HMC RESEARCH PROTOCOL

Study Title:	**Q**atar **PRE**gnancy **C**ov**I**d **OU**tcome **S**tudy (Q-PRECIOUS)
Principal Investigator:	Dr. Salwa Abu Yaqoup, Sr. Consultant and Obstetric chair

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NOTE: After completion, kindly delete the instructions provided beneath each section.

1. Synopsis

In this section provide a brief summary of the research study (250-300 words).
The synopsis consists of 1-2 sentences of background, then a concise objective for the research followed by a brief description of research participants, interventions, methods, data collected and proposed analysis ending with the anticipated outcome(s).
Someone who knows nothing about the research should be able to get a clear snap shot of the proposed research and intended outcome.

2. Abbreviations and Acronyms

List abbreviations, acronyms and terms of reference used in the protocol; provide definitions for each as needed

SARS-CoV-2
suspected COVID-19: they have symptoms but have not been tested/awaiting test results/tested negative
confirmed SARS-CoV-2 infection: tested positive for SARS-CoV-2

3. Introduction / Background

Introduction

The coronavirus disease 2019 or 'COVID-19' is respiratory tract infection caused by the novel coronavirus strain initially (1). On 12th March 2020, the World Health Organization declared it as a 'pandemic' outbreak of utmost international concern. Majority of the published evidence have originated from China, where the first coronavirus patient was identified in the Wuhan City in December 2019 (2,3). Previous emerging infections such as, H1N1 influenza virus, Zika virus, severe acute respiratory syndrome corona virus (SARS-CoV) and Middle East respiratory syndrome corona virus (MERSCoV) have shown to have significant impact on maternal as well as perinatal outcomes (4,5).

Epidemiology, transmission and symptoms

Ever since the first case report in China, the infection has been growing at an accelerating pace and has spread across nearly 213 countries worldwide, infecting over 2.8 million people, resulting 206,018 deaths worldwide (as of 26th April 2020)(6). The reported prevalence ranges from 13% at two medical centers in the United States to 43.5% confirmed cases reported during a joint mission by the World Health Organization at Wuhan province in China.

While a vast majority of cases were categorized as mild or uncomplicated, almost 14% of the patient required hospitalization and/or oxygen support and approximately 5% needed an intensive care admission to survive (7). Common clinical manifestations reported among hospitalized patients were

fever (83-100%), cough (59-82%), myalgia (11-35%), headache (7-8%), and diarrhea (2-10%). All patients had an abnormal radiographic chest imaging (3,8,9).

The two routes by which COVID-19 can be spread is through close contact with an infected person wherein the respiratory secretions are transmitted through the eyes, mouth, nose or airways. The second route of transmission is by touching one's own mouth, nose or eyes after touching the surface, object or the hand of an infected person contaminated with respiratory secretions (10).

National Institutes of Health in the United States has classified the disease severity based on the following symptoms,

Severity	**Symptoms**
Asymptomatic	Positive test for SARS-CoV-2 but no symptoms
Mild illness	Any signs and symptoms (eg, fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging.
Moderate illness	Evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SaO2) >93 percent on room air at sea level.
Severe illness	Respiratory frequency >30 breaths per minute, SaO2 ≤93 percent on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300, or lung infiltrates >50 percent.
Critical illness	Respiratory failure, septic shock, and/or multiple organ dysfunction.

COVID-19 and its impact on pregnancy

The obstetrical population is considered vulnerable. Pregnancy involves multiple interactions with the health care system and eventually all are admitted to the hospital for delivery, therefore, managing pregnant population presents a unique challenge during this pandemic. Additionally, the physiological changes and partial immune suppression during pregnancy makes the pregnant women and newborn babies susceptible to several infections. Post-partum hemorrhage, maternal sepsis, preeclampsia, premature rupture of membrane are the most common adverse events reported to have caused by this disease in pregnant women (11).

There are currently limited data on fCOVID-19 infections during pregnancy. Anecdotal evidence suggests that pregnant women do not appear to be different than the general population in terms of disease transmission. In addition, neonatal vertical transmission has been suspected in a neonate of a COVID-19 positive mother (12). Recently, poor maternal and neonatal outcomes including critical care admission, preterm normal and cesarean delivery, premature rupture of the membrane or PROM , fetal distress, stillbirth, and multiple organ dysfunction (1,11,13-17).

Importance of Registry

From the limited information gathered about the novel coronavirus, its impact on pregnancy and newborn and the drastically increasing burden of the disease, it is vital that scientific information concerning the disease is collected and shared in a concise and practical manner. Hence, there is a need to collect case data rapidly, to pool global data on the natural history of women affected by suspected COVID-19 or confirmed SARS-CoV-2 in pregnancy to inform treatment and implement preventative strategies in this and future outbreaks. A centre-based registry, gathering case data prospectively on the effect of SARS-CoV-2 infection from healthcare systems around the world offers a method to accrue clinical outcomes on key research questions from a variety of populations and the Q-PRECIOS register will serve such purpose.

4. Objectives

In this section provide a clear statement of the primary and any secondary objectives of the study

The main aim of this study is to understand the natural course of the COVID-19 infection during pregnancy and postnatal period. To this end the registry objective are to:

1. To form a disease registry linked with other national data sources for women with suspected COVID-19 or confirmed SARS-CoV-2 in pregnancy and their neonates.
   1.1 Study the course of COVID-19 disease i.e. its symptoms, duration, progression in pregnant women
   1.2 Study the pregnancy, postnatal and neonatal effect of COVID-19 disease

   Objective justification

   The in-utero exposure of acute viral infection in some instances is proven to have short- and long-term neonatal effect during the postnatal and childhood period and the Zika virus, measles, mumps and rubella are few examples. COVID-19 is caused by a novel coronavirus strain of unknown consequences. The main purpose of this registry is to collect a baseline data and help establishing future studies and hypothesis generation.

   In addition, we will be exploring the psychological impact of COVID-19 on women during the pregnancy and postnatal period. Stress and anxiety level are increased with potential adverse pregnancy and/or neonatal outcomes especially during infectious disease outbreak. In fact, COVID-19 is associated with adverse maternal and neonatal outcomes resulting in increased level of stress and anxiety. In addition, women during the pregnancy, peripartum, and postpartum period are at increased risk of depression. A risk that has been aggravated by social and physical isolation. Indeed, the social and physical isolation, a critically needed measure to stop the virus transmission, resulted in increased stress and depression level and adversely affecting the mental and physical health of both the mother and the baby.

5. Indicate if this is a retrospective data review

- ☐ **Retrospective Chart/data Review**
- **Provide the date range of the chart review**

6. Study Methodology

This is a nationwide prospective observational registry linked with PAN-COVID UK register of pregnant women with suspected and/or confirmed diagnosis of COVID-19 infection. The enrollment period for this registry is 2 years e.g. May 1, 2020 to May 1st, 2022. Case reports or cases diagnosed ever since 27th Feb will also be included. The authors of published case reports will be contacted for permission. This registry will open for enrollment after IRB/MRC approval. Understanding the effect of COVID-19 infection on pregnancy and its outcome is imperative to help the patients and healthcare providers understand the impact of the disease on the pregnant women and their offspring. There is no intervention planned in this study, therefore, there is a minimal risk associated with this study.

Data collection:

Objective 1: To form a disease registry **linked with other national data sources** for women with suspected COVID-19 or confirmed SARS-CoV-2 in pregnancy and their neonates.

Objective 1.1: Study the course of COVID-19 disease i.e. its symptoms, duration, progression in pregnant women

Objective 1.2: Study the pregnancy and neonatal effect of COVID-19 disease

We will collect information about patient demographic, co-morbidities, clinicopathological information, COVID-19 disease sign, symptoms and its treatment, pregnancy and neonatal outcomes, and women mental health during pregnancy and postnatal period. Regarding pregnancy outcomes, our study will focus on miscarriage, fetal growth restriction and stillbirth, pre-term delivery and vertical transmission and will include fields on ultrasound diagnosis and neonatal care (for details refer to appendix 1, 2 and 3). The woman and her neonate(s) will be followed for 1 year postnatally. Regarding the neonatal outcomes, outlined in the neonatal outcome data collection sheet, includes birth weight, congenital malformations, APGAR score, Breastfeeding, COVID-19 status, respiratory symptoms, neonatal status, and discharge status.

Baseline characteristic and initial assessment will be done during the hospital admission up on COVID-19 diagnosis. Apart from that, there are 7-10 expected follow up telephone calls or online forms to be sent to the patient. The schedule and timeline of data/biospecimen collection are described in table 1.

Data Collection Form or Questionnaire	Baseline	Weekly for 4 weeks	2nd Trimester (GA 24 weeks)	3rd Trimester (GA 34 weeks)	GA 36 weeks	GA 38 weeks	6 weeks postpartum	6 Months	12 Months
Demographics, Health History and COVID-19 Questions	X								
COVID-19 Symptoms Follow-up		X	X	X			X	X	X
Pregnancy Status/Outcomes		X	X	X	X	X	X		
Depression and Anxiety*	X		X	X			X	X	X
Neonatal/Infant Outcomes							X	X	X
*Generalized Anxiety Disorder 7-item (GAD-7) scale and Edinburgh Postnatal Depression Scale (EPDS)									

7. Study Population and Study Setting/ Location

We will include all pregnant patients with suspected or confirmed COVID-19 infection at all HMC facilities including WWRC, CH, AKH, AWH and its associated quarantine sites and their offspring's. The inclusion criteria are:

1. pregnant woman with suspected or confirmed SARS-CoV-2 infection
2. postpartum women who delivered during the last six weeks and
3. neonate(s) of women included in the registry.

We will also contact corresponding authors of case reports of women with COVID-19 from February 2020 for their written consent, by email, for inclusion of the data from these reports in the PAN-COVID register.

Sample size calculation:

Based on a recently published study, 15% of pregnant women were SARS-CoV-2 positive. Out of which only 12% (1.9% of total study patients) were symptomatic. The total number of deliveries per year in Qatar is between 19000 – 21000 deliveries (1650 patients/month). Diagnosis of COVID-19 in Qatar is based on selective criteria i.e. presenting with symptoms, recent travel to endemic area or contact with a confirmed case. However, all women undergoing cesarean section are screened. Therefore and based on 95% CI and 0.05 margin of error, we anticipate a total 170 - 200 case per month.

8. Study procedures

Study Duration and Timelines

This registry is expected to enroll patients for 2 years and follow them up to 1 year postnatally i.e. the registry duration will approximately last for 4 years.

~~Study timeline:~~

Patient enrollment: 2 years

Data collection and curation: 4 years

Study visit numbers: 7-10 visits (see details below); Initial patient visit is expected to last for 30 minutes.

1. baseline,
2. weekly for 4 weeks,
3. At 24 – 34 – 36 – 38 weeks of gestation (provided that baseline and the 4 weekly follow up occurred earlier),
4. At 6 weeks, 6 and 12 months postpartum (for both mother and the baby)

Further to that, the first visit "baseline" will be collected by the primary physician who is taking care of the participating patient. All subsequent visits will be over the phone with mother. Telephone calls for follow up visit are expected to last 15 – 30 minutes.

Data analysis: interim and final

Final report: 2 months

Study procedure:

Suspected patient or patients with positive COVID results will be identified through Cerner. Patients will then be contacted trough the primary physician to explain the study and obtain consent forms once accepted. The primary physician will then collect demographic and baseline data after obtaining patient consent (appendix 1 & 2). Apart from the initial visit, there is no anticipated future study visits. Data collection will be either through the phone or using a self-administered survey that will be sent through SMS.

The maximum follow-up period is 2 years. Based on the gestational age at time of enrolment might vary e.g. if the patient was enrolled early in pregnancy e.g. during the first trimester, the enrollment period will be for 2 years whilst patient who is enrolled in third trimester will be enrolled for less than 2 years.

During the follow up, patient will be contacted over the phone.

Further, we aim to collected data about psychological status i.e. depression and anxiety disorders using the depression Edinburgh Postnatal Depression Scale (EDPS) and the Generalized Anxiety Disorder 7 (GAD-7) surveys. Both surveys, the EDPS and GAD-7, are self-administered surveys that will be sent through an SMS link to the subject. In case patient was identified as having depression or anxiety disorder, the patient will be referred to contact the national mental health helpline at 16000. In case the study team is concerned about the mental health of the subject a direct referral will be sent through Cerner and psychiatrist will be consulted.

Informed Consent

a) *How people will be **NOTIFIED OR APPROACHED** to consider being a research subject in this study?*

Patient will be notified through:

1. Advertisements such as hospital posters and social media. In this case, filling the study online form will be considered as a patient consent.
2. Referral through the primary physician. In this case, the primary physician will explain the study to the patient and document her willingness to participate in Cerner.

b) *Describe the CONSENT PROCESS procedures (When, Where, How, by Whom).*

When an eligible patient is referred by her primary physician, a study coordinator will follow-up by phone to explain the study and obtain a verbal consent to release medical information. In case of self-referral, through filling the online form or calling the study coordinator, a study coordinator will follow with a phone call to explain the study and obtain a verbal informed consent.

c) *Describe HOW LONG potential participants will have to decide on participation.*

The patient will be given a 24-hour period to decide.

d) *Describe how subjects will be SCREENED FOR ELIGIBILITY for the study.*

Patients will be screened based on a confirmatory laboratory result of a positive SARS-CoV-2 PCR results.

e) *Describe how subjects will be ENROLLED into the research study below.*

Once the laboratory result is confirmed and verbal consent is obtained, patient details will be entered into the online study database and given a study number.

Risk

The is a prospective observational registry. There minimal risk of breach of patient confidentiality. To minimize this risk, data will be entered into an electronic registry software. The software will be secured with username and password and only accessible by the study investigators for data entry. Data extraction will only be accessible to study PIs and co-PIs. Paper based data collection sheet will be secured in locked cabinets accessible only by study PIs and co-PIs. Only de-identified data will be shared amongst investigators. If a breach in confidentiality occurs, the IRB will be notified immediately.

Consent form containing the linking information between collected data and patient's identifiable information will be stored in a locked cabinet and/or password locked computer. Information on the password protected computer database will only be accessed by the investigators. Furthermore, the PI's office will remain locked. All study documentation will be stored according to the MRC guidelines

Bio-Specimens & Sample Collection

NA

Outcomes

We believe the results of this study will generate robust data. Prevalence of SARS-CoV-19 infection in pregnancy. Percentage and distribution of COVID-19 presenting sign and symptoms. Percentage of adverse pregnancy and neonatal outcomes. Description of mental status of pregnant women affected by COVID-19 infections.

Data Collection, Management & Confidentiality

a) Indicate below HOW study data will be collected for the proposed research.

☒ *Study Forms* ☒ *Study Database* ☒ *Study Web-Based/App* ☐ *Other*

Please detail how study data will be coded:

Once informed consent is obtained, patient will be given study number and entered in the registry system. Data will be stored registry database/web-portal password protected on Cerner. Only study investigators have access for data entry. For follow up purposes, study investigators will have access to the identifiable information during the data collection period. No individual identity will be disclosed in results and publications.

b) Describe below WHERE and HOW the study data is physically stored.

In case paper-based document, such as signed informed consent, and CRFs, are used it will be stored in locked cabinets. Excel file containing patient identifiable information will be password protected. Electronic CRF (eCRF) will be developed by HMC Cerner team. The requirement for QPRECIOUS forms and feasibility has been discussed with HMC Cerner team (table 2). The forms will be stored on the patient's files with access control and confidential status to prevent form access and edit.
This has already been discussed with HICT/Cerner team through Dr. Shamsa Ahmad, informatics lead at WWRC, coinvestigator in the study and Ob/Gyn consultant (below is the timeline of suggested milestones). For the purpose of this registry, the case report forms will be built in Cerner. The data will be store on central repository. The access of which will be controlled by the study PI and co-PI. To ensure the highest quality, the data will be reviewed by certain study members. The findings of this review along with other KPIs will be presented in the regular meeting of the study steering committee.

Table 2 – Data collection form build on Cerner milestones

S. No	Activity	Owner	Comments
1.	Workflow finalization and users [nurses? Physician obgyn? who will fill the forms, when the forms are filled, which facilities it is used, Clinic setup required or not], to discuss with Graham – HICT CT team and SMEs	Saji/ Hima	To check with Graham availability for meeting
2.	Include RACS team and pursue their approval from Facility with in WWRC	Dr Shamsa / Mr Gasim to discuss with RACS team on approval for forms to be designed	Share approvals with RACS document number for the forms
3	Log a change request in E service.hamad.qa	Dr Shamsa / Mr Gasim	Share interaction with Saji/ Hima/ Paul
4.	Review and analyze the forms	HICT Team	2 persons – 3 days tentative

5	Confirmation regarding the MRC approval for study	Dr Shamsa/ Mr Gasim	
6	Building the forms on CERNER on CERT environment	Cerner	2 weeks
7	Validation of Forms on CERT environment	HICT and SMEs	3 days
8	Issue resolution and revalidation	Cerner- HICT	2 days
9	Building the forms on CERNER on PROD environment	Cerner	2 weeks
10	Validation of Forms on PROD environment – HICT and Team	HICT- SMEs	3 days
11	Go Live support	HICT	1 day

c) Describe below WHO controls access to the study data

Study PI and Co-PIs combined will control access to study data. Data access request must be written and signed by two members.

d) Describe below WHO has access to the study data.

Data entry level:

Data collection/entry: HMC physicians will be eligible to enter patient initial assessment form. Follow up data study investigators and research coordinators will have access to enter patient data into the database.

Data extraction for audit, analysis, report and request of collaboration:

Data extraction access will be granted to specified personnel designated by the register steering committee.

e) Describe below HOW the study data is accessed.

Level access will be employed from HMC Cerner team. Study data will be accessed using a dedicated username and password for specified members.

f) Will subject identifiers be shared outside of HMC? If YES describe below WHOM the study data is shared

No, only deidentified data will be shared.

Subject Withdrawal/ Withdrawal of Consent

In case patient wish to be withdrawn from the study, no further contact will be made. However, collected information up to the point of withdrawal will be included in the analysis. Subjects withdraw from the study will be asked whether they are willing to allow ongoing data collection and his response will be recorded.

9. Statistical Consideration and Data Analysis

Descriptive data: Numerical data will be presented as mean and standard deviation where normally distributed or median and range where it's not normally distributed. Categorical data

will be presented as frequency and percentages. Prevalence of COVID-19 will be calculated as total number of patients who were positive over total number deliveries in the same month. Inferential analysis will be used to assess association and tests will be selected according to suitability.

10. Adverse Event Reporting

This is an observation study. There are no anticipated adverse events.

11. Ethical Consideration.

The registry will only commence after obtaining approval from IRB/HMC an in accordance with good clinical practice, and MoPH regulations

12. Sponsor, Funding & Collaborator Information

MRC

13. Dissemination of Results and Publication policy

Once the project is funded, the study team will initiate monthly meetings to discuss study plans and patient recruitment. Team leaders will also meet monthly to share study updates. Furthermore, the study results will be shared among peers in the department through presentation of study findings. Finally, once the study is completed, we aim to present our finding at the Hamad Medical Corporation Annual Research Day, local and international conferences and in peer-reviewed journals.

14. References

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15. Appendices

- Appendix 1: QP_demographics
- Appendix 2: QP_History-COVID symptoms
- Appendix 3: QP_COVID19_FU
- Appendix 4: QP_Pregnancy follow up
- Appendix 5: QP_Pregnancy outcomes
- Appendix 6: QP_Neonatal outcomes
- Appendix 7: Edinburgh Postnatal Depression Scale (EPDS)
- Appendix 8: Generalized Anxiety Disorder 7-item (GAD-7) scale
- Appendix 9: Budget sheet
- Appendix 10: scheme of delegations