UNIVERSITY OF OXFORD

INTERCOVID STUDY

The International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st)

INTERCOVID

A prospective cohort study of the effects of COVID-19 in pregnancy and the neonatal period

Study Protocol

Version 4.0

23 April 2020

Contents

Summary

INTERCOVID is a large, multi-national, prospective cohort study with the aim of assessing the effect of COVID-19 in pregnancy on maternal, fetal and neonatal outcomes worldwide. 'Exposed' cases are defined as pregnant women with: a) laboratory confirmed COVID-19; b) radiological pulmonary findings suggestive of COVID-19; c) maternal symptoms compatible with COVID-19, or d) absence of symptoms, whilst in close interaction with a person(s) with confirmed COVID-19. Each 'Exposed' case is compared with two 'non-exposed' pregnant women, considered as representative of the pregnant population at each study site. Both 'exposed' and 'non-exposed' pregnant women will be recruited at any stage of pregnancy; women and their babies will be followed up until hospital discharge post-delivery. We will also conduct a nested case/non-case analysis to identify either risk factors or effect modifiers of the outcomes. Primary outcomes will be two unweighted indices: 'maternal morbidity index' and 'severe neonatal morbidity index;' individual component of the indices will be secondary outcomes.

Assuming that COVID-19 in pregnancy increases the risk of a common outcome, such as preterm birth, from 10% to 15%, it is possible to have 80% power with 500 'exposed' women and 1000 'non-exposed' women (1:2 ratio). Our Data Monitoring Group will evaluate these estimations in interim analyses. We expect that recruitment will take place during 6 months at most. We are using the same data collection forms and data management system as in all INTERGROWTH-21st Project studies (MedSciNet, London, UK). All data will be entered locally into the online system with its built-in extensive quality control facility. Ethical approval has already been obtained from the Oxford Tropical Research Ethics Committee (OxTREC), ref no 526-20.

The study commenced field preparations on 20 April 2020 and recruitment can start immediately. Already, 42 medical institutions globally have agreed to participate. The first Zoom investigators' meeting will take place on 25 April 2020.

The translational value of the INTERCOVID Study is that we will be collecting invaluable baseline outcome data, as recommended by the Pregnancy Research Ethics for Vaccines, Epidemics and New Technologies (PREVENT) Report,[1] to inform risk-benefit analyses for future vaccine trials in pregnant women by providing "potential risk relationships between vaccination and adverse events". Failure to obtain that information runs the risk of pregnant women being denied priority access to a new vaccine or therapy, as has occurred so many times in the past.

Introduction

As a result of the COVID-19 pandemic, the world is confronting arguably one of the greatest socio-economic challenges we have faced in the last 100 years. Over 170,000 COVID-19 related deaths have already been reported and whole countries remain in lockdown with catastrophic financial consequences for society at large.

Perhaps the most dramatic feature of the pandemic is the speed with which COVID-19 has spread through the developed economies of the western hemisphere. The health sector, in its various forms, has reacted by providing emergency care on an unprecedented scale, while the scientific community has focused on evaluating the limited curative options available and the production of a vaccine to prevent future waves of the pandemic.

The most vulnerable people in the population have been identified based on the best evidence currently available and public health preventive measures have been implemented with varying degrees of compliance. However, there is still an urgent need for large-scale research focused on subpopulations that were initially considered at low risk, e.g. pregnant women, newborns and infants. It is surprising that they are considered low-risk because pregnancy is usually a principal target of infectious diseases, as was proven to be the case in the recent Zika virus epidemic. These vulnerable subpopulations have been the subject of a large number of small case reports that cannot possibly evaluate the real risk to mothers, fetuses and infants (see the Background section below).

The history of medicine contains many examples, during such acute episodes, of debates around the need to produce hard scientific evidence versus the need to implement current knowledge. This pandemic is no exception. We should remember, however, that even in the most extraordinary circumstances, solid research was required and conducted before actions or treatments were promoted at large scale. This is best illustrated by the case of the large, multicentre cluster randomised field trial, conducted in the USA to test the effectiveness of the first poliomyelitis vaccine, involving 650,000 children who received the vaccine or a placebo, and another 1.18 million who served as controls.

Our responsibility in the present situation, as researchers in the field of maternal and perinatal health, is to ensure we fully understand the effects of COVID-19 in pregnancy so that we are ready for the next phase, i.e. the testing of a vaccine in the context of a randomised clinical trial. Hence, we present a study protocol that aims to fill the scientific gap in a rigorous yet speedy manner.

Background

The published literature is confusing on the effects of infection during pregnancy with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19). Although some review articles have been published, few add much to one of the first.[2] A member of the INTERCOVID Scientific Advisory Board, Professor Jim Thornton (University of Nottingham, UK), has curated the most complete and up-to-date collection of primary sources on his blog www.ripe-tomato.org. As of 20 April 2020, 51 papers had reported primary data on COVID-19 in pregnancy (Appendix I). However, there are many problems with these sources of information.

Firstly, there has been double counting of cases. This was a particular problem with early reports from China, and rarely made clear by the authors. Using the Global Research Identifier Database www.GRID.ac, it appears only eight out of 28 published reports from China are non-overlapping. This problem also affects Western reports: at least three from New York have included overlapping cases, which the authors acknowledged.

Secondly, most reports are of very small numbers with the larger series (e.g. from Lombardy, Italy) reporting little detail. Eighteen of the 51 papers are single case reports, which are likely to be biased towards severe or unusual disease.

Thirdly, the evidence for *in utero* SARS-CoV-2 transmission to the fetus is based solely on two *JAMA* case reports from China that measured IgM levels in blood drawn from three neonates.[3,4] However, as the *JAMA* editorialists pointed out: 'No infant specimen had a positive RT-PCR test result, so there is not virologic evidence for congenital infection in these cases to support the serologic suggestion of *in utero* transmission'.[5]

Evidence for neonatal infection during the birth process itself is based on a small number of case reports of babies swabbed at different time intervals. The only neonate with significant clinical illness was also born preterm. Of the three documented neonatal deaths, two were to seriously ill mothers: one of whom later died and the other required ECMO. The third was a case report of a stillbirth from China with no other clinical details provided. Finally, to date, only one study has reported a control group.[6]

The limitations of overlap, reporting bias, uncertainty regarding fetal transmission and lack of control groups will also affect the many ongoing national and international registries, which do not prohibit data being included in more than one registry. Hence the need for a multi-national, prospective cohort study of 'exposed' cases and 'non-exposed' pregnant women, representative of the general population.

Study aim

The aim is to provide women, families, health care providers and policymakers with high-quality evidence regarding the effects of COVID-19 on maternal, fetal and neonatal outcomes by carrying out a large, **multi-national, prospective cohort study over 6 months, starting on 20 April 2020**. Monthly data monitoring and interim analyses will provide evidence of the initial trends and guide the study's strategy. The information is needed quickly and at scale to optimise maternal and newborn care, reduce maternal anxiety, inform decision-making about the allocation of resources, and guide the process toward social adaptation. Although it is generally believed that pregnant women with COVID-19 are at similar risk to the general population,[7] there are limited data available, principally from small case series without controls, which cannot answer fundamental questions relating to the effects of the disease on maternal and neonatal outcomes.

Study design

This is a large, multi-national, prospective cohort study. 'Exposed' cases are defined as pregnant women with either: a) laboratory confirmed COVID-19; b) radiological pulmonary findings suggestive of COVID-19; c) maternal symptoms compatible with COVID-19 according to a predefined list, or d) absence of symptoms, whilst in close interaction with a person(s) with confirmed COVID-19 (a proxy for asymptomatic cases, one of the main problems in controlling the pandemic).

This strategy will miss asymptomatic women who were not tested, which is a clear limitation. However, in sites without systematic testing of all pregnant women (the large majority of countries), it is not possible to detect these women at the moment. They will be potentially eligible as 'non-exposed' because they remain in the general population.

'Exposed' cases will be compared with two 'non-exposed' pregnant women per case considered as representative of the pregnant population at each study site. The selection of the 'non-exposed' women is a central point of the study to reduce selection bias. Ideally, we should select all pregnant women in the study sites, but that is clearly impractical. Instead, we decided that the two 'non-exposed women' should be selected immediately after the 'exposure' was identified at the same level of care (e.g. antenatal clinic, hospital in-patient, or labour and delivery) following the routine practice of the unit and within the possibilities of the care demands. The key issue here is the need to avoid systematic bias, i.e. through selecting women because they are too healthy or have other characteristics.

Both 'exposed' and 'non-exposed' women will be recruited at any stage of pregnancy. They and their newborns will be followed up until hospital discharge to quantify the risks associated with SARS-CoV-2 exposure.

To complement the evaluation of 'exposed' and 'non-exposed groups' we will also conduct a nested case/non-case analysis (like a retrospective case-control study) to identify socio-economic and clinical features that are either risk factors or effect modifiers of the effect of COVID-19 on outcomes (see Barros et al.[8] for this analytical strategy). This analysis will be mostly based on the data collected in the *Pregnancy and Delivery Form.*

Study outcomes

We will use, as primary outcomes, maternal pregnancy-related morbidities (e.g. pre-eclampsia and preterm birth) as separate items and construct, as we have done previously, an unweighted 'maternal morbidity index'. We will also use two unweighted composite neonatal outcomes: i) the 'severe neonatal morbidity index', including at least one severe neonatal complication such as intraventricular haemorrhage or necrotising enterocolitis, and ii) the 'neonatal morbidity and mortality index', including at least neonatal death up until hospital discharge, stay in Neonatal Intensive Care Unit (NICU) for ≥7 days, or severe neonatal complication.[9-11] Each individual component of the indices will be evaluated as secondary outcomes.

Sample size considerations

Power calculations are difficult in a large field study, when the case definition is uncertain (facilitating misclassifications) and risk factors and outcomes with unknown degrees of association and prevalence are being explored. So, having balanced power calculations and logistical demands, variations in the peak of the pandemic across sites, and the need to obtain results quickly whilst maintaining data quality, we have opted for a 2:1 'non-exposed' to 'exposed' ratio to improve power. We have estimated that COVID-19 in pregnancy could increase the risk of a common outcome, such as preterm birth, from 10% to 15%. With this rate of effect, it is possible to have 80% power with 500 'exposed' women and 1000 'non-exposed' women.

For an assumed relative risk of 1.5, at 80% power, the required sample size is 700 women per group with a 1:1 ratio. At 90% power, the required sample size is 900 per group

with the same 1:1 ratio. As expected, if we assume a relative risk of 2, at 80% power, the required sample size is 200 per group and at 90% power, the required sample size is 270 per group. It is evident, however, that there are considerable uncertainties with these calculations. We have opted to aim for a target of 500 'exposed' and 1000 'non-exposed' women because we do not envisage problems obtaining this estimated case load in a period of up to 6 months' data collection. Thus, we have taken the pragmatic approach to initiate the INTERCOVID Study within the large network of positive responses we have received and start the study the week of 20 April 2020, as planned. Our Data Monitoring Group (see below) will evaluate these estimations in interim analyses.

INTERGROWTH-21st Network

This large study benefits from the University of Oxford having hosted the well-established network of standardised researchers across the world, who have participated in the various studies of the INTERGROWTH-21st Project (intergrowth21.tghn.org) over the last 12 years. The network has produced 125 scientific papers with over 3000 citations since 2015, which have influenced national and international guidelines in the field of maternal, newborn and infant health, demonstrating its translational value. As a result, we have in place trained research staff and standardised data collection forms focused on maternal and neonatal outcomes, as well as environmental exposures at cluster level. All the documentation links to an online data collection system and quality control measures that provide information almost in real-time. For the present study, we have simply added a form relating to COVID-19, which explains why **we can start the study immediately**.

Participating medical institutions

In the week commencing 13 April 2020, a first round of invitations was sent to our global network, which has already resulted in 42 medical institutions agreeing to participate. Most have collected information in the last month about 'exposed' women that can be added to the database with the corresponding temporal 'non-exposed' women. The study duration at each site (3-6 months) will depend on the progress of the pandemic in areas that have not yet seen many cases (e.g. South America and Africa).

On 20 April 2020, a second wave of invitations was sent to 200 neonatologists and obstetricians (mostly from LMICs) that have taken the INTERGROWTH-21st e-learning

course on newborn postnatal follow-up. They have been standardised for data collection and are ideally trained to participate in a study like this. In addition, based on what happens in the first 2 weeks of the study, we are ready to activate a list of 1500 health care professionals who took the INTERGROWTH-21st e-learning courses in the last 3 years and have been trained following the same procedures and standardized practices.

Finally, we have made contact with the West African Health Organization (WAHO), which has access to a network of medical institutions in 12 countries in sub-Saharan Africa, in addition to our existing collaborators in Ghana, Kenya and Nigeria, so as to target as broad an area of the continent as possible.

A major feature of this phased strategy is that we are involving countries that are at different stages of the disease trajectory, including those with very few reported cases. Thus, by the end of the study, we expect to have the most updated understanding at global level of the maternal, fetal and neonatal morbidity and mortality associated with COVID-19. **We will also have assembled an invaluable platform for future clinical trials aimed at testing therapies or vaccines in pregnant women.**

Ethical considerations

Ethical approval has already been obtained from the Oxford Tropical Research Ethics Committee (OxTREC), ref no 526-20. Informed consent will be obtained according to local practices. The approved consent form includes the statement that anonymised clinical information, test results and images can be 'shared with academic collaborators around the world including the Bill & Melinda Gates Foundation and commercial companies'. Those medical institutions that require local approval as well are doing so, but they do not envisage much delay in starting the study. It is important to stress that the study will not interfere with the clinical management of affected women that will be carried out based on current guidelines.[12]

Publication policy

We will adopt the publication policy that has served the INTERGROWTH-21st Project successfully for the last 12 years: namely that the Principal Investigators and leading contributors at each site will be co-authors on all publications resulting from the INTERCOVID Study.

Data management

We will use the same data management system that was specifically developed for the INTERGROWTH-21st Project studies (MedSciNet, London, UK). It is coordinated centrally by the same team that has accumulated extensive experience with our previous studies. All data will be entered locally into the on-line system with its built-in extensive quality control facility. Queries can be dispatched immediately to the study sites, which provides continuously clean data sets for intermediate analysis.

Data sharing

The intention is to pursue an open data policy in keeping with the principles set out in the Wellcome Trust statement on sharing data during the COVID-19 pandemic (31 January 2020),[13] to which the Bill & Melinda Gates Foundation and all major journals are signatories. Our commitment is to ensure that all stakeholders have rapid access to emerging findings that could aid the global response.

Study Committees

Scientific Advisory Board

We have established a Scientific Advisory Board, with global representation, consisting of experts in maternal, newborn health, epidemiology, virology and public health.

Data Monitoring Group

An independent Data Monitoring Group, (School of Public Health at Berkeley), will evaluate the study's progress every 2 weeks to guide the recruitment process and conduct interim analyses, without statistical testing, informing an external evaluation committee.

Acknowledgements

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APPENDIX I (Ripe-tomato.org)

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INTERCOVID: a prospective cohort study in pregnancy and the neonatal period
(INTERGROWTH 21st Project, University of Oxford)

INTERCOVID Study aim

The aim is to provide women, families, health care providers and policy makers with high-quality evidence regarding the effects of COVID-19 on maternal, fetal and neonatal outcomes by carrying out a large, **multi-national, prospective cohort study over 6 months, starting on 20 April 2020**. Monthly data monitoring and interim analyses will provide evidence of the initial trends and guide the study's strategy. The information is needed quickly and at scale to optimise pregnancy care, reduce maternal anxiety, inform decision-making about the allocation of resources, and guide the process toward social adaptation. Although it is generally believed that pregnant women with COVID-19 are at similar risk to the general population (*NEJM* April 17, 2020), there are limited data available, principally from small case series without controls, which cannot answer fundamental questions relating to the effects of the disease on maternal and neonatal outcomes.

Study design and outcomes

This is a large, multi-national, prospective cohort study. 'Exposed' cases are defined as pregnant women with: a) laboratory confirmed COVID-19; b) radiological pulmonary findings suggestive of COVID-19; c) symptoms compatible with COVID-19 according to a predefined list, or d) no symptoms, whilst in close interaction with a person(s) with confirmed COVID-19 infection (a proxy for asymptomatic cases, one of the main problems in controlling the pandemic). 'Exposed' cases (and two 'non-exposed' pregnant women per case as representative of the general population) will be recruited at any stage of pregnancy. Both 'exposed' and 'non-exposed' women and their newborns will be followed until hospital discharge to quantify the risks associated with SARS-CoV-2 exposure. We will also conduct a nested case/non-case analysis to identify socio-economic and clinical features that are either risk factors or effect modifiers of the outcomes (see *JAMA Pediatrics* 2015 for this analytical strategy).

We will use, as primary outcomes, maternal pregnancy-related morbidities (e.g. pre-eclampsia and preterm birth) as separate items and construct, as we have done previously, an unweighted 'maternal morbidity index'. We will also use two unweighted composite neonatal outcomes: i) the 'severe neonatal morbidity index', including at least one severe neonatal complication such as intraventricular haemorrhage or necrotising enterocolitis, and ii) the 'neonatal morbidity and mortality index', including at least neonatal death up until hospital discharge, stay in Neonatal Intensive Care Unit (NICU) for ≥7 days, or severe neonatal complication. Each individual component of the indices will be secondary outcomes.

Sample size considerations

Power calculations are difficult in a large field study, when the case definition is uncertain (facilitating misclassifications) and risk factors and outcomes with unknown degrees of association and prevalence are being explored. So, having balanced power calculations and logistical demands, variations in the peak of the pandemic across sites, and the need to obtain results quickly whilst maintaining data quality, we have opted for a 2:1 'non-exposed' to 'exposed' ratio to improve power. We have estimated that COVID-19 in pregnancy could increase the risk of a common outcome, such as preterm birth, from 10% to 15%. With this rate of effect, it is possible to have 80% power with 500 'exposed' women and 1000 'non-exposed' women. We do not envisage problems obtaining the estimated case load needed in up to 6 months' data collection. Thus, taking all these issues into account, including the considerable uncertainties, we have taken a pragmatic approach and decided to initiate the INTERCOVID Study next week, as planned. Our Data Monitoring Group (see below) will evaluate these estimations in interim analyses.

INTERGROWTH-21st Network

This large study benefits from the University of Oxford having hosted the well-established network of standardised researchers across the world, who have participated over the last 12 years in the various studies of the INTERGROWTH-21st Project. The network has produced 125 scientific papers with over 3000 citations since 2015, which have influenced national and international guidelines in the field of maternal, newborn and infant health, demonstrating its translational value. As a result, we have in place trained research staff and standardised data collection forms focused on maternal and neonatal outcomes, as well as environmental exposures at cluster level. All the documentation links to an online data collection system and QC measures that provide information almost in real-time. For the present study, we have simply added a form relating to COVID-19, which explains why **we can start the study immediately**.

Participating medical institutions

In the last week, a first round of invitations was sent to our global network, which has resulted in 42 medical institutions agreeing to participate. Most have collected information in the last few weeks about 'exposed' women that can be added to the database with the corresponding temporal 'non-exposed' women. The study duration (3-6 months) at each site will depend on the progress of the pandemic in areas that have not yet seen many cases (e.g. South America and Africa).

On 20 April 2020, a second wave of invitations was sent to 200 neonatologists and obstetricians (mostly from LMICs) that have taken the INTERGROWTH-21st e-learning course on newborn postnatal follow-up. They have been standardised for data collection and are ideally trained to participate in a study like this. In addition, based on what happens in the first 2 weeks of the study, we are ready to activate a list of 1500 health care professionals who took the INTERGROWTH-21st e-learning courses in the last 3 years and have been trained following the same procedures and standardized practices.

Finally, we have made contact with the West African Health Organization (WAHO), which has access to a network of medical institutions in 12 countries in sub-Saharan Africa, in addition to our existing collaborators in Ghana, Kenya and Nigeria, so as to target as broad an area of the continent as possible.

A major feature of this phased strategy is that we are involving countries that are at different stages of the disease trajectory, including those with very few reported cases. Thus, by the end of the study, we expect to have the most updated understanding at global level of the maternal, fetal and neonatal morbidity and mortality associated with COVID-19. **We will also have assembled an invaluable global platform for future clinical trials aimed at testing therapies or vaccines in pregnant women.**

Ethical considerations

Ethical approval has already been obtained from the Oxford Tropical Research Ethics Committee (OxTREC), ref no 526-20. Informed consent will be obtained according to local practices. The approved consent form includes the statement that anonymised clinical information, test results and images can be **'shared with academic collaborators around the world including the Bill & Melinda Gates Foundation and commercial companies'**. Those medical institutions that require local approval as well are doing so, but they do not envisage much delay in starting the study. It is important to stress that the study will not interfere with the clinical management of affected women that will be carried out based on current guidelines.

Publication policy

We will adopt the publication policy that has successfully served the INTERGROWTH-21st Project for the last 12 years: namely that the Principal Investigators and leading contributors at each site will be co-authors on all publications resulting from the INTERCOVID Study.

Data management

We will use the same data management system that was specifically developed for the INTERGROWTH-21st Project studies (MedSciNet, London, UK). It is coordinated centrally by the same team that has accumulated extensive experience with our previous studies. All data will be entered locally into the on-line system with its built-in extensive QC facility. Queries can be dispatched immediately to the study sites, which provides continuously clean data sets for intermediate analysis.

Data sharing

The intention is to pursue an open data policy in keeping with the principles set out in the Wellcome Trust statement on sharing data during the COVID-19 pandemic (31 January 2020), to which the Bill & Melinda Gates Foundation is a signatory. Our commitment is to ensure that all stakeholders have rapid access to emerging findings that could aid the global response.

Scientific Advisory Board and Data Monitoring Group

We have established a Scientific Advisory Board, with global representation, consisting of experts in maternal, newborn health, epidemiology, virology and public health. An independent Data Monitoring Group, (School of Public Health at Berkeley), will evaluate the study's progress every 2 weeks to guide the recruitment process and conduct interim analyses, without statistical testing, informing an external evaluation committee.