Understanding COVID-19 infection in pregnant women and their babies

periCOVID

Short Title: COVID-19 infection in pregnancy and the newborn (code: **periCOVID**)

Standard Operating Procedure

PHE Reference:	
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LIST OF ABBREVIATIONS

APGARS	Appearance, pulse, grimace, activity, respiration score
BAPM	British Association of Perinatal Medicine
COVID-19	Coronavirus disease 19
ICF	Informed Consent Form
ICU	Intensive care unit
NICU	Neonatal intensive care unit
PHE	Public Health England
RCOG	Royal College of Obstetrics and Gynaecology
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SGUL	St. George's, University of London
SOP	Standard operating procedure
SST	Serum separating tube

1.0 INTRODUCTION

1.1 Study purpose

This surveillance has been set up as part of Public Health England's (PHE) response to the national outbreak of the novel coronavirus. It aims to answer important questions about the impact of the novel coronavirus on pregnant women and their infants, and the mode of transmission from mother to baby. By collecting sequential samples from pregnant women with confirmed coronavirus disease and, after childbirth, from the newborn infant, we hope to better understand the risk and mode of perinatal transmission of the novel coronavirus in order to develop an evidence base for recommendations, guidance and policy decisions for the clinical and public health management of pregnant women, their infants and the healthcare staff that care for them.

1.2 Objectives

1.2.1 Primary Objective

- To assess the risk of COVID-19 infection in newborn infants born to pregnant women with confirmed COVID-19 infection and determine possible routes of mother-to-child transmission

1.2.2 Secondary Objectives

- To test for SARS-CoV-2 in the pregnant woman
- To test for SARS-CoV-2 in the placenta and cord blood at birth
- To test for SARS-CoV-2 in newborn infants of women with confirmed COVID-19
- To assess the immune responses to SARS-CoV-2 in pregnant women and their babies
- To determine whether SARS-CoV-2 is found in breast milk
- To determine whether SARS-CoV-2 is found in neonatal urine and faeces
- To determine the duration of excretion of SARS-CoV-2 in all mother and baby samples
- To genetically sequence SARS-CoV-2 samples

1.3 Scope of this standard operating procedure (SOP)

This SOP is intended for all research staff involved in the periCOVID study. However, this does not replace the protocol that all researchers involved in periCOVID study should familiarise themselves with.

2.0 STUDY TIMELINE FLOWCHART

Recruitment

- Informed consent form to be signed by patient and stored locally by clinical staff
- Clinical questionnaire to be completed and entered into REDCap database by clinical staff
- Recruitment samples to be taken around the time of COVID-19 diagnosis and sent to SGUL via DX delivery by clinical staff or via Royal Mail by participants
- Clinical staff to provide patient with one month follow up sample kit upon discharge from hospital or at her next antenatal appointment

One month follow up (if not delivered within 4 weeks of COVID-19 diagnosis)

- Pregnant woman to take all swab samples from herself and bring to her follow up appointment
- Blood sample to be taken from pregnant woman by clinical staff at the follow up appointment
- All samples (swabs and blood) from pregnant women to be sent to SGUL via DX delivery by clinical staff or via Rotal Mail by participants

Delivery

- Mother and baby clinical questionnaires to be completed and entered into REDCap database by clinical staff
- Delivery samples to be taken at the time of or within 48 hours of delivery and sent to SGUL via DX delivery by clinical staff or via Royal mail by participants
- Mother to be discharged home with all mother and baby follow up sample kits after delivery

Weekly postnatal follow up samples (EVERY WEEK for 5 weeks)

- Swab samples from mother and baby to be taken weekly by the mother at home
- Sample kits to be packaged and sent to SGUL by the mother via Royal Mail

Six-week postnatal follow up

- Mother to take all swab samples from herself and baby at home and bring the swabs to the follow up appointment with gold top blood bottles
- Blood to be taken from mother and baby at final appointment by clinical staff
- All samples (swabs and blood) from mother and baby to be sent to SGUL via DX delivery by clinical staff or via Royal Mail by participants

3.0 RECRUITMENT OF PARTICIPANTS

3.1 Advertising

This surveillance will be advertised to obstetricians and neonatologists across England through various channels including email and tweets, professional societies such as RCOG and BAPM.

Details of the surveillance, including the protocol, information leaflets, consent forms, standard operating procedure (SOP) will be available online (http://www.pericovid.com).

Obstetric teams interested in participating will be able to access all the information online and provide patient information leaflet and consent forms to pregnant women with COVID-19 confirmed at their hospital.

3.2 Participation

3.2.1 Inclusion criteria:

Any pregnant woman aged above 18 years with confirmed COVID-19 infection ≥24 weeks gestation (i.e. viable foetus) in England

3.2.2 Exclusion criteria:

If the mother is under 18 years, in prison or unable to give informed consent for other reasons (e.g. learning difficulties, language barriers)

3.3 Enrolment process

All pregnant women ≥24 weeks gestation with a laboratory confirmed diagnosis of COVID-19 infection should be sensitised to the study through the provision of a participant information leaflet and informed consent form (ICF) which will be made available to hospital-based recruiting clinicians and will also be available to download from the periCOVID website (http://www.pericovid.com).

The woman should be given sufficient time by the clinician to consider the information provided and ask any questions. If she agrees to take part, then she will be asked to complete and sign the ICF. The woman should then be provided with a copy of the ICF for her records and the original document stored locally.

Women can also be enrolled directly into the study by contacting the periCOVID team via the study website or by email. Women will need to sign a hard copy of the ICF and scan and return it to the team by email in order to enrol via this method.

Each recruited pregnant woman will be allocated a unique identifier number once she has been registered in the study. This number will be printed on the labels in the sample packs allocated to the mother at the beginning of the study. The woman will have the prefix “M” on her unique identifier number and the baby, once it is born, will have the prefix “B” on their unique identifier number. This is to aid differentiation between samples from the mother and the baby. In the case of multiple pregnancies, the different infants will be indicated by the suffix A, B, C etc (for example, in the case of twins, their unique identifier numbers would be B1001A and B1001B)

Once the patient is enrolled in the study, the clinician can begin to input the patient’s clinical data into their REDCap record. If the clinician has not received their REDCap log in details by this point, they are advised to contact the periCOVID team by email (pericovid@sgul.ac.uk).

4.0 CLINICAL QUESTIONNAIRES

4.1 Questionnaire at recruitment

At recruitment, the clinician or the periCOVID team will be required to complete a short online questionnaire about the newly consented pregnant woman using the participant's medical records.

This questionnaire aims to capture baseline data relating to the mother's medical history, her current pregnancy and the clinical course of her COVID-19 infection including:

- Maternal characteristics (age, ethnicity, significant past medical history)
- Onset and duration of symptoms
- Method of SARS-CoV-2 confirmation (PCR results, swab type, commercial platform)
- Pregnancy information (gestational age at diagnosis, number of foetuses, pregnancy related complications, radiology findings, laboratory findings, ventilation support, ICU admission, estimated foetal weight, foetal abnormalities)

4.2 Questionnaire at delivery

Following the delivery of the baby, the study team will also complete a short online questionnaire about the delivery, and the status of the newborn at birth and until hospital discharge using the mother's and infant's clinical records.

This questionnaire aims to capture data relating to both the mother and infant, including:

- Pregnancy outcome (livebirth, stillbirth, miscarriage, termination)
- Delivery information (gestational age at delivery, delivery method, intrapartum or postpartum complications, placental pathology)
- Neonatal outcomes (evidence of COVID-19, APGARS, NICU admission, respiratory morbidity, duration and type of ventilation support, infectious morbidity, neurological morbidity)

5.0 CLINICAL SAMPLES

5.1 Sample collection schedule

Timing of sample *(preferred timeframe)*	**Origin of samples**	**Samples required**
At recruitment (*within 14 days of diagnosis of COVID-19*)	Mother	Blood (serum) 5ml Throat swab Rectal swab Urine swab
One month after diagnosis of COVID-19 (*within 3-6 weeks of diagnosis of COVID-19, if baby not delivered*)	Mother	Blood (serum) 5ml Throat swab Rectal swab Urine swab
At delivery (*within 48 hours of delivery*)	Mother	Blood (serum) 5ml Throat swab Rectal swab Urine swab Breast milk (colostrum) Cord blood (5ml) High vaginal swab Placenta swabs (x2) Amniotic fluid swab (in planned C-section)
	Baby	Nasal swab Stool swab Urine swab
Weekly postnatal samples *(on Monday-Wednesday each week)*	Mother	Throat swab Rectal swab Urine swab
	Baby	Nasal swab Stool swab Urine swab
Six-week postnatal follow up *(within 2-8 weeks of delivery)*	Mother	Blood (serum) 5ml Breast milk Throat swab Rectal swab Urine swab
	Baby	Blood (serum) 2-5ml Nasal swab Urine swab Stool swab

* samples that are underlined must be taken by a suitably trained healthcare professional

5.2 Sample collection kits

The periCOVID team will provide recruiting hospitals with sample collection packs containing the following pre-prepared kits in order for samples to be collected from participants at different time points. Each pack will contain all equipment required to safely package the samples and send to the SGUL laboratory for processing.

Each sample kit will also contain pre-printed labels with the patient's unique identifier number and a specimen collection form which should be returned to SGUL along with the samples to aid processing in the lab. No identifiable patient information should be included on these forms.

Women who are recruited directly into the surveillance by the periCOVID team will be sent their sample collection kits via Royal Mail and will be required to present each kit to their responsible clinician for the collection of their samples. Each sample kit will contain all of the equipment required to return the collected samples to SGUL via Royal Mail. The collection of these samples will be at the discretion of the participant's responsible clinician. The samples collected will remain the property of the participant until received by SGUL.

5.2.1. Recruitment pack (for samples from the pregnant woman at the time of COVID-19 diagnosis):

- one gold-topped blood bottle (SST) for collection of maternal blood (5ml)
- **three** swabs in viral/universal transport medium - for the collection of samples from the throat, rectum (faeces) and urine

5.2.2. One month after diagnosis of COVID-19 sample kit:

- one gold-topped blood bottle (SST) for collection of maternal blood (5ml)
- **three** swabs in viral/universal transport medium - for the collection of samples from the throat, rectum (faeces) and urine

5.2.3. Delivery pack (containing three kits for samples from the mother and baby around the time of delivery):

- **Birth (a) (for samples from the mother around the time of delivery):**
  - one gold-topped blood bottle (SST) for collection of maternal blood (5ml)
  - **four** swabs in viral/universal transport medium - for the collection of maternal samples from the throat, rectum (faeces), urine and breast milk (colostrum)

- **Birth (b) (for samples to be taken during delivery):**

  - one gold-topped blood bottle (SST) for cord blood (5ml)

  - **four** swabs in viral/universal transport medium for collection of:

    i. placenta swabs (x2) for collection of samples from the maternal **and** foetal side of the placenta

    ii. high vaginal swab

    iii. amniotic fluid (membrane) swab - **ONLY to be performed in patients who deliver via a planned Caesarean section**

- **Birth (c) (for samples from the baby around the time of delivery):**

  - **three** swabs in viral/universal transport medium - for the collection of infant samples from the nose, stool and urine

5.2.4. Weekly sample kits following the delivery of the baby (for five weeks):

- **three** swabs in viral/universal transport medium - for the collection of maternal samples from the throat, rectum (faeces) and urine

- **three** swabs in viral/universal transport medium - for the collection of infant samples from the nose, stool and urine

NOTE: the mother will be required to send these samples to SGUL using the pre-paid pre-labelled envelope enclosed within the kit

5.2.5. Six week follow up sample pack (final kit):

- **two** gold-topped blood bottle (SST) – for collection of maternal blood (5ml) and infant blood (2-5ml) blood

- **four** swabs in viral/universal transport medium - for the collection of maternal samples from the throat, rectum (faeces), urine and breast milk

- **three** paediatric swabs in viral/universal transport medium - for the collection of infant samples from nose, stool and urine

See **section 2.0** for the study timeline flow chart

5.3 Sample timings

5.3.1 Recruitment samples from the pregnant woman

The periCOVID team will work with the recruiting obstetric teams to obtain timely samples from the mother following her diagnosis of COVID-19 in the most pragmatic way.

Where possible, recruitment samples should be obtained from the participant while she is hospitalised with COVID-19 (if appropriate infection control procedures are in place) or at the participant's home if the local team has the facility to undertake home visits safely with appropriate personal protective equipment.

Alternatively, the recruitment samples may be taken within 14 days from symptom onset if this can be arranged, or, if this is not possible, when the woman attends the hospital for her next antenatal or other appointment.

5.3.2 Follow up samples from the pregnant woman one month after COVID-19 diagnosis

For women who are enrolled by clinicians at a designated study site, the pregnant woman should be provided with the one month follow up sample kit prior to discharge from hospital following her admission with COVID-19 or at her next antenatal clinic appointment, dependent on which is more convenient for the patient. Women who are enrolled directly by the periCOVID team will be provided with this kit at the point of recruitment and should liaise with their responsible clinician to determine the most appropriate time for these samples to be taken.

All enrolled women should be offered an appointment approximately one month after their COVID-19 diagnosis (within 3-6 weeks) in order to have a blood sample taken (10ml blood in a gold-topped blood bottle) and submit their follow up throat, urine and rectal swabs to their clinical team. All samples should then be sent to SGUL by clinical staff using the pre-paid pre-labelled envelope provided. If recruitment samples have not yet been taken during the one month period after onset of COVID-19 symptoms in the pregnant woman, then the recruitment samples should be taken first and the one month follow samples delayed for one month after the recruitment samples are taken where possible

If the woman delivers before the time these samples were due, this step should be omitted and clinicians should proceed to take the delivery samples at the time of delivery.

5.3.3 Samples from mother and baby taken around the time of delivery

It is advised that the delivery kits be kept on labour ward in anticipation of the arrival of women who are enrolled into the study by clinical teams at designated study sites.

Women who are enrolled directly into the study by the periCOVID team should inform their responsible clinician of their enrolment into the study prior to delivery to determine whether they would be happy to take these samples. The samples should be sent to SGUL by Royal Mail after delivery at the earliest convenient time for the participant.

Time critical samples (cord blood and placenta swabs) should be taken at the time of delivery by trained staff. All other samples should be collected from the mother and baby within 48 hours of delivery where possible.

Amniotic fluid (membrane) swabs should only be performed in patients who deliver via a planned Caesarean section to prevent contamination by other bodily fluids.

5.3.4 Weekly postnatal samples from mother and baby

Upon discharge from hospital following the delivery of her infant, the mother will be provided with a box containing **six** follow up sample kits. Five of the kits will contain swabs for the mother and baby, and sixth kit will also contain gold-topped blood bottles for the final blood sample in addition to the swabs (see **section 5.3.5**).

Each kit will contain all of the equipment required in order for the mother to collect the samples from herself and her baby at home, as well as an information sheet advising the mother of the safest way to collect the samples. Information regarding how samples can be taken and how to safely package the items will also be made available on the periCOVID website. (http://www.pericovid.com).

The mother will be required to label each swab with a pre-printed label with her and her baby's unique identifier number and complete the specimen collection forms by documenting the date of sample collection and which samples she has collected.

The samples along with the sample form should then be packaged in the pre-paid pre-labelled envelope in accordance with the enclosed instructions and sent to the periCOVID team at SGUL by the mother.

The mother is encouraged to send the samples on the same day that she collects them and to send the samples during the first half of the week where possible (either **Monday, Tuesday or Wednesday)** to allow time for the samples to arrive at SGUL for processing before the end of the week.

5.3.5 Follow up samples from mother and baby at six weeks

The final follow up kit will contain two gold top blood bottles in addition to the mother and baby swabs. The clinical team should arrange with the mother to take blood samples from her and her baby at around six weeks postpartum. The mother will be advised to collect all swab samples prior to attending this appointment and bring the samples with her to hand over to the clinical team. Once the blood samples have been taken, they should then be sent along with the swabs to SGUL by the clinical team using the pre-addressed envelope provided.

5.4 Sample collection standards

- All blood samples will be taken at the time of routine blood samples where possible
- All samples should be labelled with the participant's unique identifier number
- Specimen collection forms should be completed to match the details provided on each sample and included with samples posted to SGUL
- All samples should be packaged in accordance with the instructions provided in the kits and sent to SGUL in the pre-paid pre-labelled envelope provided
- The results of the samples will not be available in real time and, therefore, will have no impact on management of individual patients.

6.0 LABORATORY STANDARDS

6.1 Sample storage

All samples will be stored at -70 degrees Celcius until analysis at the PHE laboratory at St George's, University of London.

During the consenting process, participants will be given the option of donating their and their baby's anonymous blood samples to SGUL for future studies and/or the PHE Seroepidemiology Unit collection, where the blood samples will be stored for five years. If the participant does not consent to this, their samples will be destroyed after analysis; this decision will not preclude them from participating in this study.

6.2 Laboratory assays

6.2.1 Swab testing

Briefly, RNA will be extracted using commercial kits and an RT-qPCR assay for the detection of SARS-CoV-2 RNA will be run on each sample.

6.2.2 Serum testing

Serum samples will be tested in an ELISA that uses an immunocomplex of the novel CoVID19 recombinant antigen-human anti-CoVID19 IgG/IgM HRP-labelled anti-human IgG/IgM tracer antibody, already in use at PHE Porton.

At a minimum, for immunological assays will be performed on blood obtained at the following time points:

- from the mother at recruitment (up to 14 days after the diagnosis of COVID-19), at follow up one month later, at delivery and six weeks postpartum
- from the infant at six weeks postpartum
- from cord blood taken during delivery.

7.0 DATA ENTRY, ANALYSIS AND PRESENTATION

7.1 Data entry and quality assurance

A secure electronic database has been developed for the purpose of this study using REDCap. All participant data will be entered into the REDCap database by the clinician or laboratory staff in accordance with the REDCap user manuals.

Participant forms on the REDCap database will be audited weekly by the study co-ordinator; any errors or critical omissions in data will be fed back to the relevant local lead clinician or the laboratory staff in order for the error to be rectified.

7.2 Data storage and analysis

Data collection will be co-ordinated between PHE Colindale and SGUL, where all the data will be held and all data analysis performed. The Chief Investigator will act as custodian for the surveillance data. Each mother who has participated in the study will be provided with a report of her individual results once the study has concluded.

7.3 Data anonymity

All patient data will be anonymised and guarantees of confidentiality and anonymity given to the research participants will be honoured, unless there are clear and overriding reasons to do otherwise.

8.0 WITHDRAWAL OF PARTICIPANTS

Participants will be able to withdraw consent for participation at any time without prejudice. The Investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

If the participant decides to withdraw, explanation is not mandatory, but would be appreciated and if provided this will be recorded in detail. If a subject chooses to withdraw and does not want any data or samples collected used in the service evaluation they will inform the investigators in writing of this decision.

A participant's withdrawal must be documented by the clinician in their REDCap record in order for this to be reflected in the database.