are collected prospectively using a RedCap web database
Risk Categorisation:	Risk A
Project Leader:	David Baud, MD-PhD Département de gynécologie-obstétrique et génétique médicale, CHUV, Avenue Pierre-Decker 2, 1011 Lausanne david.baud@chuv.ch Alice Panchaud, PhD, Département des centre interdisciplinaires, Service de Pharmacie Rte Bugnon 17, 1011 Lausanne-CHUV. alice.panchaud@chuv.ch

PROTOCOL SIGNATURE FORM

Title: Registry for pregnant women exposed to SARS-CoV 2

The project leaders have approved the protocol version ***3, 19th march 2020,*** and confirms hereby to conduct the project according to the protocol, the Swiss legal requirements [1, 2], current version of the World Medical Association Declaration of Helsinki [3] and the principles and procedures for integrity in scientific research involving human beings.

Project leader :

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Date: 20.03.2020 _____ Signature: _____

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GLOSSARY OF ABBREVATIONS

BASEC	*Business Administration System for Ethical Committees*
CRF	*Case report form*
FOPH	*Federal Office of Public Health*
HRA	*Human Research Act*
HRO	*Ordinance on Human*
SARS	*severe acute respiratory syndrome*
SARS-CoV-2	*coronavirus involve in the 2019-2020 pandemic*

1 BACKGROUND AND PROJECT RATIONALE

The present outbreak of a coronavirus-associated acute respiratory disease called coronavirus disease 19 (COVID-19) is the third documented spillover of an animal coronavirus to humans in only two decades that has resulted in a major epidemic. The two previous coronaviruses-associated acute respiratory disease responsible - the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) – have shown to be associated severe adverse pregnancy outcomes, such as miscarriage, premature delivery, intrauterine growth restriction, and maternal death. Vertical transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for the present outbreak, has not yet been detected, whereas perinatal transmission has been suspected in one case. Consequences of infection with SARS-CoV-2 for pregnancies are uncertain, as epidemiological and clinical information is missing so far in this specific population. The recent experience with Zika virus and the knowledge on several other pathogens (e.g. influenza, cytomegalovirus, toxoplasmosis) suggests that emerging pathogens should be considered as potential risks for the feto-maternal health. Therefore, a reliable data collection aiming to better characterise the risks associated to SARS-CoV-2 infection in pregnancy should be set up during the current epidemic. This will allow to develop evidence based clinical recommendations for the care of SARS-CoV-2infected pregnant women, missing so far.

This project will use the same strategy used for the zika pregnancy register (CER-VD is 2016 – 00801). (*Harness shared data in international Zika registry;* BMJ. 2016; *An international registry for women exposed to Zika virus during pregnancy: time for answers*; Lancet Infect Dis. 2016). Thus, this study is an adaption of the zika pregnancy register to the SARS-CoV-2 specificities (COVI-Preg).

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and Objectives

The project will launch a prospective structured data collection (COVI-Preg) to allow future research projects leading to a better characterisation of the risks associated to SARS-COV 2 infection during pregnancy.

<u>Research aims</u>

i. To describe the course of SARS-CoV-2 infection during pregnancy and the risk of adverse maternal outcomes (e.g. severity of maternal symptoms, ICU admission, death)
ii. To quantify the risk of adverse pregnancy outcomes (e.g. miscarriages, stillbirth, growth restriction) and neonatal outcomes (e.g. NICU, prematurity, death, birth defects) associated with confirmed SARS-CoV-2 infection, compared with pregnant women with a negative status for SARS-CoV-2
iii. To assess the risk of vertical transmission and congenital lesions
ii. To identify additional risk factors and risk modifiers (e.g. symptomatic infection, amniotic fluid positive for SARS-CoV-2, co-infections) in SARS-CoV-2 infected pregnant women

2.2 Variables

Time of collection		Variable groups
Enrolment	**Baseline characteristics**	Baseline Demographics: age (years), marital status (cat), ethnicity (cat), education (cat), country of residence (cat) Maternal comorbidities: BMI (y), diabetes (pregestational, gestational with or without medication) (y), thyroid function imbalances (y), hypertension (y), heart disease (y), chronic obstructive lung disease (y), other illnesses (y), alcohol-tobacco-recreational drug used during pregnancy (y, n), maternal medications (t, d) Ongoing pregnancy information: last menstrual period (d), gestational age at enrolment (n), gravidity (n), parity (n), multiple gestation (y), first trimester screening (y, results) Maternal serological and immunization status when available at enrolment: Toxoplasmosis (pos), Cytomegalovirus (pos), Varicella Zoster Virus (pos), Herpes Simplex Virus (pos), Rubella (pos), Syphillis (pos), HIV (pos), Hepatitis C (pos), Hepatitis B (pos), Lymphocytic Choriomeningitis Virus (pos), influenza vaccine (y), pertussis vaccine (y) Maternal and neonatal genetic testing when available at enrolment: trisomy screening (y, results), non-invasive prenatal testing (i.e. analysis of fetal DNA in maternal blood) (y; results), invasive genetic testing performed (amniocentesis, chorionic villus sampling) (y, results)
	Exposure	SARS-CoV-2 maternal evaluation: test performed (y, d, pos), SARS-CoV-2 symptoms (cat), other tests performed (Influenza, Respiratory-Syncytial Virus) (y, d, pos),
Follow-up	**Vertical transmission**	Amniotic fluid testing: test performed (y, d, pos); Placenta testing: test performed (y; d, pos); Products of fetal loss if applicable: test performed (y, d, pos); Newborn testing: test performed (y; d, pos); Human Milk: test performed (y; d, pos)
	Maternal natural history	Abnormal lab result during the course of the disease if tested: thrombocytopenia (y), lymphocytopenia (y), anemia (y), C-reactive protein (y), lactate dehydrogenase U/L (>245) (y), ALT, U/L (>40) (y) Abnormal imaging during the course of the disease if performed: X-ray test performed (y, d, pos), CT scan test performed (y, d, pos), MRI test performed (y, d, pos) Complication: sepsis (y, dur), respiratory failure (y, dur), acute respiratory distress syndrome (y, dur), heart failure (y, dur), septic shock (y, dur), coagulopathy (y, dur), renal failure (y, dur), and disseminated intravascular coagulopathy (y, dur) Treatment: antiviral (name, dos, dur), antibiotic (name, dos, dur), corticosteroids as SARS-CoV-2 treatment (name, dos, dur), chloroquine (name, dos, dur), intravenous immunoglobulin (name, dos, dur), Hospital admission (y, dur, time from illness onset), High-flow nasal cannula oxygen therapy (y, dur, time from illness onset), ICU admission (y, dur, time from illness onset), non-invasive mechanical ventilation (y, dur, duration, time from illness onset), invasive mechanical ventilation (y, dur, time from illness onset), ECMO (y, dur, time from illness onset), renal replacement therapy (y, dur, duration, time from illness onset)
	Pregnancy outcomes	Pregnancy outcomes: multiple gestation (y), pregnancy termination (elective or spontaneous) (y), stillbirth (y), spontaneous preterm (y), iatrogenic preterm (y), fetal lung maturation (y) Prenatal imaging: dating US results and measurements (d, n, t), subsequent US results and measurements (d, n, t), if abnormal: IUGR type (y), oligoamnios (y), polyhydramnios (y), other anomalies (y, t)
	Infant outcomes	Standard information: gestational age at delivery (n), mode of delivery (cat), sex (cat), weight (n), height (n), Apgar scores (n), umbilical arterial and venous blood pH (n), physical examination (if abnormal, neurological exam, splenomegaly, hepatomegaly, birth defect, and other findings) (y, d, pos), NICU admission (y, dur), feeding method at discharge (cat) Imaging and further investigations: blood count (y, d, pos, t), screening for other infectious diseases (y, d, cat, pos, t), magnetic resonance imaging (y, d, pos, t), other abnormalities (y, d, t)

years: years; cat.: predefined categories; y: yes, no, unknown; d: date; n: numbers; t: free text; pos: (positive/abnormal, negative/normal, unknown); dur: duration; dos: dosage; ICU: Intensive care unit; ECMO: extracorporeal membrane oxygenation;

The information collected for the purpose of COVI-PREG is information exclusively collected in clinical routine for the care of patients. Thus, no extra tests or medical exams will be performed outside the clinical routine for the purpose of the registry. If, in the future, the development of

the knowledge about the Covid-19 justifies such an approach, this will be the subject of an amendment to the EC.

2.3 Project design

Health facilities with antenatal clinics globally willing to participate to the collaborative SARS-CoV 2 pregnancy registry will share information on one or several pregnant patient(s) meeting the inclusion criteria through a web-based database. The database will be created using RedCap stream-lined process, a secure web application for building and managing online surveys and databases (http://projectredcap.org/). For each patient enrolled, the same set of information will be requested.

The steps in the process are:

a. A short initial form gathering information on any new SARS-COV-2 pregnancy registry collaborator willing to collaborate will enable to provide a login to the data base (name, email, work institution, patient inform consent). This form will be made available via a web-link. Only collaborators with a username and password transmitted by the registry management will be authorized to enter data.

Information on pregnant patient gathered in (b) and (c) will be collected and stored coded:

b. Enrolment form will include baseline information and information about the SARS-COV-2 status. This form will be available after the "login" in the REDCap database using the login information (user name and password) provided by the registry team after (a).
c. Follow-up forms including detailed information on maternal, obstetrical and neonatal outcomes, as well as prenatal additional SARS-COV-2 testing results. A follow-up reminder will be sent to the SARS-COV-2 pregnancy registry collaborator by email through the RedCap database to complete the follow-up phase starting within 2 weeks after birth. To allow the physician to link the follow-up to the right patient, the date of enrolment and the patient study ID will be mentioned in each follow-up reminder.

3. PROJECT POPULATION and Study procedures

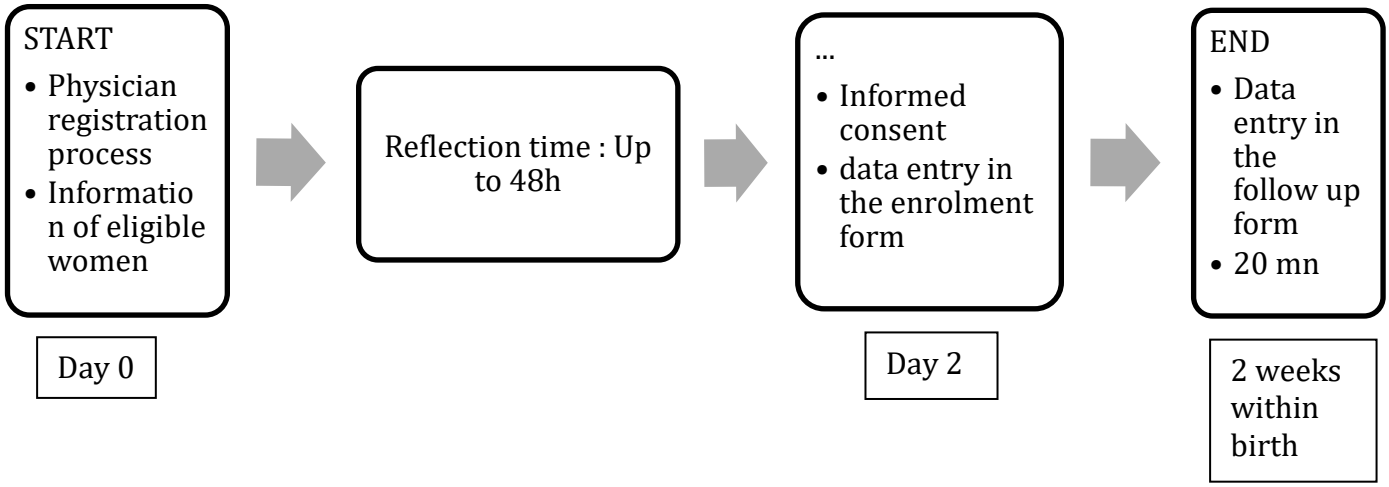
3.1 Project population, inclusion and exclusion criteria

SARS-CoV-2 registry population. The registry population is composed by pregnant women with a suspicion of SARS-CoV-2 infection (i.e positive testing to SARS-CoV-2 with the pharyngeal and/or deep nasopharyngeal swab RT-PCR test and/or severe symptoms suggesting a SARS-CoV-2 maternal infection) within facilities with antenatal clinics following their pregnancy.
Inclusion criterion: Pregnant women with a suspicion of infection by SARS-CoV-2
Exclusion criterion: Patients considered as minor in their jurisdiction and patients who have not given their informed consent or are not able to consent for themselves will not be considerate eligible in the registry.
Sample size: ≅ 800-1000 but some aims will not need to reach the full sample size (strong association suspected for several risks).
Study duration: April 2020-April 2024

3.2 Recruitment, screening and informed consent procedure

Patients will be recruited based on the judgment of the registry collaborator who participate to their care or is being mandated by a physician providing or participating to their care.
Information letter and written consent in French, English, Spanish, Portuguese, Chinese and Italian will be available on the web site of the registry.
Each physician enrolled in the registry will be responsible for the conservation of consents forms according to local regulation.
The reflection time granted to the patients is 48 hours. The total duration of the study for the patients is equivalent to the duration of the pregnancy from inclusion to the outcome plus 2 weeks.

3.3 Study procedures and duration



Inclusion in the registry will not result in an additional visit. The information to be entered in the register is collected in clinical routine for the care of patients. If in the future, the development of knowledge about the Covid-19 justifies such an approach, this will be the subject of an amendment to the EC.
The patient will be informed orally as well as by the information letter and the consent form. It is up to the patient to inform the father of the child of this study if he has parental authority. This information can also be transmitted by a member of the research team designated by the attending physician if the patient requests it.

3.4 Withdrawal and discontinuation

There will be no consequence on the care of the patient in the event of withdrawal of consent. Data already collected will be analyzed and the code that links the patient's identity to REDCap will be destroyed by the collaborator who entered the data. Patient will be notified by the information letter and by the consent form.

3 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

It will be evaluated for each future research question by the Registry Scientific Advisory Committee and a biomedical research Ethics committee.

Interim analysis to get an early appraisal of study findings might be considered for some aims and will be submitted for approval to a biomedical research Ethics committee.

4.2. Handling of missing data

To limit the number of missing data we have developed a clear data entry form using data entry helpers (subtitles, examples), limited number of open-ended questions, a predefined range of values when applicable, user-friendly case report form environment using branching logic to reduce fields to fill in, correction of systematic inconsistencies and aberrant value checks.
We will also stay available for assistance by mail. We expect limited number of missing data, and a sensibility analysis will be performed if necessary.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the sponsor.

5.2 Notification of safety and protective measures (HRO Art. 20)

The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21.
Registry project leaders might decide to stop the registry if appropriate (e.g. in case of incomplete or poor-quality information).
The registry will be stopped once the number of patients studied suffices to answer the questions that motivated the registry. The registry data will be kept available until answers to the questions that motivated the registry have all been published. Then, the registry data will be archived.

5.4 Procedure for investigations involving radiation sources

There is no investigations involving radiation sources.

5.5 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

5.6 End of project
Upon project completion or discontinuation, the Ethics Committee is notified within 90 days.

5.7 Insurance
In the event of project-related damage or injuries, the liability of the CHUV provides compensation, except for claims that arise from misconduct or gross negligence.

6 FURTHER ASPECTS

6.1 Overall ethical considerations
For each future research overall ethical considerations will be evaluated by The Registry Scientific Advisory Committee and the competent biomedical research Ethics committee.
Any research project using data gathered through this register will be carried out in accordance to a research plan and with principles enunciated in the current version of the Declaration of Helsinki (DoH), the Essentials of Good Epidemiological Practice issued by Public Health Schweiz (EGEP) or similar, the Swiss Law and Swiss regulatory authority's requirements or similar as applicable. A written approval from a biomedical research Ethics committee will be asked before sharing any data from the registry.

6.2 Risk-Benefit Assessment
Data generation, transmission, storage and analysis of health related personal data within this registry will follow strictly the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5. Minimal risk to the participant is expected by the enrolment in the registry as all health data provided will be stored coded.
The data gathered will allow future research to better characterize the risks associated to SARS-COV 2 infection during pregnancy.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures
For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.
Quality interim monitoring will be done the first week, month and then each 3 months to monitor data quality (rate of missing data, outliers)

7.2 Data recording and source data
The registry will be done using an electronic Case Report Form (Redcap®)
Data sources will stay under the responsibility of physicians.

7.3 Confidentiality and coding
Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project.
Each doctor participating in the register will be required to code the data with the id-number generate by redcap, and keep the list of participants secure according to local regulation.

7.4 Retention and destruction of study data and biological material

When the registry is closed, the data will be stored in a password-protected folder on the CHUV's secure server for ten year.

The data will be available to any research group in the world following the data-sharing initiative provided that they have a clear, non-redundant research question and a biomedical research Ethics committee approval (a list of on-going research projects will be kept available).

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

The CHUV is funding this project.

Authorship (including that of registry committee members) in scientific publications will have to satisfy the conditions of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (www.icmje.org/icmje-recommendations.pdf.).

We declare no potential conflicts of interest

9 REFERENCES

1. Ordinance on Human Research with the Exception of Clinical trials (HRO) https://www.admin.ch/opc/en/classified-compilation/20121177/index.html
2. Human Research Act (HRA) http://www.admin.ch/opc/en/classified-compilation/20121176/201401010000/810.305.pdf
3. Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects)
4. STROBE statement (http://www.jclinepi.com/article/S0895-4356(07)00436-2/pdf)