ISUOG VIRTUAL INTERNATIONAL SYMPOSIUM 2021

State-of-the-art Ultrasound Imaging in Obstetrics and Gynecology

17-18 April 2021

REGISTER NOW ▸

Using ultrasound together with other technologies to improve the lifelong health of women and babies

- Two streams of scientific content over two days, delivered through the ISUOG virtual platform which will exceed your expectations
- A mixture of lectures and practical, interactive training, including scan demonstrations, pattern recognition sessions and case report discussion
- Leading international and local experts in obstetrics, gynecology and imaging
- Live program delivered from 7:30 - 18:30 Calgary, Canada time (Mountain Daylight Time)
- Content available on Demand, at a time, pace and location to suit you until 17 May 2021
- All non-member registration fees include a 12-month ISUOG basic membership

Provisional program

Sessions will run simultaneously, providing two streams of content both days.

Highlights include:

- Obstetrics: the first trimester, beyond the routine mid-trimester fetal ultrasound scan, screening to improve pregnancy outcomes, fetal growth and health, ultrasound in labor, and more
- Gynecology: ectopic pregnancy, miscarriage, endometriosis, menopause, ovarian tumors, tubal and uterine pathology, and more
- Special sessions include advanced imaging/MRI, fetal therapy and COVID

The symposium will be co-chaired by:

Jo-Ann Johnson (Canada),
Denise Pugash (Canada)

Symposium Advisory Group

Shabnam Bobdiwala (UK)
George Condous (Australia)
Karen Fung-Kee-Fung (Canada)
Jon Hyett (Australia)
Simon Meagher (Australia)
Liona Poon (Hong Kong)
Angela Ranzini (USA)
Magdalena Sanz Cortes (USA)

Who should attend?

This interactive course is designed for Maternal Fetal Medicine (MFMs), OB-GYNs, Radiologists, Sonographers, Geneticists, Researchers, Trainees/ Residents and other maternity care providers. The program will appeal to a wide global audience, with a focus on North American educational needs.

See you ONLINE in 2021! For more information, please visit:
isuog.org/event/17th-isuog-international-symposium.html

isuog.org

Pregnancy and neonatal outcomes of COVID-19: co-reporting of common outcomes from PAN-COVID and AAP SONPM registries

E. Mullins*, M. Hudak*, J. Banerjee, T. Getzlaff, J. Townson, K. Barnette, R. Playle, T. Bourne, C. Lees, on behalf of PAN-COVID investigators and the National Perinatal COVID-19 Registry Study Group[#]

Dr Edward Mullins, PhD
Clinical Lecturer in Obstetrics and Gynaecology
Du Cane Road, London, W12 0HS
Department of Metabolism, Digestion and Reproduction, Imperial College London

Mark L. Hudak, MD
Professor and Chair of Pediatrics
University of Florida College of Medicine – Jacksonville
653-1 W. 8th St.
Jacksonville, FL 32209

Dr Jayanta Banerjee, MD (Res)
Neonatal consultant and Hon Clinical Sen Lecturer
Du Cane Road, London, W12 0HS
Imperial College Healthcare NHS Trust
Institute of Reproductive and Developmental Biology, Imperial College London

Trace Getzlaff BS CS
Database Administrator
Department of Pediatrics
University of Florida College of Medicine - Jacksonville

Julia Townson, PhD
Senior Research Fellow/Senior Trial Manager,
Centre for Trials Research, College of Biomedical and Life Sciences
Cardiff University

Kim Barnette, RRT-NPS, CCRC
Research Administrator, Division of Neonatology
University of Florida Jacksonville Physicians Inc.
655 West 8th Street
Jacksonville, FL 32209

Rebecca Playle PhD
Deputy Director of Statistics
Centre for Trials Research, College of Biomedical ad Life Sciences
Cardiff University

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.23619

Prof Tom Bourne, PhD
Professor of Practice, Imperial College London
Consultant Gyanecologist, Queen Charlotte's and Chelsea Hospital

Corresponding author

Prof Christoph Lees, MD
Professor of Obstetrics and Hon Consultant Obstetrician
Lead, Centre for Fetal Care
Imperial College Healthcare NHS Trust
Institute of Reproductive and Developmental Biology, Imperial College London
c.lees@imperial.ac.uk

*Joint first authors.

#PAN-COVID collaborators are listed in Appendix S1; National Perinatal COVID-19 Registry Study Group investigators are listed in Appendix S2.

Short title: Pregnancy and neonatal outcomes of COVID-19

Keywords: SARS-CoV-2, outcome, stillbirth, fetal growth restriction, coronavirus, preterm delivery, perinatal

Contribution

What are the novel findings of this work?

Preterm delivery occurred in a higher proportion of women with SARS-CoV-2 infection in the PAN-COVID and AAP SONPM registries compared to contemporaneous and historical national data in the UK and US. The majority of preterm deliveries occurred between 32+0 and 36+6 weeks' gestation. SARS-CoV-2 infection in pregnancy did not appear to be associated with a clinically significant effect on fetal growth, adverse neonatal outcome or the rate of stillbirth. Although maternal death was uncommon, the rate was higher than expected based on UK and US population data, which is likely explained by under-ascertainment of women affected by milder or asymptomatic infection in pregnancy in the PAN-COVID study although not in the AAP SONPM study.

What are the clinical implications of this work?

Pregnant women should be counselled that SARS-CoV-2 infection increases the risk of pre-term delivery but not stillbirth, early neonatal death or a small baby. Healthcare providers should recommend SARS-CoV-2 vaccination in pregnant women and women planning pregnancy, alongside enhanced social distancing.

Abstract

Objective: Few large cohort studies have reported data on maternal, fetal, perinatal and neonatal outcomes associated with SARS-CoV-2 infection in pregnancy. We report the outcome of infected pregnancies from a collaboration formed early during the pandemic between the investigators of two registries, the UK and global Pregnancy and Neonatal outcomes in COVID-19 (PAN-COVID) study and the US American Academy of Pediatrics Section on Neonatal Perinatal Medicine (AAP SONPM) National Perinatal COVID-19 Registry.

Methods: This was an analysis of data from the PAN-COVID registry (January 1st to July 25th 2020), which includes pregnancies with suspected or confirmed maternal SARS-CoV-2 infection at any stage in pregnancy, and the AAP SONPM National Perinatal COVID-19 registry (April 4th to August 8th 2020), which includes pregnancies with positive maternal testing for SARS-CoV-2 from 14 days before delivery to 3 days after delivery. The registries collected data on maternal, fetal, perinatal and neonatal outcomes. The PAN-COVID results are presented both overall for pregnancies with suspected or confirmed SARS-CoV-2 infection and separately in those with confirmed infection.

Results We report on 4005 pregnant women with suspected or confirmed SARS-CoV-2 infection (1606 from PAN-COVID and 2399 from AAP SONPM). For obstetric outcomes, in PAN-COVID overall, those with confirmed infection in PAN-COVID and AAP SONPM, respectively, maternal death occurred in 0.5%, 0.5% and 0.2% of cases, early neonatal death in 0.2%, 0.3% and 0.3% of cases and stillbirth in 0.5%, 0.6% and 0.4% of cases. Delivery was pre-term (<37 weeks' gestation) in 12.0% of all women in PAN-COVID, in 16.2% of those women with confirmed infection in PAN-COVID and in 15.7% of women in AAP SONPM. Extremely preterm delivery (< 27 weeks' gestation) occurred in 0.5% of cases in PAN-COVID and 0.3% in AAP SONPM. Neonatal SARS-CoV-2 infection was reported in 0.8% of all deliveries in PAN-COVID, in 2.0% in those with confirmed infection in PAN-COVID and in 1.8% in AAP SONPM; the proportions of neonates tested were 9.5%, 20.7% and 87.2%, respectively. The rates of a SGA neonate were 8.2% in PAN-COVID overall, 9.7% in those with confirmed infection and 9.6% in AAP SONPM. Mean gestational age adjusted birth-weight z-scores were -0.03 in PAN-COVID and -0.18 in AAP SONPM.

Conclusions The findings from the UK and US registries of pregnancies with SARS-CoV-2 infection were remarkably concordant. Preterm delivery affected a higher proportion of women than expected based on historical and contemporaneous national data. The proportions of pregnancies affected by stillbirth, a small for gestational age infant or early neonatal death were comparable to those in historical and contemporaneous UK and US data. Although maternal death was uncommon, the rate was higher than expected based on UK and US population data, which is likely explained by under-ascertainment of women affected by milder or asymptomatic infection in pregnancy in the PAN-COVID study although not in the AAP SONPM study. The data presented support strong guidance for enhanced precautions to prevent SARS-CoV-2 infection in pregnancy, particularly in the context of increased risks of preterm delivery and maternal mortality, and for priority vaccination of women planning pregnancy.

Introduction

At the onset of the COVID-19 pandemic, the WHO designated pregnant women as a vulnerable group based on preliminary reports of increased risk of stillbirth, preterm birth and fetal growth restriction (FGR) and extrapolation from experience with previous respiratory virus outbreaks, including SARS, MERS [1,2,3] and influenza. SARS-CoV-2 outcome data, derived predominantly from case series, have variably reported diagnostic testing, maternal, fetal and neonatal outcomes, and transmission to the neonate[4]. Clinical outcomes appeared to be worse for pregnant compared with non-pregnant women infected with SARS[5,1] or H1N1 influenza[1,6]. Pregnant women were assumed to be at heightened risk of morbidity and mortality from SARS-CoV-2 infection, particularly when symptomatic[7].

Current knowledge about the effect of SARS-CoV-2 infection in pregnancy has been gathered largely from case reports, case series and population surveillance systems in high income countries. These data have focused particularly on the maternal outcomes of women with symptomatic disease, and maternal death, stillbirth and neonatal death have been reported to each occur in around 1% of cases in this context[8]. The risk of an infant testing positive for SARS-CoV-2 is approximately 2.5% in women admitted to hospital with symptomatic disease[8]. Few reports provide robust evidence of transplacental vertical transmission [9].

The results from a living systematic review and meta-analysis suggest that pregnant women with symptomatic SARS-CoV-2 infection are less likely to present with fever and myalgia and more likely to receive intensive care, to require ventilation and to experience a higher risk of preterm birth compared with non-pregnant women[10].

Centre-based registries gather case data prospectively on the effect of SARS-CoV-2 infection from healthcare systems around the world and offer both a practical and scalable method to accrue clinical outcomes on key research questions from a variety of populations and healthcare systems. Two pregnancy registries in English speaking countries have analogous aims and a similar design. The UK's Pregnancy and Neonatal Outcomes of COVID-19 (PAN-

COVID) study utilizes a dataset that collected outcome data focussed on determining the effect of SARS-CoV-2 infection on the risk of miscarriage, fetal growth restriction, stillbirth, pre-term delivery, vertical transmission (suspected or confirmed) and early-onset symptomatic neonatal SARS-CoV-2 infection[11]. It includes fields on ultrasound diagnosis and neonatal care that are not included in other more general studies. The American Academy of Pediatrics (AAP) Section on Neonatal Perinatal Medicine (SONPM) National Perinatal COVID-19 Registry collects data on women who have tested positive for SARS-CoV-2 in samples obtained from 14 days before to 3 days after delivery. Both registries collect maternal demographic and symptomatology data as well as perinatal and neonatal outcomes. In this study, we report the outcomes of pregnancies with SARS-CoV-2 infection, using data from the PAN-COVID study and the AAP SONPM National Perinatal COVID-19 Registry.

Methods

The PAN-COVID study used a purpose-built Elsevier Macro database and collected outcome data from pregnant women with confirmed or suspected SARS-CoV-2 infection who delivered from 1st January 2020 onwards, and their neonates. The PAN-COVID study was sponsored by Imperial College London and funded by the UK Research Institute (UKRI) and NIHR. The protocol for the PAN-COVID study is detailed elsewhere[11], and we briefly describe the methodology below. The study has 177 participating centres in the UK and 10 countries around the world. The main objectives of the PAN-COVID study were to establish a UK and international disease registry for women with confirmed or suspected SARS-CoV-2 infection in pregnancy. Women with suspected SARS-CoV-2 infection were included because capacity for SARS-CoV-2 PCR testing in the UK was limited to hospital-admitted patients until April 2020 and we expected the majority of women with infection not to have received testing before this time. SARS-CoV-2 infection was considered suspected when an untested pregnant woman reported symptoms that her healthcare professionals thought were likely due to SARS-CoV-2. As such, until 30 May 2020, the PAN-COVID study collected data on women with COVID-defining symptoms but no confirmatory test, on women who had a positive test and on women with COVID symptoms and a confirmatory test. From 1 July 2020, symptom data on all participants were collected.

The PAN-COVID study focused on the following research question: in women recruited to the PAN-COVID registry with confirmed or suspected SARS-CoV-2 infection, what were the incidences of miscarriage, fetal growth restriction, stillbirth, pre-term birth and SARS-CoV-2 transmission to the fetus or neonate by vertical or other routes of infection? Recruitment was by verbal consent to limit person-to-person contact during study conduct in the pandemic, and retrospective inclusion was permitted. Weekly contact open sessions were co-ordinated by NW London CRN and the study management team to motivate staff to recruit and enter data. The UK CRN support network of research midwives was facilitated by Urgent Public Health research designation. The study was registered with ISRCTN (ISRCTN68026880). Regional Ethics Committee and Health Research Authority approval for the study was gained.

The AAP SONPM National Perinatal COVID-19 Registry collected data via a REDCap database from pregnant women who tested positive for SARS-CoV-2 in specimens obtained from 14 days before delivery to 3 days after delivery, and opened on 4th April 2020. The AAP SONPM study has 288 participating centres across the United States. The AAP SONPM registry contained information for all maternal/infant dyads entered as of 8th August 2020. It was funded by the University of Florida and in-kind contributions from participating centers. The registry rapidly accrued detailed data on pregnancy, perinatal and neonatal outcomes from mother/infant dyads to assess the impact of SARS-CoV-2 infection across a range of US healthcare settings. Each participating site had the protocol reviewed by its IRB. Each of the hundreds of IRBs that performed the review deemed that the protocol did not require informed consent because all submitted data were de-identified. The University of Florida co-ordinating site undertook: (1) Registration of sites after receiving a letter of approval from its IRB to participate and a signed confidentiality agreement from the site investigator that pledged there would be no sharing of any data beyond the de-identified data that were submitted to the central Registry; (2) Receipt of de-identified data and sharing of reports with participating sites.

Outcomes

PAN-COVID study

In the PAN-COVID study, assessment of outcome required follow-up by individual healthcare professionals who accessed medical records available to them routinely as part of the clinical care team. When a pregnant woman with suspected or confirmed SARS-CoV-2 infection was registered in the database, they were automatically assigned a unique participant identification number. The limit for data collection was 28 days after the delivery or pregnancy loss of the last woman registered.

AAP SONPM National Perinatal COVID-19 Registry

In the AAP SONPM registry, participating investigators extracted outcome data from the hospital electronic medical record and electronically transmitted de-identified data to a REDCap database housed on a secure University of Florida server.

Statistical analysis

The PAN-COVID dataset in the current study was defined as those data records with delivery up to and including 25th July 2020. Pre-specified sample size estimation was not carried out in the PAN-COVID study given that the aim of this observational study was to collate the outcome all consecutive eligible cases in participating centres during an 18-month period from the start of data collection. The PAN-COVID data are reported for all participants with suspected or confirmed SARS-CoV-2 infection, up to and including the censor date, as well as separately for the subset of those with confirmed infection, in order to provide a comparison set for the AAP SOPNM dataset, which included only confirmed cases.

The AAP SONPM dataset in the current study included information for all maternal/infant dyads entered as of 8th August 2020. The AAP SONPM National Registry was conceived as an observational study, and no *a priori* calculation of sample size was performed.

The estimated representative pre-COVID pandemic incidences of miscarriage, SGA and stillbirth in the UK were 30%, 10%, 0.2% respectively. The corresponding prior assumptions of expected outcome proportions during the COVID pandemic were 40%, 15% and 0.4%, respectively. A sample size of 500 would allow estimation of the width of a 95% confidence interval for the proportion of miscarriage as 40 ± 4.2%, for SGA 15 ± 2.9% and for stillbirth 0.4 ± 0.3%. These figures are meant only as a guide, and reference proportions may change over this period. These figures were based on proportions within the UK only; reference proportions vary by country but are of a similar order to those in the UK.

Gestational age at birth was calculated from the expected due date (EDD) and the date of delivery recorded; the date of the last menstrual period was used when EDD was unavailable. In the PAN-COVID study, in multiple pregnancies, birth weight of the first-born infant was collected, while, in the AAP SONPM registry, birth weights of all infants were included. In the current study, birth weight was reported for all singletons and first-born multiples with GA between 22 and 45 weeks. Birth-weight z-scores were calculated according to Fenton et al.[12]. Birthweight z-scores were gestational-age and gender adjusted and limited to be within +/- 4. Missing data for neonatal gender, gestational age and birth weight restricted the number of cases with available data for birth-weight z-score.

Appropriate quantitative analyses were conducted by a dedicated study statistician. Descriptive statistics are presented as number with percentage, or as mean with standard deviation, as appropriate. Selected outcomes (pre-term delivery (23+0 to 36+6 weeks), intra-uterine death/stillbirth (>22+0 weeks) and early neonatal death (≤7 days) were compared between the two registries using 95% confidence intervals for differences[13].

Results

From January 1st 2020 to July 25th 2020, 1606 women with confirmed or suspected SARS-CoV-2 infection at any stage in pregnancy were recruited to the PAN-COVID study; from 4th April 2020 to August 8th 2020, 2399 women with positive maternal testing for SARS-CoV-2 from 14 days before delivery to 3 days after delivery were recruited to the AAP SONPM registry.

Of the 1606 women in the PAN-COVID dataset, data on pregnancy outcome were available for 1601 (99.7%). Livebirth occurred in 1570 (98.1%), miscarriage in 23 (1.4%) and stillbirth/IUD in 8 (0.5%) women. A total of 1593 liveborn neonates resulted from 1548 singleton, 21 twin and 1 triplet gestations. Outcomes relating to the neonates were available for 1454/1593 (91.3%) cases, and data for the purposes of calculating birthweight z-score were available for 1423/1593 (89.3%) cases. Birthweight was available for 1572 pregnancies. In the AAP SONPM registry, there were 2399 mothers with 2446 infants (including 47 mothers who delivered two twin infants) at data censoring on 8th August 2020. Outcome data were available for all mothers and infants. Data for the purposes of calculating birth-weight z-score were available for 2421 neonates.

Demographic details of the mothers are presented in Table 1 and key outcome measures are presented in Table 2. Mean age of the participating women was 32 years (SD 5.4) in the PAN-COVID registry and 28.6 years (SD 8.9) in the AAP SONPM registry. Body mass index (BMI) data were collected in the PAN-COVID study only, with mean maternal BMI of 27.8 (SD 6.4).

Ethnicity classifications were based on those relevant to the origins of the study and are not directly comparable. In the PAN-COVID study, 1066/1603 (66.5%) women were European/North American, 31/1066 (1.9%) were Middle Eastern, 18/1066 (1.1%) were North African, 67/1066 (4.2%) were from Africa south of the Sahara or Caribbean, 120/1066 (7.5%) were from the Indian subcontinent, 148/1066 (9.2%) were SE Asian, 13/1066 (0.8%) were South or Middle American and 140/1066 (8.7%) had 'other' ethnicity. In the AAP

SONPM study, 895 (41.2%) women were white, 9 (0.4%) were American Indian or Alaska Native American, 12 (0.5%) were Native Hawaiian or Other Pacific Islander, 604 (25.1%) were Black or African, 100 (4.2%) were Asian and 737 (30.7%) had other ethnicity; in 35 (1.5%) women racial origin was unknown or not recorded, and in 7 (0.3%) women this field was unanswered/blank. In the AAP SONPM registry, there was almost an equal spread between Hispanic (n=1170) and non-Hispanic (n=1163) ethnicity (ethnicity was unknown or not reported in 66 women). Acknowledging the differences in national data ethnicity classifications, there were lower numbers of women of white ethnicity and higher numbers of women of black or Asian ethnicity than in historic birth statistics for the UK and US (Table 4).

The PAN-COVID study collected data on pre-morbidities in pregnant women in both PAN-COVID overall (n=1604) and in those with confirmed infection (n=651); the majority of the women in both of these groups had no pre-morbidities (63.7% and 61.9% respectively). Common pre-morbidities included gestational diabetes mellitus (n=131; 8.2% and n=63; 9.7%), respiratory disease such as asthma or COPD (n=96; 6% and n=32; 4.9%), pregnancy induced hypertension (n=59; 3.7% and n=30; 4.6%) and chronic hypertension (n=28; 1.7% and n=15; 2.3%). The PAN-COVID study reported on smoking status of the mothers. Among all women (n=1600) and women with confirmed infection (n=647), respectively, 88 (5.5%) and 25 (3.9%) continued smoking throughout pregnancy, 200 (12.5%) and 51 (7.9%) stopped smoking before becoming pregnant, and 81 (5.1%) and 25 (3.9%) stopped smoking after conception.

In the overall PAN-COVID cohort, suspected or confirmed SARS-CoV-2 infection occurred in the first, second or third trimester in 161/1554 (10.4%), 719/1554 (46.3%) and 674/1554 (43.4%) women, respectively; in those with confirmed infection, the corresponding rates were 7/620 (1.1%), 230/620 (37.1%) and 383/620 (61.8%), respectively.

Symptomatology of the mothers at presentation in the two studies is reported in Table 1, and the main outcomes are presented in Table 2.

Maternal mortality

Maternal death was reported in 8/1605 (0.50%) women overall in PAN-COVID, in 3/651 (0.46%) of those women with confirmed infection and in 4/2399 (0.17%) AAP SONPM registrants.

Delivery

Vaginal delivery occurred in 880/1593 (55.2%) cases overall in the PAN-COVID study, in 334/641 (52.1%) of those with confirmed infection and in 1498/2429 (61.7%) AAP SONPM participants. Pre-term delivery (23+0 to 36+6 weeks' gestation) occurred in 190/1578 (12.0%) women overall in PAN-COVID, in 103/635 (16.2%) women in those with confirmed infection and in 382/2431 (15.7%) neonates in AAP SONPM (Figure 1). The majority of the preterm deliveries occurred between 32 0/7 and 36 6/7 weeks' gestation. Spontaneous onset of pre-term labour followed by pre-term vaginal delivery occurred in 40/1578 (2.5%) women overall in PAN-COVID, in 22/635 (3.5%) of those with confirmed infection and in 89/2429 (3.7%) neonates in AAP SONPM. Extremely preterm delivery (< 27 weeks' gestation) occurred in 0.5% of cases in PAN-COVID and in 0.3% in AAP SONPM. Further details of the main outcomes for PAN-COVID and AAP SONPM are presented in Table 3.

Birthweight

The proportion of cases with a small for gestational age (SGA) infant (birth weight <10th percentile for gestational age) was 8.2% in PAN-COVID overall, 9.7% in those with confirmed infection and 9.6% in AAP SONPM (Figure 2). Mean birth weight z-score in AAP SONPM was significantly lower than that in PAN-COVID overall (percentage point difference, 0.14; CI 0.08 to 0.21), but there was no difference noted between the confirmed infections in PAN-COVID and AAP SONPM.

Perinatal mortality

Early neonatal death occurred in 3/1454 (0.2%) infants overall in PAN-COVID, in 2/628 (0.3%) infants of women with confirmed infection in PAN COVID and in 8/2431 (0.3%) infants in AAP SONPM. There were no differences in the rate of intra-uterine death or stillbirth between PAN-COVID overall (8/1601 (0.5%)), those with confirmed infection (4/647 (0.6%)) and AAP SONPM (10/2446 (0.4%)) (Table 3).

Neonatal SARS-CoV-2 infection

Neonatal SARS-CoV-2 screening was carried out in 2134/2431 (88%) liveborn infants in AAP SONPM and in 152/1593 (9.5%) in PAN-COVID overall. A neonatal swab positive for SARS-CoV-2 was found in 44/2444 (1.8%) infants in AAP SONPM, in 14/1578 (0.8%) infants in PAN-COVID overall and in 13/647 (2.0%) infants of women with confirmed infection in PAN-COVID.

Discussion

Maternal deaths related to suspected or confirmed SARS-CoV-2 infection were uncommon in both the PAN-COVID and AAP SONPM studies. Maternal death before discharge from hospital affected a higher proportion of cases compared to the rates reported in UK population surveillance studies (9.8 women per 100,000 maternities)[14]. Maternal mortality in both the PAN-COVID and AAP-SOPNM registries was lower than in other cohort studies of pregnant women admitted to hospital with SARS-COV-2 infection[15–17]. This is likely to be due to the low proportion of pregnant women with infection who were diagnosed and eligible for inclusion. By 1st July 2020, 250,000 cases of COVID-19 had been diagnosed in England, and it was estimated that there had been 3.4 million infections, i.e. fewer than 10% of infections were known[18,19]. When compared to the estimated infection fatality ratio of 0.03% in women and men aged 15-44 in the UK REACT 2 study[19], the assumption that 10% of infections in pregnant women were diagnosed as cases would equate to our reported mortality ratio to being closer to the expected infection fatality ratio.

On the other hand, the high perinatal maternal mortality rate of 167 per 100,000 cases in AAP SONPM, compared to a pre-COVID rate of 17.3 per 100,000 cases to 1 year after birth, cannot be attributed to under inclusion of women with asymptomatic SARS-CoV-2 infection. Early in the pandemic, most US centres implemented universal COVID-19 testing of all pregnant women admitted to the labour and delivery unit. In both registries, when the cause of death was known, all maternal deaths were associated with SARS-CoV-2 infection and, hence, each death represents an additional mortality above the expected baseline rate.

Neither registry reported any neonatal deaths attributable to SARS-CoV-2 infection. The proportion of pregnancies affected by early neonatal death (ENND) was no higher than would be expected based on England and Wales ONS data (0.2%)[20] or the USA from CDC data (0.38%) [21]. An increase in prematurity might be expected to lead to an increase in ENND; however, most preterm babies were born between 32 and 36 weeks' gestation, when the risk for ENND is low.

In both studies, suspected or confirmed SARS-CoV-2 infection resulted in fewer than 10% of babies being born small for gestational age and did not change the expected distribution of birth weight z-scores. The proportion of pregnancies resulting in stillbirth (1 in 200) is comparable to that reported in a UK population surveillance study (5.64 per 1000 total births)[22], slightly greater than that reported in provisional Office of National Statistics (ONS) data for January to September 2020 (0.39%)[23], and comparable to that reported in USA National Vital Statistics System data (611.7 per 100,000 live births) [24]. This is reassuring given that case reports of pregnant women with MERS or SARS infection suggested increased rates of stillbirth and fetal growth restriction[4].

Common to both registries was a high proportion of cases with pre-term delivery: 12.0% in PAN-COVID and 15.7% in AAP SONPM. The rate was 60% higher in PAN-COVID than is expected for England and Wales based on ONS data for January-September 2020 (7.5%)[23], and 57% higher in AAP SONPM than expected based on US National Vital Statistics Reports for 2018 (10%)[25]. As the proportion of women with spontaneous labour and pre-term vaginal delivery was low, a high proportion of pre-term deliveries may have been due to physician concern about adverse effects of SARS-CoV-2 infection on the maternal or fetal condition.

Case series have reported low rates of perinatal transmission of SARS-CoV-2 infection [9,26,27]. The proportion of positive neonatal tests for SARS-CoV-2 was approximately 9% in PAN-COVID overall and 10% in those with confirmed infection. A lower rate of 2% was found in AAP SONPM. This difference reflects the near-universal testing strategy in AAP SONPM (2134 of 2431 (87%) livebirths) and selective testing in PAN-COVID (152/1593 (9.5%) neonates tested).

Strengths and weaknesses

This combined PAN-COVID and AAP SONPM report comprises the largest individual patient dataset of maternal and neonatal outcomes among women with suspected or confirmed SARS-CoV-2 infection. There are some differences in the populations, for example in mean maternal age and race/ethnicity distributions; however, demographic and outcome data

from these two registries are otherwise comparable and support the generalisability of the findings.

Preterm delivery was more frequent in both cohorts than expected from contemporaneous and historical UK and US national data; the proportions of cases with spontaneous pre-term vaginal delivery and pre-term caesarean section were comparable between the studies despite the different healthcare settings.

In the PAN-COVID study, the higher than expected proportion of women included who died can be explained in part by under-ascertainment of pregnant women with SARS-CoV-2 who had mild or asymptomatic infection and the registry study design.

Although data were collected from a range of healthcare settings, the majority of participants originated from the US and UK, with 11.1% of women in the PAN-COVID study being from centres in Italy, China, Greece, Indonesia or India. This was a centre-based registry and centres with little exposure to COVID-19 or those which were overwhelmed during the pandemic may have been less motivated or able to participate.

In the PAN-COVID study, it was difficult to associate SARS-CoV-2 infection directly with miscarriage. Patient inclusion occurred during the height of the pandemic, when many early-pregnancy units were closed in the UK. It is plausible that a higher proportion of women than usual may have miscarried without seeking help from a healthcare professional.

Policy-makers and healthcare providers.

Although maternal death was uncommon, a higher proportion of women participating in these studies died in comparison to contemporaneous and historical national rates of maternal mortality in the UK and US. In PAN-COVID, this was due in part to under-ascertainment of women with SARS-CoV-2 infection in pregnancy who had mild or asymptomatic infection.

It is reassuring that SARS-COV-2 infection does not appear to change the expected birth weight distribution or increase the rate of stillbirth. The proportion of women with pre-term

birth, as reported in other cohorts and meta-analyses [8,10,28], is higher than expected in comparison with national contemporaneous and historical data, but may have been influenced by provider decision to deliver early to prevent potential maternal or infant morbidity.

These data support public health guidance issued by numerous countries that advises pregnant women to exercise effective measures to reduce their risk of infection. The data also support priority vaccination of women who plan to become pregnant, in order to reduce the likelihood of preterm delivery and maternal mortality. Such guidance could be incorporated into pre-conception recommendations by national clinical advisory bodies.

The likelihood of and risk factors for true perinatal transmission to the neonate remain ill-defined and poorly understood. National and international healthcare bodies should develop recommendations for the timing and modality of testing of neonates born to pregnant women with SARS-CoV-2 infection to facilitate consistent and meaningful evaluation of vertical transmission.

Acknowledgements

PAN-COVID was funded by the UK National Institute for Health Research and supported by UK Clinical Research Networkand the Urgent Public Health committee. We are grateful to Dr Nigel Simpson for his advice throughout the study.

EM was funded by an NIHR Academic Clinical Lecturer award.

CCL is supported by the UK National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare National Health Service Trust and Imperial College London.

The AAP SONPM was funded by the University of Florida College of Medicine Division of Neonatology and by the in-kind contributions of participating centres.

Alison Perry and Karina Aashamar, study management and administration, Women's Health Research Centre, Imperial College London.

Infrastructure support for this research was provided by the NIHR Imperial Biomedical Research Centre (BRC).

We are grateful for the support provided by NIHR Clinical Research Network (CRN) in England and for the work of Abiola Ojuade and Regimantas Pestininkas at CRN North West London.

PAN-COVID data team at the Centre for Trials Research, Cardiff University: Rebecca Milton, Nigel Kirby, Matthew Robinson-Burt, Christopher Lloyd, Kim Munnery,

We are grateful to Professor Helen Ward, Imperial College, for her comments on this manuscript.

Funding statement

The PAN-COVID registry is funded by the United Kingdom Research Institute (UKRI) and National Institute of Health and Research (NIHR) through COVID-19 Rapid Response Call 2, grant reference MC_PC 19066

The AAP SONPM Registry is funded by the University of Florida College of Medicine Division of Neonatology.

Data Sharing

PAN-COVID: De-identified participant data will be made available to the scientific community with as few restrictions as feasible, whilst retaining exclusive use until the publication of major outputs. Data will be available via the corresponding author.

AAP SONPM: Registry cannot share data due to Data Use Agreements with many of the participating centers that prohibit this.

Competing interest statement

None declared

References

1. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, Ng PC, Lam PWY, Ho LC, To WWK, Lai ST, Yan, WW, Tan PYH Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. *Am J Obstet Gynecol*. 2004;191(1):292-297. doi:10.1016/j.ajog.2003.11.019
2. Li AM, Ng PC, Severe acute respiratory syndrome (SARS) in neonates and children. *Arch Dis Child Fetal Neonatal Ed*. 2005;90(6):461-465. doi:10.1136/adc.2005.075309
3. Shek CC, Ng PC, Fung GPG, Fung GPG, Cheng FW, Chan PKS, Peiris MJS, Lee KH, Wong SF, Cheung HM, Li AM, Hon EKL, Yeun CK, Chow CB, Tam JS, Chiu MC, Fok TF, Infants born to mothers with severe acute respiratory syndrome. *Pediatrics*. 2003;112(4). doi:10.1542/peds.112.4.e254
4. Mullins E, Evans D, Viner RM, O'Brien P, Morris E. Coronavirus in pregnancy and delivery: rapid review. *Ultrasound Obstet Gynecol*. 2020;55(5):586-592. doi:10.1002/uog.22014
5. Lam CM, Wong F, Leung N, Chow M. A case-controlled study comparing clinical course and outcomes of pregnant and non-pregnant women with severe acute respiratory syndrome. 2004;111(August):771-774.
6. Pierce M, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M. Perinatal outcomes after maternal 2009/H1N1 infection: National cohort study. *Bmj*. 2011;342(7811):1-8. doi:10.1136/bmj.d3214
7. Liu H, Wang L-L, Zhao S-J, Kwak-Kim J, Mor G, Liao A-H. Why are pregnant women susceptible to viral infection: an immunological viewpoint? *J Reprod Immunol*. Published online 2020. doi:https://doi.org/10.1016/j.jri.2020.103122
8. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, O'Brien P, Quigley M, Borcklehurst P, Kurinczuk J, Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: National population based cohort study. *BMJ*. 2020;369(m2107). doi:10.1136/bmj.m2107
9. Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan, V, Suffee C, Do Cao J, Benachi A, De Luca D, Transplacental transmission of SARS-CoV-2 infection. *Nat Commun*. Published online 2020. doi:10.1038/s41467-020-17436-6
10. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, Debenham L, Llavall AC, Dixit A, Zhou D, Balaji R, Lee SI, Qui X, Yuan M, Coomar D, van Wely M, van Leeuwen E, Kostova E, Kunst H, Khalil A, Tiberi S, Brizuela V, Broutet N, Kara E, Kim CR, Thorson A, Oladapo OT, MOfenson L, Zamora J, Thangaratinam S, Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis. *BMJ*. 2020;370. doi:10.1136/bmj.m3320
11. Banerjee J, Mullins E, Townson J, Playle R, Shaw C, Kirby N, Munnery K, Bourne Tm Teoh TG, Dhanjal M, Poon L, Wright A, Lees C, Pregnancy and neonatal outcomes in COVID-19: study protocol for a global registry of women with suspected or confirmed SARS-CoV-2 infection in pregnancy and their neonates, understanding natural history to guide treatment and prevention. *BMJ Open*. 2021;11(1):e041247. doi:10.1136/bmjopen-2020-041247
12. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr*. 2013;13(1). doi:10.1186/1471-2431-

13-59
13. Newcombe R. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med*. 1998;17(8):873-890.
14. MBRRACE. *Saving Lives, Improving Mothers' Care Learned to Inform Maternity Care from theUK and Ireland Confidential Enquiries into Maternal and Morbidity 2014–16*.; 2018.
15. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, O'Brien P, Quigley M, Borcklehurst P, Kurinczuk J, Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: National population based cohort study. *BMJ*. 2020;369(m2107). doi:10.1136/bmj.m2107
16. Sotiriadis A, Chatzakis C. Pregnant women with SARS-CoV-2 infection are at higher risk of death and pneumonia : propensity score matched analysis of a nationwide prospective cohort (COV19Mx). doi:10.1002/uog.23575
17. The WAPM (World Association of Perinatal Medicine) Working Group on COVID-19 Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection. *Ultrasound Obstet Gynecol*. 2021;57:232-241. doi:10.1002/uog.23107
18. GOV.UK. Coronavirus (COVID-19) in the UK, Cases in United Kingdom. Gov.Uk Website. Accessed December 17, 2020. https://coronavirus.data.gov.uk/details/cases
19. Ward H, Atchison C, Whitaker M, Ainslie, KEC, Elliot J, Okell L, Redd R, Ashby D, Donnelly CA, Barclay W, Darzi A, Cooke G, Riley S, Elliot P, Antibody prevalence for SARS-CoV-2 following the peak of the pandemic in England : REACT2 study in 100 , 000 adults Corresponding authors. *MedRxiv*. Published online 2020:1-20. http://www.ncbi.nlm.nih.gov/pubmed/32987007%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7518804
20. ONS. Infant mortality (birth cohort) tables in England and Wales. Published 2017. Accessed December 3, 2020. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/infantmortalitybirthcohorttablesinenglandandwales
21. Ely DM, Driscoll AK. Infant mortality in the United States, 2018: Data from the period linked birth/infant death file. *Natl Vital Stat Reports*. 2020;69(7):1-17.
22. *MBRRACE-UK Perinatal Mortality Surveillance Report, UK Perinatal Deaths for Births from January to December 2016.* 2018. https://www.npeu.ox.ac.uk/downloads/files/mbrrace-uk/reports/MBRRACE-UK Perinatal Surveillance Full Report for 2016 - June 2018.pdf
23. ONS. Provisional births in England and Wales: 2020. Births, deaths and marriages.
24. Hoyert DL, Gregory ECW. Cause of Fetal Death: Data From the Fetal Death Report, 2014. *Natl Vital Stat Rep*. 2016;65(7):1-25.
25. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK. Births: Final data for 2018. *Natl Vital Stat Reports*. 2019;68(13):1980-2018.
26. Yang P, Wang X, Liu P, Wei C, He B, Zheng J, Zhao D, Clinical characteristics and risk assessment of newborns born to mothers with COVID-19. *J Clin Virol*. Published online 2020. doi:10.1016/j.jcv.2020.104356
27. Liu W, Wang J, Li W, Zhou Z, Liu S, Rong Z. Clinical characteristics of 19 neonates born to mothers with COVID-19. *Front Med*. Published online 2020. doi:10.1007/s11684-020-0772-y
28. Flaherman VJ, Afshar Y, Boscardin WJ, Keller RL, Mardy AH, Prahl MK, Phillips CT, Asiodu IV, Berghella V, Chambers B, Crear-Perry J, Jamieson DJ, Jacoby VL, Gaw SL,

Infant Outcomes Following Maternal Infection With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): First Report From the Pregnancy Coronavirus Outcomes Registry (PRIORITY) Study. *Clin Infect Dis*. 2020;2(March):1-4. doi:10.1093/cid/ciaa1411

Figure legends

Figure 1 Gestational age at birth in pregnancies with suspected or confirmed SARS-CoV-2 infection in PAN-COVID study, overall and in those with confirmed infection, and in pregnancies with confirmed SARS-CoV-2 infection in AAP-SONPM registry.

Figure 2 Birth weight percentiles of infants born to mothers with suspected or confirmed SARS-CoV-2 infection in PAN-COVID study, overall and in those with confirmed infection, and in pregnancies with confirmed SARS-CoV-2 infection in AAP-SONPM registry.

Appendix S1 PAN-COVID project partners and investigators

Appendix S2 AAP SONPM National Registry for Surveillance and Epidemiology of Perinatal COVID-19 Infections Participating Centers and Staff

Table 1 Maternal demographics and symptomatology in pregnancies with suspected or confirmed SARS-CoV-2 infection in PAN-COVID study, overall and in those with confirmed infection, and in pregnancies with confirmed SARS-CoV-2 infection in AAP-SONPM registry

	PAN-COVID		
Variable	**All inclusions (n=1606)**	**Confirmed infection (n=651)**	**AAP SONPM (n=2399)**
Age at registration (years)	32.0 (5.4)	31.8 (5.5)	28.6 (8.9)
BMI (kg/m²)*	27.8 (6.4)	28.2 (6.2)	—
Maternal symptoms at presentation			
Asymptomatic	—	—	1820 (75.9%)
Fever	588/1216 (48.4%)	134/349 (38.4%)	195 (8.1%)
New, persistent cough	687/1216 (56.5%)	130/349 (37.2%)	—
Shortness of breath	343/1216 (28.2%)	77/349 (22.1%)	—
URTI	—	—	337 (14.1%)
LRTI	—	—	143 (6.0%)
Chest pain	121/1216 (10.0%)	20/349 (5.7%)	—
Anosmia	229/1216 (18.8%)	36/349 (10.3%)	—
Anosmia/ageusia	—	—	75 (3.1%)
Hoarse voice	101/1216 (8.3%)	8/349 (2.3%)	—
Myalgia	203/1216 (16.7%)	34/349 (9.7%)	—
Myalgia and fatigue	—	—	118 (4.9%)
Fatigue	381/1216 (31.3%)	49/349 (14.0%)	—
Diarrhoea	73/1216 (6.0%)	22/349 (6.3%)	—

GI symptoms (diarrhoea, vomiting, nausea)	—	—	63 (2.6%)
Loss of appetite	134/1216 (11.0%)	24/349 (6.9%)	—
Abdominal pain	34/1216 (2.8%)	6/349 (1.7%)	—
Delirium	14/1216 (1.2%)	1/349 (0.3%)	—
None of the above	159/1216 (13.1%)	134/349 (38.4%)	—
Other/nothing selected	—	—	99 (4.1%)
Ethnicity			
European / North American	1066/1603 (66.5%)	319/648 (49.2%)	989 (41.2%)
Middle East	31/1603 (1.9%)	11/648 (1.7%)	
Northern Africa	18/1603 (1.1%)	9/648 (1.4%)	
Africa South of Sahara / Caribbean	67/1603 (4.2%)	38/648 (5.9%)	604 (25%)
Asia			100 (4.2%)
Indian subcontinent	120/1603 (7.5%)	79/648 (12.2%)	
SE Asia	148/1603 (9.2%)	108/648 (16.7%)	
South - Middle America	13/1603 (0.8%)	11/648 (1.7%)	
Other	140/1603 (8.7%)	73/648 (11.3%)	737 (30.7%)

Data are given as mean (SD) n/N (%) or n (%). Available data are presented. *Data available for 1585 and 648 women in PAN-COVID all inclusions and PAN-COVID confirmed infection, respectively.

Table 2 Maternal and neonatal outcomes in pregnancies with suspected or confirmed SARS-CoV-2 infection in PAN-COVID study, overall and in those with confirmed infection, and in pregnancies with confirmed SARS-CoV-2 infection in AAP-SONPM registry.

	PAN-COVID		
Outcome	**All inclusions (n=1606)**	**Confirmed infection (n=651)**	**AAP SONPM (n=2399)**
Maternal death	8/1605 (0.5%)	3 (0.5%)	4 (0.17%)
Early neonatal death	3/1454 (0.2%)‡	2/628 (0.3%)‡	8/2431 (0.3%)‡
Pregnancy outcomes			
Livebirth	1570/1601 (98.1%)	631/647 (97.5%)	2431/2446 (99.5%)‡
Miscarriage	23/1601 (1.4%)	12/647 (1.9%)	5/2446 (0.2%)‡
Intra-uterine death/stillbirth	8/1601 (0.5%)	4/647 (0.6%)	10/2446 (0.4%)‡
Mode of delivery (all births)			
Vaginal	880/1593 (55.2%)‡	334/641 (52.1%)‡	1498/2429 (61.7%)‡
Caesarean section	713/1593 (44.8%)‡	307/641 (47.9%)‡	931/2429 (38.3%)‡
Pre-term delivery	190/1578 (12.0%)	103/635 (16.2%)	382/2441 (15.7%)‡
Spontaneous onset of pre-term labour and vaginal delivery	40/1578 (2.5%)	22/635 (3.5%)	89/2429 (3.7%)‡
Pre-term caesarean section	113/1578 (7.2%)	64/635 (10.1%)	245/2429 (10.1%)‡
GA at birth (22+0 to 45 weeks) (all births)			
22+0 to 26+6 weeks	10/1562 (0.6%)	8/629 (1.3%)	12/2441 (0.5%)‡
27+0 to 31+6 weeks	25/1562 (1.6%)	16/629 (2.5%)	49/2441 (2.0%)‡
32+0 to 36+6 weeks	158/1562 (10.1%)	82/629 (13.0%)	330/2441 (13.5%)‡
37+0 to 45+0 weeks	1369/1562 (87.6%)	523/629 (83.2%)	2050/2441 (84.0%)‡
Birth weight†			
Percentile			
<0.5th	9/1423 (0.6%)	3/577 (0.5%)	4/2421 (0.2%)‡
0.5th to 2nd	16/1423 (1.1%)	7/577 (1.2%)	46/2421 (1.9%)‡
2.1st to 9.9th	92/1423 (6.5%)	46/577 (8.0%)	182/2421 (7.5%)‡
10th to 25th	219/1423 (15.4%)	85/577 (14.7%)	480/2421 (19.8%)‡
25.1st to 50th	383/1423 (26.9%)	167/577 (28.9%)	714/2421 (29.5%)‡
50.1st to 75th	383/1423 (26.9%)	160/577 (27.7%)	607/2421 (25.1%)‡
75.1st to 91st	224/1423 (15.7%)	77/577 (13.3%)	262/2421 (10.8%)‡
91.1st to 98th	75/1423 (5.3%)	24/577 (4.2%)	93/2421 (3.8%)‡
98.1st to 99.6th	13/1423 (0.9%)	3/577 (0.5%)	18/2421 (0.7%)‡

>99.6th	9/1423 (0.6%)	5/577 (0.9%)	15/2421 (0.6%)‡
z-score			
All singletons/first-born multiples	-0.03 (0.95)	-0.10 (0.94)	-0.18 (0.94)‡
Singletons only	-0.03 (0.91)§	-0.11 (0.89)*	
Positive neonatal SARS-CoV-2 swab among:			
All tested neonates	14/152 (9.2%)‡	13/131 (9.9%)‡	44/2134 (2.1%)‡
All deliveries	14/1578 (0.8%)**	13/635 (2%)**	44/2441 (1.8%)‡

Data are given as n/N (%), mean (SD) or n (%). Available data are presented. Numbers are expressed as percentage of women, unless indicated otherwise. ‡Number expressed as percentage of individual neonates/fetuses. †Reported for all singletons and first-born multiples with GA between 22 and 45 weeks and z-score between +/- 4. **Not all neonates were tested; data are presented for comparison with AAP-SONPM. § n=1401 1391. *n=567. GA, gestational age.

Table 3 Difference in rates of adverse perinatal outcome between pregnancies with confirmed or suspected SARS-CoV-2 infection in PAN-COVID study and pregnancies with confirmed SARS-CoV-2 infection in AAP SONPM registry

Outcome	PAN-COVID (all inclusions) vs AAP SONPM	PAN-COVID (confirmed infection) vs AAP SONPM
Preterm delivery	-3.6 (-5.7 to -1.4)	0.6 (-2.5 to 3.9)
Intra-uterine death/stillbirth	0.1 (-0.3 to 0.6)	0.2 (-0.3 to 1.1)
Early neonatal death	-0.1 (-0.5 to 0.3)	-0.01 (-0.4 to 0.8)

Data are percentage point difference in rate of outcome (95% CI).

Table 4 UK and US maternity ethnicity data

	England & Wales*	USA**
White	71.6%	51.6%
Black	4.2%	14.6%
Asian	8.7%	6.4%
Other	15.5%	27.4%

*2015-2019 aggregate ONS birth statistics data.
**National Vital Statistics Reports (NVSR), Vol. 68, No. 13: Births: Final Data for 2018, November 27, 2019.

Figure 1

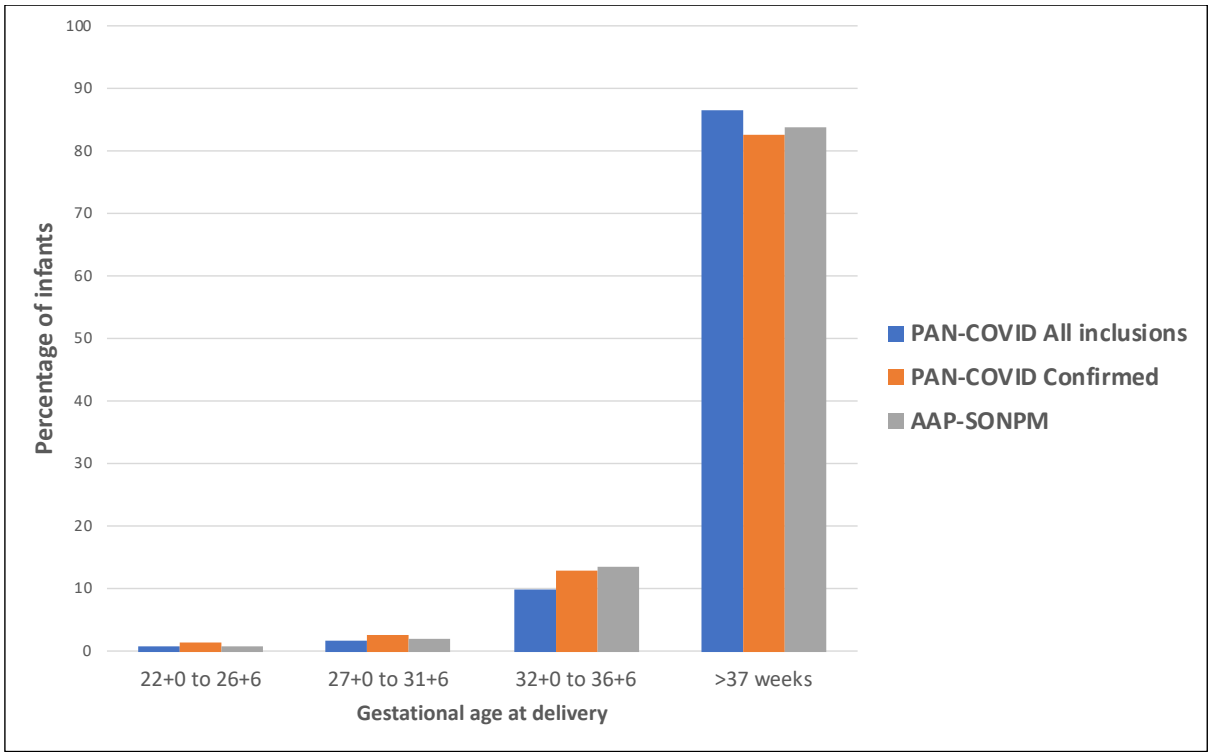

Figure 2