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Full length article

Pregnancy and neonatal outcomes of COVID-19: The PAN-COVID study

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ABSTRACT

Objective: To assess perinatal outcomes for pregnancies affected by suspected or confirmed SARS-CoV-2 infection.
Methods: Prospective, web-based registry. Pregnant women were invited to participate if they had suspected or confirmed SARS-CoV-2 infection between 1st January 2020 and 31st March 2021 to assess the impact of infection on maternal and perinatal outcomes including miscarriage, stillbirth, fetal growth restriction, pre-term birth and transmission to the infant.
Results: Between April 2020 and March 2021, the study recruited 8239 participants who had suspected or confirmed SARs-CoV-2 infection episodes in pregnancy between January 2020 and March 2021.
Maternal death affected 14/8197 (0.2%) participants, 176/8187 (2.2%) of participants required ventilatory support. Pre-eclampsia affected 389/8189 (4.8%) participants, eclampsia was reported in 40/ 8024 (0.5%) of all participants.
Stillbirth affected 35/8187 (0.4 %) participants. In participants delivering within 2 weeks of delivery 21/2686 (0.8 %) were affected by stillbirth compared with 8/4596 (0.2 %) delivering ≥ 2 weeks after infection (95 % CI 0.3–1.0). SGA affected 744/7696 (9.3 %) of livebirths, FGR affected 360/8175 (4.4 %) of all pregnancies.
Pre-term birth occurred in 922/8066 (11.5%), the majority of these were indicated pre-term births, 220/7987 (2.8%) participants experienced spontaneous pre-term births. Early neonatal deaths affected 11/8050 livebirths. Of all neonates, 80/7993 (1.0%) tested positive for SARS-CoV-2.
Conclusions: Infection was associated with indicated pre-term birth, most commonly for fetal compromise. The overall proportions of women affected by SGA and FGR were not higher than expected, however there was the proportion affected by stillbirth in participants delivering within 2 weeks of infection was significantly higher than those delivering ≥ 2 weeks after infection. We suggest that clinicians' threshold for delivery should be low if there are concerns with fetal movements or fetal heart rate monitoring in the time around infection.
The proportion affected by pre-eclampsia amongst participants was not higher than would be expected, although we report a higher than expected proportion affected by eclampsia. There appears to be no effect on birthweight or congenital malformations in women affected by SARS-CoV-2 infection in pregnancy and neonatal infection is uncommon.
This study reflects a population with a range of infection severity for SARS-COV-2 in pregnancy, generalisable to whole obstetric populations.

Introduction

Much information on the effect of SARS-CoV-2 infection in pregnancy has been derived from reported outcomes in women with symptomatic infection and/or those hospitalised. However, in view of the lack of testing in the initial months of the pandemic and the high

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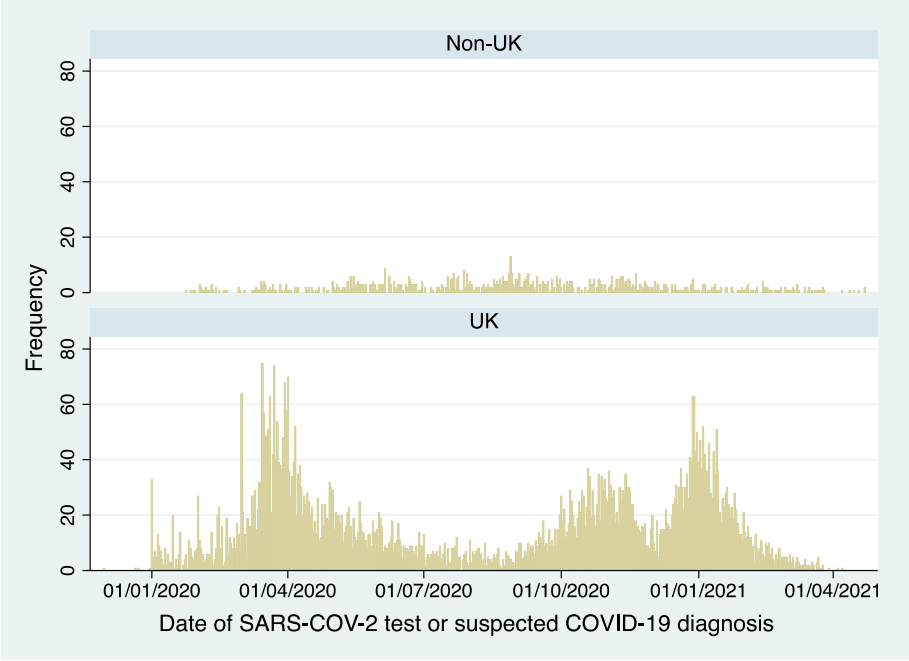

Fig. 1. Frequency histogram for all recruited participants from UK and non-UK centres.

proportion of asymptomatic and mild SARS-CoV-2 infections, the impact of less severe infections in pregnancy has not been captured. It is likely that only a small proportion of women with SARS-CoV-2 infection in pregnancy would be admitted to hospital at the time of a positive PCR test.

In view of this, we designed the PAN-COVID study as a global registry for rapid set-up to recruit women with suspected or confirmed SARS-CoV-2 at any point during their pregnancy. This would include those hospitalised and not hospitalised to gain information on the impact of infection on key perinatal outcomes.

We developed research questions from queries raised by pregnant women in our maternity services, including the impact of infection on miscarriage, stillbirth, fetal growth restriction, pre-term birth and transmission of SARS-CoV-2 to the baby as well as maternal health. We aimed to capture a focussed dataset, feasible for staff working within the constraints of the pandemic, in a range of healthcare settings.

Multiple global registries, e.g. PRIORITY, COVI-PREG, ICMR were established at similar times. As the pandemic progressed, non-pharmaceutical interventions and improvements in treatment for SARS-CoV-2 changed the way pregnant women and their babies were affected by the virus. Variants of the virus were shown to cause more severe disease in women in pregnancy than the wildtype virus [1]. The impact of ethnicity and pre-existing medical conditions on pregnant women with SARS-CoV-2 and the increased risk of pre-term birth became apparent [2–4]. We co-reported our interim findings with the AAP SOPNM registry [3] in February 2021 and called for the prioritisation of vaccination for women in or planning pregnancy.

Methods

Study design

A detailed description of the PAN-COVID methods has been published [5]; in brief, this was a prospective web- based registry, allowing individual clinical centres to enter data via an online central database. Pregnant women were invited to participate if they had suspected or confirmed SARS-CoV-2 infection between 1st January 2020 and 31st March 2021.

We collected data in UK and centres in other countries (described as non-UK for the purpose of this manuscript) and analysed overall and UK/non-UK data.

Study participants

Eligible participants were aged between 18 and 50 years of age and had suspected or confirmed SARS-CoV-2 infection in pregnancy between 1/1/20 and 31/3/21.

Study conduct

Ethical approval was granted by the North West – Haydock REC, reference 20/NW/0212.

Clinical Research Network (CRN) North West London was our co-ordinating CRN and supported our study management team to undertake, with the assistance of established key networks such as the NIHR Reproductive Health and Childbirth Champions, rapid setup of study centres by our data team at the Centre for Trials Research (CTR), Cardiff University.

Eligible women were approached by study investigators for their consent to participate in the study. Data was collected from participants' and their medical records by study investigators.

Statistical analysis

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 outcomes for all consecutive eligible cases in participating centres during an 18-month period from the start of data collection. Once PAN-COVID closed, all logic check, incomplete entries, and missing data queries were collated and sent out to sites. Any data queries that remained unresolved after several attempted site contacts were denoted missing data.

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. Birth-weight z-scores were calculated according to Fenton et al. [6], were gestational-age and gender adjusted and limited to be within +/− 4.

Sample sizes are given for all outcomes in all tables and vary

Table 1
Participants by country, all participants.

Country	Participants (n)	%
ALB	12	0.15
ARG	19	0.23
AUT	3	0.04
CHL	54	0.66
CHN*	54	0.66
CZE	15	0.18
EGY	10	0.12
GBR	7395	89.76
GRC	136	1.65
IDN	109	1.32
IND	239	2.9
ITA	193	2.34
Total	**8239**	**100**

*The participants from HKG (n = 6) were included under CHN.

according to numbers of responses obtained. No hypothesis testing has been included since the study was not designed to determine differences, we have however provided 95 % Confidence Intervals (CI) for selected differences that may be of clinical relevance. It must be noted however that sample sizes for many of the rarer outcomes in the non-UK data are very small and all proportions and CIs must be interpreted in this light.

Participants with confirmed and suspected infections were analysed together as in our interim data paper [3], their pregnancy outcomes were similar and because in the early stages of the pandemic, SARs-CoV-2 testing was only available to those admitted to hospital in the UK.

Data cleaning and descriptive analyses were conducted using SPSS V27.0 and Stata V17.0.

Results

Between April 2020 and March 2021, the study recruited 8239 women who had suspected or confirmed SARs-CoV-2 infection episodes between January 2020 and March 2021 (Fig. 1).

Data were collected from a range of healthcare settings, 7395/8239 (89.8 %) participants were recruited by UK centres, 844/8239 (10.2 %) of women from centres in Italy, China, Greece, Indonesia, India, Argentina, China, Czech Republic, Albania, Austria, Egypt and Chile (non-UK centres, Table 1). Multiple, competing registries were established during the pandemic and our original aim of providing a global registry was not fully achieved.

Participants from the UK had a higher mean age, had a higher proportion with European/North American ethnicity and had a higher proportion of women who were current or ex-smokers compared with

Table 2
Demographics of UK and non-UK participants.

	All participants	*N* UK	UK (SARS-CoV-2 suspected and confirmed)	*N* Non-UK	Non-UK (SARS-CoV-2 suspected and confirmed)
	N, Mean (SD)		**Mean (SD)**		**Mean (SD)**
Age at registration (years)	8239 (31.0 (5.4))	7395	31.2 (5.3)	844	29.4 (5.8)
BMI (kg/m2)*	8080 (27.7 (6.5))	7259	27.8 (6.6)	821	27.1 (5.0)
	N (%)		**N (%)**		**N (%)**
Ethnicity	**8212**	**7368**		**844**	
European / North American	5794 (70.6 %)		5543 (75.2 %)		251 (29.7 %)
Middle East	133 (1.6 %)		105 (1.4 %)		28 (3.3 %)
Northern Africa	111 (1.4 %)		88 (1.2 %)		23 (2.7 %)
Africa south of Sahara / Caribbean	327 (4.0 %)		293 (4.0 %)		34 (4.0 %)
Indian subcontinent	789 (9.6 %)		575 (7.8 %)		214 (25.4 %)
SE Asia	495 (6.0 %)		361 (4.9 %)		134 (15.9 %)
South - Middle America	113 (1.4 %)		32 (0.4 %)		81 (9.6 %)
Other	450 (5.5 %)		371 (5.0 %)		79 (9.4 %)
Smoking status	**8193**	**7354**		**839**	
Never smoked	6359 (77.6 %)		5597 (76.1 %)		762 (90.8 %)
Current smoker	476 (5.8 %)		458 (6.2 %)		18 (2.2 %)
Stopped smoking before this pregnancy	969 (11.8 %)		918 (12.5 %)		51 (6.1 %)
Stopped in pregnancy	389 (4.8 %)		381 (5.2 %)		8 (1.0 %)

* BMI measurement taken either at booking (N = 7,899) or pre-pregnancy (N = 162) (with N = 178 missing time of BMI measurement).

Table 3
Maternal symptoms at presentation.

Presenting symptom (% yes)	All participants	*N* UK	UK (SARS-CoV-2 suspected and confirmed)	*N* Non-UK	Non-UK (SARS-CoV-2 suspected and confirmed)
	N (%)		N (%)		N (%)
At least 1 symptom^	**7747**	**6931**	**5563 (80.3 %)**	**816**	**261 (32.0 %)**
Fever	3018 (39.0 %)		2862 (41.3 %)		156 (19.1 %)
New, persistent cough	3514 (45.4 %)		3388 (48.9 %)		126 (15.4 %)
Shortness of breath	2110 (27.2 %)		2058 (29.7 %)		52 (6.4 %)
Chest pain	737 (9.5 %)		730 (10.5 %)		7 (0.9 %)
Anosmia	2233 (28.8 %)		2172 (31.3 %)		61 (7.5 %)
Hoarse voice	598 (7.7 %)		587 (8.5 %)		11 (1.3 %)
Myalgia	1637 (21.1 %)		1580 (22.8 %)		57 (7.0 %)
Fatigue	2637 (34.0 %)		2597 (37.5 %)		40 (4.9 %)
Diarrhoea	429 (5.5 %)		417 (6.0 %)		12 (1.5 %)
Loss of appetite	1030 (13.3 %)		998 (14.4 %)		32 (3.9 %)
Abdominal pain	306 (4.0 %)		301 (4.3 %)		5 (0.6 %)
Delirium	70 (0.9 %)		70 (1.0 %)		0 (0.0 %)
None of the above	1804 (23.3 %)		1266 (18.3 %)		538 (65.9 %)

^ This is the percentage of participants who had at least one symptom; In addition, for 492 participants symptoms were not collected at the start of the project, the database was then changed to collect these data on 8th June 2020.

Table 4
Key perinatal outcomes in UK and non-UK participants. TOP –termination of pregnancy.

Outcomes	All participants	UK (SARS-CoV-2 suspected and confirmed)		Non-UK (SARS-CoV-2 suspected and confirmed)	
	N (%)	N UK	N (%)	N non-UK	N (%)
Maternal death	14/8197 (0.2 %)	7365	1 (<0.001 %)	832	13 (1.6 %)
Early neonatal death	11/8050 (0.1 %)	7260	7 (0.1 %)	790	4 (0.5 %)
Pre-eclampsia	389/8189 (4.8 %)	7355	302 (4.1 %)	834	87 (10.4 %)
Eclampsia	41/8192 (0.5 %)	7358	28 (0.4 %)	834	13 (1.6 %)
Ventilatory support for COVID-19	**8187**	**7356**		**831**	
Non-invasive ventilation	103 (1.3 %)		90 (1.2 %)		13 (1.6 %)
Intubation and ventilation	73 (0.9 %)		56 (0.8 %)		17 (2.1 %)
Pregnancy outcomes	**8187**	**7364**		**823**	
Liveborn	8066 (98.5 %)		7267 (98.7 %)		799 (97.1 %)
Miscarriage	82 (1.0 %)		71 (1.0 %)		11 (1.3 %)
Intra-uterine death/ stillbirth (>22 + 6 weeks Gestation)	35 (0.4 %)		22 (0.3 %)		13 (1.6 %)
TOP	4 (0.1 %)		4 (0.1 %)		0 (0.0 %)
Mode of delivery (all births)	**8168**	**7350**		**818**	
Vaginal	4753 (58.2 %)		4385 (59.7 %)		368 (45.0 %)
Caesarean section	3404 (41.7 %)		2958 (40.2 %)		446 (54.5 %)
TOP	11 (0.1 %)		7 (0.1 %)		4 (0.5 %)
Induced (% yes)	3081 (37.7 %)	**7344**	**2918 (39.7 %)**	**819**	**163 (19.9 %)**
All indicated deliveries	**3650**	**3213**		**437**	
Maternal hypoxia	115 (3.2 %)		67 (2.1 %)		48 (11.0 %)
Fetal compromise	871 (23.9 %)		804 (25.0 %)		67 (15.3 %)
Other	2664 (73.0 %)		2342 (72.9 %)		322 (73.7 %)
Pre-term delivery (live births only)	**922 (11.5 %)**	**7216**	**790 (10.9 %)**	**771**	**132 (17.1 %)**
Spontaneous preterm vaginal birth (live births only)	220/922 (23.9 %)	790	200 (25.3 %)	132	20 (15.2 %)
Mode of delivery (pre-term live deliveries)	**921**	**790**		**131**	
Vaginal	344 (37.4 %)		311 (39.4 %)		33 (25.2 %)
Caesarean section	577 (62.6 %)		479 (60.6 %)		98 (74.8 %)
	595	500		95	
Pre-term indicated live deliveries					
Maternal hypoxia	76 (12.8 %)		51 (10.2 %)		25 (26.3 %)
Fetal compromise	182 (30.6 %)		163 (32.6 %)		19 (20.0 %)
Other	337 (56.6 %)		286 (57.2 %)		51 (53.7 %)
Labour induced (pre-term live deliveries)	921	789		132	
Yes	174 (18.9 %)		159 (20.2 %)		15 (11.4 %)
Outcomes					
Baby gender (% male)	4097 (50.9 %)	7260	3681 (50.7 %)	790	416 (52.7 %)
APGAR score at 5 mins: mean(sd)	9.3 (1.2 %)	7163	9.3 (1.2 %)	778	8.9 (1.1 %)

non-UK centres (Table 2).

The proportion of asymptomatic participants overall was 1804/7747 (23.3 %), this was higher in non-UK centres (538/816, 65.9 %) compared with UK centres (5563/6931, 18.3 %) (Table 3). All listed presenting symptoms were more common in UK participants than those from non-UK centres.

Maternal death affected 1/7365 (<0.001 %) of UK participants and 13/832 (1.6 %) of non-UK participants. Ventilatory support was needed by 176/8187 (2.2 %) of participants overall, 146/7356 (2.0 %) of UK participants and 30/831 (3.7 %) of non-UK participants.

Pre-term delivery, stillbirth and early neonatal death were higher in non-UK participants (Table 4). Delivery by caesarean section was more common in non-UK participants. Spontaneous pre-term birth affected 200/7216 (2.7 %) of UK participants and 20/771 (2.6 %) of non-UK participants. Amongst participants with indicated pre-term delivery, delivery for maternal hypoxia was high in non-UK participants 25/95 (26.3 %) compared with 51/500 (10.2 %) in UK participants.

The proportion of small for gestational age (SGA, <10th percentile) was 744/7976 (9.3 %) overall, 595/7207 (8.3 %) in UK participants and 149/769 (19.3 %) in non-UK participants (Table 5). FGR was diagnosed in 360/8175 (4.4 %) of participants, 339/7341 (4.6 %) of UK participants vs 21/834 (2.5 %) of non-UK participants. Congenital malformations were reported in 119/8154 (1.5 %) of participants.

The proportion of participants affected by stillbirth was higher in those delivering within two weeks of first date of suspected or confirmed infection with SARS-CoV-2 compared with those delivering more than two weeks later, 0.8 % vs 0.2 %, (95 % CI 0.3–1.0) (Table 6). Participants who delivered more than two weeks after initial infection had a higher proportion affected by fetal growth restriction than those delivering within two weeks of infection, 3.5 % vs 4.8 % (95 % CI 0.4 to 2.2).

Pre-eclampsia was diagnosed in 388/8123 (4.8 %) of all participants. Eclampsia was reported in 40/ 8024 (0.5 %) of all participants.

SARS-CoV-2 was detected in 80/7993 (1.0 %) of all neonates and in 80/998 (8.1 %) of those tested (Table 7). The proportion tested was higher in non-UK participants, where 406/751 (54.1 %) of babies were tested, compared with 80/7993 (8.2 %) of UK participants. Neonatal complications affected 518/8076 (6.4 %) of all participants, 20/8046 (0.3 %) were affected by pneumonia and 374/8046 (4.6 %) by

Table 5
Birthweight and fetal growth restriction in participants.

	All participants	UK (SARS-CoV-2 suspected and confirmed)		Non-UK (SARS-CoV-2 suspected and confirmed)	
		N UK	Mean (SD)	N Non-UK	Mean (SD)
Birth-weight Z-score (live births)					
All singletons/first born multiples, mean(sd)	7917 (-0.1 (1.0))	7171	−0.0 (0.9)	746	−0.4 (1.1)
Singletons only, mean (sd)	7791 (-0.1 (0.9))	7054	−0.0 (0.9)	737	−0.4 (1.1)
Birth-weight (live births) percentile	**7976**	**7207**	**N (%)**	**769**	**N (%)**
<0.5	64 (0.8 %)		30 (0.4 %)		34 (4.4 %)
0.5 to 2.0	113 (1.4 %)		85 (1.2 %)		28 (3.6 %)
2.1 to 9.9	567 (7.1 %)		480 (6.7 %)		87 (11.3 %)
10.0 to 25.0	1258 (15.8 %)		1112 (15.4 %)		146 (19.0 %)
25.1 to 75.0	4289 (53.8 %)		3934 (54.6 %)		355 (46.2 %)
75.1 to 91.0	1139 (14.3 %)		1066 (14.8 %)		73 (9.5 %)
91.1 to 98.0	377 (4.7 %)		356 (4.9 %)		21 (2.7 %)
98.1 to 99.6	88 (1.1 %)		82 (1.1 %)		6 (0.8 %)
>99.6	81 (1.0 %)		62 (0.9 %)		19 (2.5 %)
SGA	**744 (9.3 %)**		**595 (8.3 %)**		**149 (19 %)**
Fetal growth restriction (% yes)	360/8175 (4.4 %)	**7341**	339 (4.6 %)	**834**	21 (2.5 %)
AC or EFW < 3rd centile	105/336 (31.2 %)	317	96 (30.3 %)	19	9 (47.4 %)
AC or EFW < 10th centile	147/272 (54.0 %)	258	138 (53.5 %)	14	9 (64.3 %)
a) Umbilical artery or uterine artery PI > 95th percentile	43/336 (12.8 %)	317	38 (12.0 %)	19	5 (26.3 %)
b) AC or EFW reduced from 20/40 scan and crossed 50 percentiles	71/336 (21.1 %)	317	68 (21.5 %)	19	3 (15.6 %)
c) Cerebro-umbilical ratio < 5th centile	11/336 (3.3 %)	317	9 (2.8 %)	19	2 (10.5 %)

respiratory distress syndrome. Non-UK participants had lower proportions affected by transient tachypnoea of the newborn (TTN), although number of cases in the non-UK sample for infant complications were small.

Discussion

Overall, the proportion of participating women affected by stillbirth was not higher than the rate reported in UK ONS data, 3.8/1000 maternities in 2019 and 3.9/1000 maternities in 2020 [7]. However, the 2 week period around the infection with SARS-CoV-2 was associated with a significantly higher proportion of pregnancies affected by stillbirth, approximately double the rate reported in UK ONS data, 3.8/1000 maternities in 2019 and 3.9/1000 maternities in 2020 [7]. Population surveillance data from UK women admitted to hospital with SARS-CoV-2 infection reports stillbirth affecting 2.1 % of symptomatic and 2.4 % of asymptomatic women with SARS-CoV-2 [1].

There is no reported evidence of abnormal growth parameters or Doppler studies in women affected by SARS-CoV 2 infection in pregnancy [8,9]. The assumption that risk of stillbirth in women with SARS-CoV-2 infection could be mitigated by increased fetal ultrasound surveillance remains untested. We would suggest that antenatal care of all women in pregnancy with SARS-CoV-2 should include a low threshold for delivery in the period within 2 weeks of infection if there are any concerns regarding reduced fetal movements or CTG abnormalities. Strategies to mitigate the risk of stillbirth require further evaluation.

Ongoing pregnancy with delivery >2 weeks after SARS-CoV-2 infection was associated with a higher proportion affected by FGR compared to those with delivery within 2 weeks of infection. This may simply be a function of incident FGR diagnosis in ongoing pregnancy. SARS-CoV-2 infection has been shown to cause a villitis with inflammation at the maternal/fetal interface [10] which may impair placental function and lead to FGR.

Consistent with our previous report [3] and others reports [9], and contrary to other reports based predominantly on pregnant women in hospitals [11] we did not find that fetal growth or SGA is affected by SARS CoV-2 infection. In our study, there was a higher than expected proportion of SGA in participants from non-UK centres, which may reflect a focus on recruitment of women hospitalised for pregnancy complications.

Pre-term birth affected 10.9 % of PANCOVID participants, 50 % higher than the background rate of 7.3 % in the UK [12]. Of those participants with pre-term birth, the majority had indicated pre-term delivery, for reasons including fetal distress and maternal hypoxia. SARS-CoV-2 infection was not associated with spontaneous pre-term birth in our participants, the proportion affected byt this was below the background rate for the UK [12]. The high proportion of participants having indicated pre-term delivery may have affected the rate of spontaneous pre-term birth.

Multiple other studies have shown an association of SARS-COV-2 with indicated pre-term birth. INTERCOVID reported pre-term birth in 22.5 % of participants; however it should be noted that in their control group (pregnant women without SARS-CoV-2 infection) 13.6 % of women experienced pre-term birth, suggesting that the study was carried out in centres with high background rates of pre-term birth and may not be generalizable [11]. The UKOSS/ISARIC data from 01/03/2020 to 28/02/2021 reported that 681/5479 (12.4 %) pregnant women admitted to hospital with confirmed SARS-CoV-2 experienced pre-term deliveries (22–36^{+6} weeks gestation) [1], perhaps reflecting increased disease severity in that exclusively hospitalised cohort.

Congenital malformations in our participants affected a proportion comparable with the background rate of 213.3 per 10,000 total births in

Table 6
Stillbirth and fetal growth restriction in participants delivering within 2 weeks or 2 weeks or more after SARS CoV 2 infection.

Outcome	All participants			UK participants			Non-UK participants		
	N	Delivering < 2 weeks of infection	Delivering ≥ 2 weeks of infection	*N*	Delivering < 2 weeks of infection	Delivering ≥ 2 weeks of infection	*N*	Delivering < 2 weeks of infection	Delivering ≥ 2 weeks of infection
Stillbirth	7282	21/2686 (0.8 %)	8/4596 (0.2 %)	6614	12/2136 (0.6 %)	7/4478 (0.2 %)	668	9/550 (1.6 %)	1/118 (0.9 %)
FGR	7311	95/2703 (3.5 %)	223/4608 (4.8 %)	6634	82/2147 (3.8 %)	222/4487 (5.0 %)	677	13/556 (2.3 %)	1/121 (0.8 %)

Table 7
Neonatal outcomes in UK and non-UK participants.

Outcomes	All participants	*N* total UK	UK (SARS-CoV-2 suspected and confirmed)	*N* Total Non-UK	Non-UK (SARS-CoV-2 suspected and confirmed)
	n/N (%)		n (%)		N (%)
Has the infant(s) been tested for SARS-COV-2? (% yes)	**998/7993 (12.5 %)**	**7242**	592 (8.2 %)	**751**	406 (54.1 %)
% Test positive/All tested neonates	80/998 (8.1 %)	592	56 (9.5 %)	406	24 (6.0 %)
Liveborn deliveries	80/998 (8.1 %)	592	56 (9.5 %)	406	24 (6.0 %)
%Test positive/total neonates in cohort	80 (1.0 %)	**7242**	56 (0.8 %)	**751**	24 (3.2 %)
Type of sample taken to test for SARS-COV-2:	**954**	**556**		**398**	
Nasopharyngeal swab	888 (93.1 %)		496 (89.2 %)		392 (98.5 %)
Cord blood	3 (0.3 %)		0 (0.0 %)		3 (0.8 %)
Placenta	2 (0.2 %)		1 (0.2 %)		1 (0.3 %)
Other	61 (6.4 %)		59 (10.6 %)		2 (0.5 %)
Did the participant's first neonate experience any complications? (% yes)	**898/8046 (11.2 %)**	**7257**	**858 (11.8 %)**	**789**	**40 (5.1 %)**
Transient tachypnea of newborn	124 (1.5 %)	852	118 (1.6 %)	40	6 (0.7 %)
Respiratory distress syndrome	374 (4.6 %)		354 (4.9 %)		20 (2.5 %)
Pneumonia	20 (0.3 %)		19 (0.3 %)		1 (0.1 %)
None of the above	423 (5.3 %)		410 (5.6 %)		13 (1.6 %)
Proportion neonates re-admitted to neonatal unit within 28 days	**593 (7.5 %)**	**7209**	587 (8.1 %)	**753**	6 (0.8 %)

the UK [13].

Transmission from mother to fetus and neonate was not reliably discernible using our data, as there was a lack of systematic testing of neonates born to mothers affected by SARs-CoV-2 infection in pregnancy, particularly in UK centres. The 1 % of neonates testing positive for SARS-CoV-2 in PANCOVID is comparable with UKOSS data [1] but lower than in the INTERCOVID study [11]. Testing amongst our participants in the UK was not routine and targeted to infants showing respiratory symptoms and stratified by risk status of the mother [14]. The higher proportion of neonates with positive tests in non-UK vs UK centres (3 % vs 1 %) suggests that universal testing may detect cases more reliably than targeted testing. Comparable rates of pneumonia in UK and non-UK participants suggests that this may not impact on immediate management or outcomes for neonates, however the long-term effects of vertical transmission and/or early neonatal infection with SARS-COV-2 are currently unknown.

The risk of vertical or early neonatal transmission appears low, early neonatal death was not increased above background rates for the UK of 0.2 % [15]. There is a need for international consensus on the optimal samples to determine infant infection and testing strategies for infants of women with SARS-CoV-2. Women with SARS-CoV-2 in pregnancy can be generally reassured that infants are unlikely to contract SARS-CoV-2 whilst in-utero, there is no signal apparent for increases in congenital malformations above the background risk of 1 % and infants' respiratory morbidity is similar to that of infants born to women without SARS-CoV-2 infection in pregnancy.

The numbers of women who died were small in our study, particularly from UK centres and this study does not have power to assess whether this proportion was higher than the background rate for maternal mortality in pre-pandemic UK population surveillance data of 8.8 per 100,000 maternities [16]. UKOSS data up to February 2021 in women admitted to hospital with SARS-CoV-2 infection reported case fatality rate (CFR) of 0.6 % (95 % CI 0.3–0.6 %) [1]. INTERCOVID reported a 1.6 % CFR and increased risk of maternal death with SARS-CoV-2 infection compared to those without, RR 22.6 (95 % CI 2.88–172.11) [17].

The proportion of participants affected by pre-eclampsia (4.6 %) was no higher than reported rates of 2–8 % in the latest statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP) [18], is comparable with the non-infected, control group in the INTERCOVID study [11,17] and was higher than the 1.9 % reported by UKOSS [1]. Our data do not support the association between SARS-COV-2 infection and an increase in incidence of pre-eclampsia. However, eclampsia was more common than expected for the UK, 2.7 per 10,000 births [19] suggesting that infection could be associated with more severe manifestations of this vascular syndrome.

Strengths and limitations

This study comprises one of the largest prospective, individual patient datasets of perinatal outcomes among women with suspected or confirmed SARS-CoV-2 infection to date.

Early pregnancy units laegely closed during the first wave of the pandemic limiting data collection, we are not able to assess the miscarriage risk associated with SARS-CoV-2 infection.

The proportion of women affected by maternal deaths in our cohort was low, likely due to our study design requiring consent from the participant or their relative. It is likely that our study underestimates the risk of infection and maternal death.

Conclusions

This study reflects a population with a range of infection severity for SARS-COV-2 in pregnancy, making it generalisable to whole obstetric populations. Infection is associated with indicated pre-term birth, primarily for fetal compromise. Whilst the overall proportions of women affected by SGA and FGR were not higher than expected, there was a significant difference in the proportion affected by Stillbirth and FGR in the participants delivering < 2 weeks/≥ 2 weeks respectively. We suggest that clinicians' threshold for delivery should be low if there are concerns with fetal movements or fetal heart rate monitoring in this period.

There appears to be no effect on birthweight or increase in congenital malformations in women affected by SARS-CoV-2 infection in pregnancy and neonatal infection is uncommon. The effect of infection on miscarriage was not determined. The rate of pre-eclampsia amongst participants was not higher than would be expected.

We believe a co-ordinated, global study of pandemic viruses' impact on women in pregnancy should be planned now to allow rapid, global response to future pandemics and the avoidance of multiple, parallel studies with differing inclusion criteria and outcome sets. A core outcome set should be developed for this purpose. Study design for future global registries to rapidly assess the impact of pandemic viruses in pregnancy should include methodology for dealing with data from

different healthcare settings.

Contribution

What are the novel findings of this work?

Infection is associated with indicated pre-term birth, primarily for fetal compromise. Whilst the overall proportions of women affected by SGA and FGR were not higher than expected, there was a significant difference in the proportion affected by Stillbirth and FGR in the participants delivering < 2 weeks/≥ 2 weeks after infection respectively.

There appears to be no effect on birthweight or increase in congenital malformations in women affected by SARS-CoV-2 infection in pregnancy and neonatal infection is uncommon. The effect of infection on miscarriage was not determined. The rate of pre-eclampsia amongst participants was not higher than would be expected.

What are the clinical implications of this work?

This study reflects a population with a range of infection severity for SARS-COV-2 in pregnancy, making it generalisable to whole obstetric populations. We suggest that clinicians' threshold for delivery should be low if there are concerns with fetal movements or fetal heart rate monitoring in the two weeks after infection.

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.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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