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Coronavirus in pregnancy and delivery: rapid review

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CONTRIBUTION

What are the novel findings of this work?

This is the most up-to-date review of COVID-19 in pregnancy, with comparison with previous outbreaks of novel coronavirus in pregnancy. We discuss the limited data available, the limited evidence base for clinical practice, possible therapeutic options in pregnancy and future research.

What are the clinical implications of this work?

A version of this rapid review, with searches up to 25th February 2020, informed the RCOG's guidance on COVID-19 in pregnancy.

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ABSTRACT

OBJECTIVES Person-to-person spread of COVID-19 in the UK has now been confirmed. There are limited case series reporting the impact on women affected by coronaviruses (CoV) during pregnancy. In women affected by SARS and MERS, the case fatality rate appeared higher in women affected in pregnancy compared with non-pregnant women. We conducted a rapid review to guide health policy and management of women affected by COVID-19 during pregnancy, which was used to develop the RCOG guidelines on COVID-19 infection in pregnancy.

METHODS Searches were conducted in PubMed and MedRxiv to identify primary case reports, case series, observational studies and randomised controlled trials describing women affected by coronavirus in pregnancy. Data were extracted from relevant papers. This review has been used to develop guidelines with representatives of the RCPCH and RCOG who provided expert consensus on areas in which data were lacking.

RESULTS From 9965 results in PubMed and 600 in MedRxiv, 23 relevant studies (case reports and case series) were identified. From reports of 32 women to date affected by COVID-19 in pregnancy, delivering 30 babies (one set of twins, three ongoing pregnancies), seven (22%) were asymptomatic and two (6%) were admitted to the intensive care unit (ICU) (one of whom remained on extracorporeal membrane oxygenation). No maternal deaths have been reported to date. Delivery was by Cesarean section in 27 cases and by vaginal delivery in two, and 15 (47%) delivered preterm. There was one stillbirth and one neonatal death. In 25 babies, no cases of vertical transmission were reported; 15 were reported as being tested with RT-PCR after delivery. Case fatality rates for SARS and MERS were 15% and 27%, respectively. SARS was associated with miscarriage or intrauterine death in five cases, and fetal growth restriction was noted in two ongoing pregnancies affected by SARS in the third trimester.

CONCLUSIONS Serious morbidity occurred in 2/32 women with COVID-19, both of whom required ICU care. Compared with SARS and MERS, COVID-19 appears less lethal, acknowledging the limited number of cases reported to date and one woman who remains in a critical condition. Preterm delivery affected 47% of women hospitalized with COVID-19, which may put considerable pressure on neonatal services if the UK's reasonable worst-case scenario of 80% of the population being affected is realized. Based on this review, the RCOG (in consultation with the RCPCH) developed guidance for delivery and neonatal care which recommends that delivery mode be determined primarily by obstetric indication and recommends against routine separation of COVID-19-affected mothers and babies. We hope this review will be helpful for maternity and neonatal services planning their response to COVID-19.

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INTRODUCTION

The common human coronaviruses 229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus) and HKU1 (beta coronavirus) cause the common cold. Three human coronaviruses cause more severe, acute illnesses; MERS-CoV causes Middle East Respiratory Syndrome (MERS), SARS-CoV causes severe acute respiratory syndrome (SARS) and SARS-CoV-2 causes COVID-19.

There are limited case series reporting on the impact of coronaviruses (CoV) during pregnancy. In women affected by SARS and MERS, the case fatality rate appeared higher in women affected in pregnancy compared with non-pregnant women.

Person-to-person spread of COIVD-19 in the UK has now been confirmed. To guide treatment and prevention in women affected by COVID-19 during pregnancy in the current outbreak, we conducted a rapid review.

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METHODS

Searches were conducted in PubMed and MedRxiv on 25th February 2020 (Appendix S1) and updated on 10th March to identify primary case reports, case series and randomised controlled trials describing women of any age affected by coronavirus in pregnancy or the postnatal period. There were no date or language restrictions on the search. References of relevant papers were searched manually for relevant studies.

Due to time constraints, one reviewer (E.M.), conducted the search, reviewed full texts and extracted data on demographics, maternal outcomes, maternal diagnostic testing, maternal imaging, fetal outcomes, perinatal outcomes, neonatal outcomes and neonatal diagnostic testing. Comparison of outcomes for COVID-19, SARS and MERS is presented.

The review was not registered in PROSPERO and corresponding authors were not contacted due to time constraints. The quality of included studies was assessed subjectively and classified as anecdotal, low, medium or high. Ethical approval was not required for this review.

This review has been used to develop interim guidance on COVID-19 infection in pregnancy, with representatives of the RCPCH and RCOG providing expert consensus on areas in which data were lacking. This guidance has now been published in full by the RCOG (1).

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RESULTS

The search of PubMed identified 9965 results; 69 abstracts were screened and 46 were excluded due to the study not including pregnant women or humans, or being an *in-vitro* study. Twenty-three relevant studies were identified, their full texts were reviewed and all 23 were included. It is highly likely that there was overlap in cases reported to be affected by SARS. The search of MedRxiv identified 600 results; 39 abstracts were screened and no relevant studies were identified.

There was inconsistent reporting of maternal, perinatal and neonatal outcomes across case reports and series. All studies were case reports or series and all were classified subjectively as being of low quality. A narrative review is presented. Pregnancy, perinatal and neonatal outcomes in included cases are summarized in Table 1.

Maternal outcomes

COVID-19 To date, 32 women affected by COVID-19 in pregnancy, including one with a twin pregnancy, have been reported, delivering 30 infants (2–5). Twenty-seven delivered by Cesarean and two by vaginal delivery. Women who delivered did so within 13 days of onset of illness; three pregnancies were ongoing.

In cases in which maternal morbidity and mortality were reported (*n*=23), two women required intensive care unit (ICU) admission and mechanical ventilation and one developed multiorgan dysfunction and was still on extracorporeal membrane oxygenation (ECMO) when her case was reported. When reported (*n*=17), all symptomatic women had viral changes apparent on computed tomographic (CT) chest imaging. There were no maternal deaths to date (2,3).

SARS The case fatality rate (CFR) was 15% for all reported cases of SARS in pregnancy (6–11). A case–control study comparing 10 pregnant and 40 non-pregnant women affected by SARS in Hong Kong reported an ICU admission rate of 60% and a CFR of 40% in the pregnant group, compared with respective values of 17.5% and 0% in the non-pregnant group (9). All women affected by SARS had CT or chest X-ray evidence of pneumonia (Table 2).

MERS In pregnant women affected by MERS, 7/11 (64%) were admitted to ICU, and CFR was 3/11 (27%) (12–17).

Early pregnancy

COVID-19 There are currently no data on first-trimester COVID-19 infection.

SARS Miscarriage affected 4/7 women with first-trimester SARS infection (8), all of whom had an ultrasound finding at 3–5 weeks of pregnancy of unknown location or unknown viability, in which ongoing pregnancy at 13 weeks would be expected in 38% and 50%, respectively (acknowledging the complexity in this area (18,19)). Those with fetal heart activity recorded (n=2) did not miscarry, neither did a woman in whom the diagnosis was retrospective and did not undergo ultrasound examination.

MERS A single case of a woman with MERS in the first trimester has been reported. This woman was asymptomatic and went on to have a term delivery (20).

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Second/third-trimester pregnancy loss

COVID-19 One woman affected by COVID-19 presented at 34 weeks with a fever and sore throat; her condition deteriorated during admission and she required ICU and ECMO. The woman had a stillbirth, delivered by Cesarean section. No information on chronology or fetal monitoring was reported.

SARS In cases of SARS reported after the first trimester, Zhang et al. reported a series of five women affected by SARS (two in the second trimester, three in third trimester) in which there was loss of one fetus in a twin pregnancy with the other surviving to delivery. It is not clear if the loss occurred in the second or third trimester; this has been arbitrarily recorded as occurring in the third trimester (21).

MERS Two pregnancy losses were reported in pregnancies affected by MERS. In the first case, the woman became ill at 19 weeks gestation and experienced vaginal bleeding resulting in late fetal loss at 20 weeks (17). It should be noted that this woman declined chest radiography and medications because of her concerns about their effect on pregnancy. The second case presented at 34 weeks with pre-eclampsia and MERS and was found to have had an intrauterine death; this woman delivered vaginally and recovered after ICU admission without ventilatory support (14).

Prematurity

COVID-19 15/32 (47%) women affected by COVID-19 delivered preterm. In the study of Chen et al., all (n=9) mothers were delivered electively by Cesarean section, two of which were at 36 weeks' gestation (2). In the study of Zhu et al., seven women delivered by Cesarean section and two by vaginal delivery (4). 5/9 women (6/10 babies) delivered preterm. The indication for delivery is not reported; however, six babies were affected by fetal distress prior to delivery and it seems reasonable to assume that fetal condition contributed. Wang et al. reported on one woman who delivered at 30 weeks for fetal distress (3). Liu et al. reported on 13 women, of whom seven delivered preterm by Cesarean section; indication for delivery was not reported (5).

SARS 4/16 pregnancies with SARS that were not affected by miscarriage resulted in preterm delivery at 26, 28, 32 and 33 weeks' gestation (20). Data on timing of delivery were not reported in the series of five women from Zhang et al. (21).

MERS 3/11 pregnancies with MERS were delivered preterm by Cesarean section (one at 24 weeks and two at 32 weeks for maternal hypoxemia) (12,20).

Fetal growth and placental effects

COVID-19 Women affected by COVID-19 who delivered did so within 13 days of onset of illness; fetal growth is unlikely to be affected in this time period (2–5). There were no data on fetal growth in the three ongoing pregnancies at the time of publication (5). No placental pathology is available to date.

SARS Placentas from pregnancies affected by SARS showed early changes that are seen in pregnancies with fetal growth restriction (fibrin deposition) when delivery occurred ≤1 week after onset of illness; birth weight was normal in these pregnancies. When delivery was 5–7 weeks after onset of illness, there was fetal growth restriction in 2/3 pregnancies (8) and their placentas showed more severe changes (areas with loss of blood supply, avascular villi, and bleeding behind placenta, placental abruption) (22).

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MERS 4/11 women with MERS went on to deliver a healthy baby at term, although birth weight was not reported in 3/4 of these cases. In one case, vaginal bleeding was reported at 37 weeks, causing fetal compromise and necessitating emergency Cesarean section resulting in the delivery of a male infant weighing 3140g and in good condition. Abruption was apparent on placental examination (13).

Delivery and postnatal

COVID-19 Chen et al. reported on nine women with COVID-19 delivering by Cesarean section from 36 weeks onwards, of which two were preterm. In two women at term, fetal distress was reported. In six women with COVID-19 who delivered by Cesarean section and subsequently underwent testing, there was no evidence of COVID-19 in the amniotic fluid, umbilical cord blood, neonatal throat swab or breastmilk samples (2). A news report of a baby of a COVID-19 infected mother testing positive at 30 hours after delivery has not been reported in a scientific journal.

Zhu et al. reported COVID-19 in nine women delivering 10 infants (seven by Cesarean section and two by vaginal delivery), of whom only three mothers became symptomatic after delivery. The indication for delivery was not reported. This cohort had COVID-19 from 31 weeks onwards, 6/9 pregnancies showed fetal distress and 5/9 women (6/10 babies) delivered preterm (4).

Wang et al. reported on one woman who underwent Cesarean section for fetal distress at 30 weeks' gestation. The infant was born in good condition and samples of amniotic fluid, neonatal gastric samples, placenta and infant throat swabs were negative for COVID-19 (3).

Liu et al. reported on 10 women, all of whom delivered by Cesarean section. Vertical transmission was reported as negative in all 10 neonates. The samples and method of testing is not stated.

SARS and MERS No vertical transmission was reported for cases of SARS or MERS in pregnancies delivered by Cesarean section or vaginal delivery.

Other coronaviruses A single case series reported on neonates born to mothers positive for HCoV-229E; gastric samples in three out of seven cases were positive for HCoV-229E on reverse transcription polymerase chain reaction (RT-PCR); seroconversion was not assessed. No signs of infant infection were seen in those with positive gastric samples (23).

Neonatal outcomes

COVID-19 In the study of Chen et al., all (n=9) babies were delivered ≥36 weeks' gestation and were well at discharge (2). Zhu et al. reported on a cohort delivered at an earlier gestational age (from 31 weeks); 6/10 babies were admitted to the neonatal unit (NNU) for respiratory support, two developed disseminated intravascular coagulation (DIC) and one had multiple organ failure (4). Neonatal morbidity was more marked in this series, probably due to greater prematurity. One baby died after being born at 34 weeks. The neonate required admission at 30 min after delivery with respiratory difficulties. The baby deteriorated, developed shock, DIC and multiple organ failure, and died at 8 days postpartum. 9/10 infants were tested for COVID-19, all of which tested negative. Wang et al. reported a baby born at 30 weeks in good condition with an uneventful neonatal course (3). Liu et al reported one stillbirth and nine live births, all of which had an Apgar score (time unspecified) of 10 (5).

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SARS The baby born at 26 weeks had respiratory distress syndrome (RDS) and a bowel perforation. The baby born at 28 weeks had RDS, necrotizing enterocolitis and a patent ductus arteriosus (8,11).

MERS Among the three pregnancies with MERS that were not affected by stillbirth or intrauterine death and were delivered preterm by Cesarean section, the one born at 24 weeks resulted in neonatal death (birth weight, 240g) and the two babies delivered at 32 weeks for maternal hypoxemia have no outcomes reported (12,20).

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DISCUSSION

There are limited data on the impact of the current COVID-19 outbreak on women affected in pregnancy and their babies. All studies included in this review were case reports or series of low quality. Reported outcomes varied, with one series on COVID-19 not reporting maternal outcome.

Of the 23/32 women with COVID-19 in pregnancy for whom maternal outcomes were reported, two had serious morbidity, one of whom was still on ECMO following stillbirth at the time her care was reported. Compared with SARS and MERS, COVID-19 appears less lethal, acknowledging the limited number of cases reported to date and one woman who remains in a critical condition.

Preterm delivery affected 47% of women hospitalised with COVID-19, which may put considerable pressure on neonatal services if the UK's reasonable worst-case scenario of 80% of the population being affected is realized.

RCOG (in consultation with the RCPCH) have provided guidance for delivery and neonatal care, which recommends that delivery mode be determined primarily by obstetric indication, and recommends against routine separation of COVID-19-affected mothers and babies (1).

From the currently available data, an increase in the risk of miscarriage in women affected by COVID-19 cannot be ruled out at this stage, given the SARS data. Data from early pregnancy units are needed on affected women and matched controls.

In women affected by COVID-19 with ongoing pregnancy, surveillance for fetal growth restriction would be reasonable, given the acute and chronic placental changes observed, 2/3 ongoing pregnancies with SARS being affected by fetal growth restriction and placental abruption being noted in cases affected by MERS.

The need for provision of fetal monitoring including serial ultrasound for women with COVID-19 will be challenging for maternity services. Women will need to be monitored locally in their booking maternity units with transfer for delivery to centers with appropriate neonatal intensive care facilities for delivery. COVID-19 is associated with preterm delivery in 47% of reported cases.

In SARS and MERS-affected cases, delivery was most often indicated by maternal hypoxemia. In COVID-19, if maternal illness is not as severe, the considerations will be based more on obstetric indications for delivery.

Information on vertical transmission of COVID-19 is limited, although testing of 15 neonates born to mothers with COVID-19 was negative in all cases. Guidance on mode of delivery requires expert consensus until further information emerges. RCOG advises that decisions regarding mode of delivery should be on obstetric indication and not on presumed protection of baby against infection.

There is evidence for vertical transmission of HCoV-229E; however, seroconversion was not investigated and all infants remained well. There is no evidence for vertical transmission for any other coronavirus.

We acknowledge the limitations of this review, given that a full and comprehensive search of all medical literature would have taken more time and personnel than were available. We used a single reviewer and a limited database search in order to conduct this rapid review with expert review from the RCOG and RCPCH.

There is discrepancy between guidance for delayed cord clamping, which is a function of a lack of evidence. Consensus guidance from China advises that 'delayed cord clamping is not recommended',

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in order to reduce the risk of vertical transmission and that infants should be separated from mothers affected by COVID-19 (25). Interim guidance from ISUOG advises clinicians to consider not undertaking delayed cord clamping (26). RCOG guidance does not concur, advising that delayed cord clamping should be practiced as normal. If vaginal delivery is permitted, with exposure to maternal secretions and blood, it could be argued that 1 min of further perfusion via the placenta is unlikely to alter the risk of vertical transmission. Infants may acquire COVID-19 from their mothers after delivery via normal routes of transmission.

Guidance from China states that 'Infants should not be fed with the breast milk from mothers with confirmed or suspected of 2019-nCoV'. Guidance from the CDC is less clear but is still precautionary (27). RCOG advises against routine separation of mother and baby and gives guidance on individualized care.

If the UK's reasonable worst-case scenario of 80% of the population being affected by COVID-19 is realized and 4% require hospitalization, potentially thousands of women during pregnancy will be affected at a time when staff are likely themselves to be unwell. In previous coronavirus epidemics, there has anecdotally been a tendency towards admitting any symptomatic pregnant woman with proven infection.

A surge in workload will likely be seen in the NHS and across the world at a time when staffing is well below optimal levels. Pragmatic choices will need to be made about achievable and acceptable levels of care across the NHS with national guidance and local adaptation. Chest imaging should be undertaken in pregnant women as clinically indicated.

Therapeutics announced as being under consideration and trial during the outbreak include Kaletra (Lopinavir and Ritonavir), Remdesivir and Chloroquine. Kaletra (28) is used in the UK during pregnancy for treatment of HIV, in which the benefits of treatment outweigh the risks of toxicity seen in animal studies. The benefits of using Chloroquine outweigh the risks in the prevention and treatment of malaria during pregnancy (29). Remdesivir has been used for the treatment of Ebola in pregnant women (30). However, it should be acknowledged that Ebola is a condition with a CFR of 50%, and for which there would be higher tolerance for adverse effects of a potentially beneficial treatment than would be the case for COVID-19, in which the CFR is around 1%. It would seem reasonable not to exclude seriously ill pregnant women from trials of these therapies for COVID-19.

There is a need for systematic data reporting on women affected by COVID-19 and their pregnancies to provide an evidence base for management, treatment and prevention, and to target limited resources during the outbreak.

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Disclosure

E.M. is seconded to the Department of Health and Social Care (DHSC), England. The views in this manuscript are those of the authors and do not necessarily represent the official views of DHSC or HM Government. E.M. has applied for a UKRI/MRC grant to study COVID-19 in pregnancy. No other authors have COIs to declare. E.M. received a salary from the NIHR.

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Table 1 Overview of pregnancy, perinatal and neonatal outcomes in pregnancies affected by coronaviruses

	COVID-19		SARS			MERS		
N	32 (30 infants born, 1 twin pregnancy)		20			11		
Median age (range)	30 (25-40)							
Median gestational weeks at presentation (range)	36.5 *(31-39)*		16 *(3-32)*			24 *(6-38)*		
Symptomatic at admission	25 (78%)		20 (100%)			9 *(82%)*		
ICU admission (%)	2/23 reported (9%)*		6 *(30%)*			7 *(64%)*		
Maternal death (%)	0*#		3 *(15%)*			3 *(27%)*		
CT-chest CXR changes in symptomatic women	17/17 reported (100%) #		20 (100%)			8/9*** (89%)		
Stage of pregnancy	**2nd trimester**	**3rd Trimester**	**1st trimester**	**2nd Trimester**	**3rd Trimester**	**1st Trimester**	**2nd Trimester**	**3rd Trimester**
N	2 ongoing	30 (1 ongoing, 30 babies)	7	5	8 (9 babies)	1	5	5
Women with comorbidities	not reported	4/19 reported *(21%)*#	not reported	not reported	not reported	0	2 *(40%)*	3 *(60%)*
Admitted asymptomatic	2 (100%)	5/30 (17%)	0	0	0	1 *(100%)*	1 *(20%)*	0
ICU admission %	0	2/21 reported (9.5%)	1 *(14%)*	2 *(40%)*	3 *(38%)*	0	3 *(60%)*	4 *(80%)*
Maternal mortality %	0	0*	1 *(14%)*	1 *(20%)*	1 *(13%)*	0	1 *(20%)*	2 *(40%)*
Miscarriage or intra-uterine death	0	1/30 (3%)	4 *(57%)*	0	1 (1 twin) (13%)	0	1 (20%)***	1 *(20%)*
Any preterm delivery	0†	15/30 (50%)†	not reported	2 (40%)	2 (26%)	0	1 (20%)	2 (40%)
Spontaneous preterm delivery	0	0*	not reported	0**	1 *(13%)***	0	0	0
Fetal growth restriction post-infection	not reported	0	not reported	0	2 *(26%)*	0	0	0
Vertical transmission	-	0/25	0	0	0	0	0	0
Neonatal death		1/30 (3%)	not reported	0	0	0	1 *(20%)*	0

#Incomplete data from Liu et al.
*Incomplete data from Zhu et al.
†Ongoing pregnancies were assumed to deliver at term, based on clinical prognosis
**Incomplete data from Zhang et al. (n=5)
***One woman declined radiography because of concerns about effect on pregnancy
ICU-Intensive Care Unit, CT-computed tomography, CXR - chest X-ray

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Table 2 Details of women affected by coronavirus in pregnancy (SARS and MERS) who died as of 6th March 2020

CoV		Age	Gestation	Presentation	Comorbidities	Chest imaging	Progression	Delivery	Cause of death
COVID-19	No maternal fatalities								
SARS	**1**	44	5	Cough, headache, SOB, chills	*not reported*	Pneumonia	Secondary bacterial pneumonia, DIC, renal failure, ARDS	Miscarriage	Respiratory failure
	2	34	32	Myalgia, cough, chills	*not reported*	Pneumonia	Sepsis, ARDS, shock, abdominal wound dehiscence	Caesarean section, survived	Respiratory failure
	3	34	27	Myalgia, cough, headache, SOB, sore throat	*not reported*	Pneumonia	Secondary bacterial pneumonia, DIC, ARDS, abdominal wound dehiscence	Caesarean section, RDS, NEC, survived	MRSA pneumonia
MERS	**1**	32	38	Fever, cough, SOB	None	CXR bilateral infiltrates	Worsening pneumonia, renal failure, ARDS	Spontaneous vaginal, survived	Multi-organ failure
	2	31	24	Cough, myalgia	Asthma, pulmonary fibrosis, spontaneous pneumothoraces	Right lower lobe opacity	Worsening pneumonia, ARDS	Emergency CS for maternal hypoxaemia, died	Severe refractory hypoxia, Cardiac arrest
	3	32	32	Fever, back pain	None	CT bilateral consolidation	Septic shock,	Emergency CS for maternal hypoxaemia, died	Septic shock

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