Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: national cohort study

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Funding: Healthcare Quality Improvement Partnership programme grant (National Maternity and Perinatal Audit). The funder had no involvement in the design of the study, interpretation of the data, writing of the manuscript, or approval of the manuscript for publication.

Conflicts of interest: All authors except JvdM, TD and EM receive full or partial salary funding provided through the Healthcare Quality Improvement Partnership to the Royal College of Obstetricians and Gynaecologists. EM, TD, JJ and LW are members of the RCOG COVID-19 guidance cell which produces clinical guidance and policy documents to support the management of pregnant women during the pandemic in the UK.

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Word count

Abstract: 522

Main text: 3056

CONDENSATION

Among 342,080 births, we found that a positive SARS-CoV-2 test at the time of birth is associated with increased rates of stillbirth, preterm birth, and other adverse maternal and perinatal outcomes.

SHORT TITLE

Maternal and perinatal outcomes of pregnant women with SARS-CoV-2

AJOG AT A GLANCE

Why was this study conducted?

To determine the association between SARS-CoV-2 infection and maternal and perinatal outcomes, in the context of universal screening of women giving birth in England.

What are the key findings?

Women who tested positive for SARS-CoV-2 at birth had increased rates of fetal death, preterm birth, preeclampsia, emergency Cesarean delivery and other adverse maternal and neonatal outcomes.

What does this study add to what is already known?

SARS-CoV-2 infection at the time of birth is associated with a higher rate of fetal death and preterm birth, and other adverse maternal and neonatal outcomes. Observed increase in rates of adverse neonatal outcomes was attributed to increased preterm birth.

ABSTRACT

Objective: The aim of this study was to determine the association between SARS-CoV-2 infection at the time of birth and maternal and perinatal outcomes.

Methods: This is a population-based cohort study in England. The inclusion criteria were women with a recorded singleton birth between 29th May 2020 and 31st January 2021 in a national database of hospital admissions. Maternal and perinatal outcomes were compared between pregnant women with a laboratory-confirmed SARS-CoV-2 infection recorded in the birth episode and those without. Study outcomes were fetal death at or beyond 24 weeks' gestation (stillbirth), preterm birth (<37 weeks gestation), small for gestational age infant (SGA; birthweight <10th centile), preeclampsia/eclampsia, induction of labor, mode of birth, specialist neonatal care, composite neonatal adverse outcome indicator, maternal and neonatal length of hospital stay following birth (3 days or more), 28-day neonatal and 42-day maternal hospital readmission. Adjusted odds ratios (aOR) and their 95% confidence interval (CI) for the association between SARS-CoV-2 infection status and outcomes were calculated using logistic regression, adjusting for maternal age, ethnicity, parity, pre-existing diabetes, pre-existing hypertension and socioeconomic deprivation measured using Index of Multiple Deprivation 2019. Models were fitted with robust standard errors to account for hospital-level clustering. The analysis of the neonatal outcomes was repeated for those born at term (≥ 37 weeks' gestation) since preterm birth has been reported to be more common in pregnant women with SARS-CoV-2 infection.

Results: The analysis included 342,080 women, of whom 3,527 had laboratory-confirmed SARS-CoV-2 infection. Laboratory-confirmed SARS-CoV-2 infection was more common in women who were younger, of non-white ethnicity, primiparous, residing in the most deprived areas, or had comorbidities. Fetal death (aOR, 2.21, 95% CI 1.58-3.11; P<0.001) and preterm birth (aOR 2.17, 95% CI 1.96-2.42; P<0.001) occurred more frequently in women with SARS-CoV-2 infection than those without. Risk of preeclampsia/eclampsia (aOR 1.55, 95% CI 1.29-1.85; P<0.001), birth by emergency Cesarean delivery (aOR 1.63, 95% CI 1.51-1.76; P<0.001) and prolonged admission following birth (aOR 1.57, 95%CI 1.44-1.72; P<0.001) were significantly higher for women with SARS-CoV-2 infection than those without. There were no significant differences in the rate of other maternal outcomes.

Risk of neonatal adverse outcome (aOR 1.45, 95% CI 1.27-1.66; P<0.001), need for specialist neonatal care (aOR 1.24, 95% CI 1.02-1.51; P=0.03), and prolonged neonatal

admission following birth (aOR 1.61, 95% CI 1.49-1.75; P<0.001) were all significantly higher for infants with mothers with laboratory-confirmed SARS-CoV-2 infection. When the analysis was restricted to pregnancies delivered at term (≥37 weeks), there were no significant differences in neonatal adverse outcome (P=0.78), need for specialist neonatal care after birth (P=0.22) or neonatal readmission within four weeks of birth (P=0.05). Neonates born at term to mothers with laboratory-confirmed SARS-CoV-2 infection were more likely to have prolonged admission following birth (21.1% compared to 14.6%, aOR 1.61, 95% CI 1.49-1.75; P<0.001).

Conclusions: SARS-CoV-2 infection at the time of birth is associated with higher rates of fetal death, preterm birth, preeclampsia and emergency Cesarean delivery. There were no additional adverse neonatal outcomes, other than those related to preterm delivery. Pregnant women should be counseled regarding risks of SARS-COV-2 infection and should be considered a priority for vaccination.

Keywords: COVID-19, pregnancy, birth, fetal death, stillbirth, preterm birth, obstetrics, neonatal outcome, preeclampsia

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly around the world since the first reported case in late 2019. Studies from registries of pregnant women and single- or multicentre cohorts have reported that pregnant women with COVID-19 are at greater risk than non-pregnant women of childbearing age with COVID-19 of requiring intensive care unit (ICU) support, severe morbidity and mortality.[1–3] Delivery may improve maternal condition in women with severe COVID-19, leading to an observed increase in preterm birth and neonatal unit admission for infants of infected mothers.[1,4–6] In the general population, advanced age, obesity, minority ethnic origin, socioeconomic deprivation and comorbidities including diabetes and hypertensive disease are associated with higher risk of severe disease, a pattern which is also seen in pregnant women.[1,7] Neonatal SARS-CoV-2 infection has not been associated with adverse outcomes for the newborn.[8]

A recent international registry study demonstrated an increase in adverse maternal and neonatal outcomes for mothers infected with COVID-19 in pregnancy;[4] and a study using national data from Sweden demonstrated an increase in adverse neonatal outcomes for infants born to women with SARS-CoV-2 infection, a finding largely mediated by increased rates of preterm birth.[9]

We aimed to investigate maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection in England using data available from routinely collected electronic healthcare records.

MATERIALS AND METHODS

Study design

This study is a national population-based cohort study using Hospital Episode Statistics (HES) data from 29th May 2020 to 31st January 2021. HES contains records of all inpatient

admissions to National Health Service (NHS) hospitals in England including data on patient demographics (age, sex and ethnicity), the admission (date of admission and discharge) and clinical information. On the 29th May 2020, the Royal College of Obstetricians and Gynaecologists recommended universal screening of all women admitted to maternity services with a PCR test, in line with recommendations from NHS England to test all hospital admissions.[10,11]

Diagnostic information is coded using the International Classification of Diseases, 10th revision (ICD-10).[12] Operative procedures are described using the UK Office for Population Censuses and Surveys classification, 4th revision (OPCS-4).[13] Further details about the labor and birth are captured in the episode record (e.g., gestational age, birthweight) in supplementary data fields known as the HES 'maternity tail'. HES data is sufficiently accurate to be used for research and managerial decision-making.[14]

Cohort selection and outcome definitions

The inclusion criteria were women who had a HES record of a singleton birth between 29th May 2020 and 31st January 2021. HES includes births which occur in NHS hospitals and hospital-associated community care in England. Only 0.3% of births in England in 2020 occurred in non-NHS organizations.[15]

A maternity episode was defined as any record that contained valid information about mode of birth in either the procedure fields (OPCS-4 codes: R171 to R259) or the HES maternity tail. Multiple births, which were excluded, were defined as maternity episodes with an ICD code for a multiple birth (Z37.2–Z37.7) or strong evidence of a multiple birth in the maternity tail (more than one distinct birthweight, birth order, and infant recorded in the same birth episode). A neonatal episode was defined as any record that contained a newborn, defined as being less than one day of age at episode onset. Maternal and neonatal episodes were linked using encrypted versions of the mother's and infant's NHS number (a unique national identifier for each individual NHS user, assigned at birth)[16], available in the NHS Birth

Notifications data. These data also contained additional information on the birth such as gestational age and birthweight.[15,17]

A woman was classified as having laboratory-confirmed SARS-CoV-2 infection at the time of birth if the ICD-10 code "COVID-19, virus identified" (U07.1) was recorded in the birth episode.[18] The test used to confirm infection in NHS hospital admissions is a nasal/throat swab examined using PCR.[11]

The study outcomes derived for the cohort identified by the maternity episode included fetal death at or beyond 24 weeks' gestation (stillbirth), preterm birth (less than 37 weeks, liveborn or stillborn), small for gestational age at birth (SGA; defined as birthweight <10th centile using UK-WHO paediatric growth charts[19]), maternal diagnosis with preeclampsia or eclampsia, induction of labor, mode of birth (unassisted vaginal delivery, instrumental vaginal delivery, elective Cesarean delivery and emergency Cesarean delivery), maternal length of stay (three or more days) and 42-day readmission. The study outcomes derived for the linked maternal-neonatal cohort included the provision of specialist neonatal care, neonatal length of stay (three or more days), 28-day readmission and a composite neonatal adverse outcome indicator (E-NAOI), which includes 16 diagnoses and 7 procedures and has previously been validated in HES.[20] The definitions and coding of all study outcomes are specified in Supplementary Table 1. This dataset does not contain sufficient information to distinguish between antepartum and intrapartum fetal death (stillbirth); in England in 2018 (the latest date for which this information is available), nine in every ten stillbirths were antepartum.[21]

Maternal age was grouped into five-year periods, with women under 20 and over 40 years being aggregated into single categories. Parity was defined using records of previous births through a 'look-back' approach in HES, and handled in three categories: primiparous, multiparous without previous Cesarean delivery, and multiparous with previous Cesarean delivery.[22,23] Maternal ethnicity was coded using the Office for National Statistics categorization system from the 2001 Census and collapsed into four groups: White, South

Asian, Black, and Other Stated. Information about pre-existing diabetes and hypertension was available in the diagnosis codes attached to the birth episode, with women assumed not to have the condition if the code was not present. Index of Multiple Deprivation 2019 (IMD) provides an overall measure of multiple deprivation derived from information about income, education, employment, crime, and the living environment. IMD rankings of 32,844 "Lower Super Output Areas", with typically 1,500 inhabitants, were used to categorize women into five socioeconomic groups.[24]

Statistical analysis

Characteristics of women in the cohort with and without laboratory-confirmed SARS-CoV-2 infection at the time of birth were tabulated. Rates of maternal and perinatal outcomes were calculated in women with and without laboratory-confirmed SARS-CoV-2 infection at the time of birth. Adjusted odds ratios (aOR) and their 95% confidence interval (CI) for the association between SARS-CoV-2 infection status and outcomes were calculated using logistic regression, adjusting for maternal age, ethnicity, parity, pre-existing diabetes, pre-existing hypertension and socioeconomic deprivation measured using IMD. Models were fitted with robust standard errors to account for hospital-level clustering. The analysis of the neonatal outcomes was repeated for those born at term (at or beyond 37 weeks' gestation) since preterm birth has been reported to be more common in pregnant women with SARS-CoV-2 infection.

Data were complete for all variables except maternal ethnicity (89.1% complete) and IMD (99.4% complete). For regression analyses, missing values of ethnicity and IMD were imputed using chained equations to generate 10 datasets; estimates from these datasets were pooled using Rubin's rules.[25] Stata 16 was used for all analyses. A P value of less than 0.05 was assumed to represent statistical significance.

Ethical approval

This study used data collected to evaluate service provision and performance and therefore was exempt from ethical review by the NHS Health Research Authority. The use of personal data without individual consent was approved by the NHS Health Research Authority (16/CAG/0058).

RESULTS

The analysis included 342,080 women with singleton pregnancy who gave birth in England between 29th May 2020 and 31st January 2021, of whom 3,527 (10.3 per 1000) were recorded as having laboratory-confirmed SARS-CoV-2 infection (Figure 1, Table 1). Laboratory-confirmed SARS-CoV-2 infection was more likely in younger women, women from non-white ethnicity, those with pre-existing diabetes, pre-existing hypertension and women residing in the most socioeconomically deprived areas (Table 1).

Table 2 shows that fetal death was significantly more common in women with laboratory-confirmed SARS-CoV-2 infection at the time of birth (30/3,527 or 8.5 per 1000) than in those without (1,140/338,553 or 3.4 per 1000; aOR, 2.21, 95% CI 1.58-3.11; P<0.001). There was also a significant increase in the risk of preterm birth (5.8% in women without laboratory-confirmed SARS-CoV-2 infection; 12.1% in those with, aOR 2.17, 95% CI 1.96-2.42; P<0.001). Women with laboratory-confirmed SARS-CoV-2 infection were at increased risk of preeclampsia/eclampsia (3.9% compared to 2.5%, aOR 1.55, 95% CI 1.29-1.85; P<0.001) and emergency Cesarean delivery (27.6% compared to 18.5%, aOR 1.63, 95% CI 1.51-1.76; P<0.001), with a corresponding reduction in the rate of spontaneous vaginal delivery (49.2% compared to 54.6% in women without laboratory-confirmed SARS-CoV-2 infection, aOR 0.80, 95% CI 0.75 to 0.86). Rates of elective Cesarean delivery (10.8% compared to 13.8%, aOR 0.81, 95% CI 0.71-0.91; P<0.001) were lower in women with laboratory-confirmed SARS-CoV-2 infection than in those without. Following birth, women with SARS-CoV-2 infection were at increased risk of hospital admission lasting three days or more

(25.8% compared to 17.0%, aOR 1.57, 95% CI 1.44-1.72; P<0.001) and readmission within six weeks after birth (4.3% compared to 3.1%, aOR 1.39, 95% CI 1.10-1.76; P=0.01) than those without. No significant differences were seen in the rates of SGA (P=0.87), induction of labor (P=0.40) or instrumental vaginal delivery (P=0.20).

Of the 342,080 maternity records, 330,057 (96.5%) were linked to the neonatal record (Figure 1). Risk of neonatal adverse outcome (aOR 1.45, 95% CI 1.27-1.66; P<0.001), need for specialist neonatal care (aOR 1.24, 95% CI 1.02-1.51; P=0.03), and prolonged neonatal admission following birth (aOR 1.61, 95% CI 1.49-1.75; P<0.001) were all significantly higher for infants with mothers with laboratory-confirmed SARS-CoV-2 infection compared to those without (Table 2). When the analysis was restricted to pregnancies delivered at term (≥37 weeks), there were no significant differences in neonatal adverse outcome (P=0.78), need for specialist neonatal care after birth (P=0.22) or neonatal readmission within four weeks of birth (P=0.05) (Table 2). Term infants born to mothers with laboratory-confirmed SARS-CoV-2 infection had prolonged admission following birth (21.1% compared to 14.6%, aOR 1.61, 95% CI 1.49-1.75; P<0.001) (Table 2).

COMMENT

Principal findings

In this population-based study of women giving birth to a singleton infant in England in 2020-2021, we report that women with a record of laboratory-confirmed SARS-CoV-2 infection at the time of birth were more than twice as likely as women without SARS-CoV-2 infection to have fetal death or preterm birth. Women with SARS-CoV-2 infection were also more likely to have preeclampsia and to give birth by emergency Cesarean delivery. Both women and their neonates were more likely to have prolonged hospital stay of three days or more, and mothers were more likely to be readmitted to hospital in the postnatal period. There was no significant difference in rates of induction of labor, instrumental vaginal delivery or SGA

between women who did and did not have SARS-CoV-2 infection at the time of birth. The composite neonatal adverse outcome and specialist neonatal care were significantly higher in pregnancies with SARS-CoV-2 infection at the time of birth. However, when the analysis was restricted to term deliveries, neonatal outcomes were similar for those born to mothers with and without SARS-CoV-2 infection.

Results in the Context of What is Known

Our findings concur with those of an ongoing living systematic review which estimates the pooled association between COVID-19 and fetal death at OR 2.84 (95% CI 1.25 to 6.45);[1] with a more recent multinational case-control study which reports an association between COVID-19 and a composite neonatal adverse outcome of RR 2.14 (95% CI 1.66 to 2.75[4]); and with a recent population level study reporting an increase in adverse neonatal outcomes for infants born to women with COVID-19 infection.[9] However, the systematic review is limited by the size and number of studies available, with only nine women experiencing a stillbirth in the COVID-19 group of the pooled dataset;[1] and the case-control study was unable to report on fetal death alone, instead incorporating it into an adverse outcome including intrauterine or neonatal death, prolonged neonatal stay, or severe neonatal morbidity.[4] In the population-level study, as in our study, almost all of the association between maternal COVID-19 infection and adverse neonatal outcome was explained by increased risk of preterm birth.[9] In our study we were not able to stratify preterm birth into spontaneous and indicated/iatrogenic (where birth is initiated by the clinician); other studies have suggested that the increase in preterm birth is due to indicated delivery to improve maternal condition.[1]

The key potential bias in our study comes from misclassification of the exposure; this could be caused by selective testing (whether the chance of a woman having been tested for SARS-CoV-2 was dependent on her pregnancy outcome), selective recording (whether the chance of a woman who tested positive had that result recorded in HES was dependent on

her pregnancy outcome) or missed cases (women who had SARS-CoV-2 infection but were not recorded as such).

It is unlikely that either selective testing or recording fully explain our results. First, throughout the pandemic there was a statutory requirement to report cases of SARS-CoV-2 infection in healthcare settings.[26] Second, the laboratory-confirmed SARS-CoV-2 infection rate of 1.96% between 1st October 2020 and 31st January 2021 (when national data is available and could be compared) which we observed in all women giving birth in this period is very close to the SARS-CoV-2 infection rate of 1.74% (and within the credible intervals of 1.53% to 1.98%) reported for people between 25 and 35 years old by the Office for National Statistics (ONS) for the period 3rd October 2020 to 22nd January 2021 based on a routine national survey of households;[27] this provides evidence that universal testing of maternity admissions was fully implemented during this period.[28] The slightly higher rate may be attributed to women of childbearing age likely to be living with children and to be required to leave the house to interact with healthcare providers.[29]

These results provide further evidence that SARS-CoV-2 infection increases the risk of fetal death. The potential mechanisms may be pregnancy-specific, including placental disease with reports of abnormal inflammation of the placenta in association with maternal COVID-19.[30,31] However, the association may also be a more generic consequence of severe maternal illness in pregnancy, given that women who become seriously unwell with other illnesses are known to be at higher risk of perinatal morbidity and mortality.[32]

Our findings related to the characteristics of women infected with SARS-CoV-2, and associations with other complications including preeclampsia, preterm birth, Cesarean delivery and adverse neonatal outcomes concur with other studies in the UK and internationally.[1,4] Our results regarding length of stay and maternal readmissions are novel, but also relate to the context of care in England, where much of postnatal maternity care is provided in the community.[28]

287

288 *Clinical and research implications*

289 The finding that women with a recorded SARS-CoV-2 infection at the time of birth may have
290 an increased risk of fetal death and other adverse maternal and perinatal outcomes concurs
291 with a recent international case-control study[4] and will be of particular concern to pregnant
292 women and healthcare professionals. The overall numbers of fetal deaths are too small to
293 impact the overall national rate of stillbirth in the UK, as seen in provisional national reports
294 for 2020.[33] It is therefore important to carefully contextualise these findings when counselling
295 pregnant women.

296 However, this finding should prompt reflection on the treatment of pregnant women infected
297 with SARS-CoV-2, as well as the relative risks and benefits of vaccination. For pregnant
298 women who test positive for SARS-CoV-2 in the later stages of pregnancy, care should
299 consider the wellbeing of the baby. At term, acknowledgement of the increased risk of fetal
300 death may prompt discussion of the potential risks of ongoing expectant management of
301 pregnancy, and consideration of an earlier planned birth.

302 For women earlier in pregnancy, our findings may change the risk-benefit analysis for
303 vaccination. At present, data on the safety and efficacy of COVID-19 vaccination in
304 pregnancy are limited due to the exclusion of pregnant women in clinical trials,[34] although
305 trials are now underway to address this urgent need. This has motivated widespread
306 hesitancy about recommendation of vaccination to all pregnant women, with governments
307 and professional organizations initially recommending offering vaccination to pregnant
308 women at high risk of either occupational exposure or severe disease[35] and pregnant
309 women reluctant to take up a vaccine offer.[36] In the USA and Israel, where vaccination has
310 been recommended to those at higher risk, initial data provide a positive signal of safety and
311 efficacy in pregnant women.[37–39] Further evidence of a link between SARS-CoV-2 infection

and an increased risk of fetal death may motivate prioritization of, and encourage pregnant women to access, vaccination.

Strengths and limitations

The main strengths of this study are its large size and representative nature, covering almost the entire population of births in England during the time period. The use of HES data to understand maternity outcomes is well established and offers rich information about individual women to allow for adjustment for individual risk.[23]

The principal exposure of SARS-CoV-2 infection is defined using an ICD-10 code recorded if the woman had a laboratory-confirmed infection. The use of ICD-10 codes in this way to understand differences between admissions with and without SARS-CoV-2 infection has been established elsewhere.[9,40]

The use of administrative data including diagnostic and procedure codes to establish exposures and outcomes (including in our study pre-eclampsia, neonatal adverse outcome, and SARS-CoV-2 status) has inherent limitations as the primary purpose of data recording is for payment rather than clinical research; known limitations include under-recording and misclassification.[41] This may particularly affect pre-eclampsia where there is variation in diagnostic criteria and thresholds; gestational hypertension may be conflated with pre-eclampsia.[42]

While in our study we were able to adjust for many potential confounders, we had no information on the severity of COVID-19 illness or maternal body mass index (BMI) in our dataset. Maternal obesity is a risk factor for both severe COVID-19 and fetal death.[1,43] It is therefore possible that the observed association could be partially accounted for by differences between groups of women.

Our results should be strictly interpreted as being related to the result of a test for SARS-CoV-2 at the time of birth, rather than to any infection which occurred during pregnancy. This is an important feature given that some of the observations in women who tested positive for SARS-CoV-2, especially the increases in risk of stillbirth and preterm birth in women with a positive test, may be partly explained by variations in the rate of SARS-CoV-2 infection according to gestational age. This is different from other studies which seek to understand effects on women who are infected with SARS-CoV-2 at any point during their pregnancy, and from studies which assess population risks of fetal death measuring both direct and indirect effects.[44–46]

Conclusions

Our results demonstrate that women who have laboratory-confirmed infection with SARS-CoV-2 at the time of birth have higher rates of fetal death and preterm birth, preeclampsia and emergency Cesarean delivery, as well as prolonged maternal and neonatal admission following birth, compared to those without SARS-CoV-2 infection. There were no additional adverse neonatal outcomes, other than those related to preterm delivery. These findings should guide the counselling of pregnant women about risks of SARS-COV-2 infection during pregnancy and indicate that pregnant women should be prioritized for vaccination.

355 **ACKNOWLEDGEMENTS**

356

357 *Author contributions:* IGU, JJ, JvdM, AK conceived and designed the study. IGU performed
358 the analysis. All authors interpreted the data. JJ wrote the first draft of the manuscript with
359 supervision from JvdM and AK. IGU and JJ had full access to all the data in the study and
360 take responsibility for the integrity of the data and the accuracy of the data analysis. All
361 authors revised the paper critically for important intellectual content and provided final
362 approval of the submitted manuscript.

363

364 **Table 1.** Characteristics and study outcomes of women included in the study

	Pregnant women without laboratory-confirmed SARS-CoV-2 infection at the time of birth **n (%)**	**Pregnant women with laboratory-confirmed SARS-CoV-2 infection at the time of birth** **n (%)**	**P-value (Chi2 test)**
Number of births	338553 (100)	3527 (100)	
Maternal age in years			<0.001
≤19	8907 (2.6)	94 (2.7)	
20-24	44755 (13.2)	581 (16.5)	
25-29	93051 (27.5)	1040 (29.5)	
30-34	114639 (33.9)	1079 (30.6)	
35-39	62451 (18.5)	587 (16.6)	
40+	14750 (4.4)	146 (4.1)	
Maternal ethnicity*			<0.001
White	230202 (76.3)	1857 (58.5)	
South Asian	36834 (12.2)	768 (24.2)	
Black	13998 (4.6)	251 (7.9)	
Other	20546 (6.8)	298 (9.4)	
Obstetric history			0.13
Primiparous	142289 (42.0)	1514 (42.9)	
Multiparous with no previous CS†	156269 (46.2)	1634 (46.3)	
Multiparous with previous CS†	39995 (11.8)	379 (10.8)	
Pre-existing diabetes	3112 (0.9)	58 (1.6)	<0.001
Pre-existing hypertension	2624 (0.8)	44 (1.3)	0.002
Index of Multiple Deprivation*			<0.001
1= least deprived	50814 (15.1)	342 (9.8)	
2	57892 (17.2)	413 (11.8)	
3	65104 (19.3)	602 (17.2)	
4	75159 (22.3)	874 (25.0)	
5 = most deprived	87703 (26.1)	1265 (36.2)	

* ethnicity missing in 37326 (10.9%) of records, IMD missing in 1912 (0.6%) of records; % may not add to 100 due to rounding. †Cesarean section

365

Table 2. Comparison of study outcomes between pregnant women with and without laboratory-confirmed SARS-CoV-2 infection (ICD-10 U07.1) at the time of birth

	Pregnant women without SARS-CoV-2 infection		Pregnant women with laboratory-confirmed SARS-CoV-2 infection		Unadjusted OR (95% CI)	P value	Adjusted OR‡ (95% CI)	P value
	cases/births	%	cases/births	%				
Maternal data								
Fetal death	1140/338553	0.34	30/3527	0.85	2.54 (1.81,3.56)	<0.001	2.21 (1.58,3.11)	<0.001
Preterm birth	18572/322494	5.8	369/3047	12.1	2.25 (2.03,2.50)	<0.001	2.17 (1.96,2.42)	<0.001
Small for gestational age	17521/320188	5.5	191/3009	6.4	1.17 (1.00,1.37)	0.05	0.99 (0.84,1.16)	0.87
Preeclampsia/eclampsia	8591/338553	2.5	139/3527	3.9	1.58 (1.32,1.89)	<0.001	1.55 (1.29,1.85)	<0.001
Induction of labor	96651/236822	40.8	940/2382	39.5	0.95 (0.82,1.08)	0.42	0.95 (0.83,1.08)	0.40
Elective Cesarean delivery	46843/338553	13.8	380/3527	10.8	0.75 (0.67,0.85)	<0.001	0.81 (0.71,0.91)	<0.001
Emergency Cesarean delivery	62479/338553	18.5	975/3527	27.6	1.69 (1.56,1.83)	<0.001	1.63 (1.51,1.76)	<0.001
Instrumental vaginal delivery	43393/338553	12.9	422/3527	12.0	0.92 (0.83,1.03)	0.14	0.93 (0.82,1.04)	0.20
Unassisted delivery	184989/338553	54.6	1734/3527	49.2	0.80 (0.75,0.86)	<0.001	0.76 (0.70,0.82)	<0.001
Maternal length of stay (3+days)	55529/326248	17.0	857/3321	25.8	1.70 (1.55,1.85)	<0.001	1.57 (1.44,1.72)	<0.001
Maternal readmission (42-day)	8660/281178	3.1	78/1818	4.3	1.41 (1.11,1.78)	0.004	1.39 (1.10,1.76)	0.01
Maternal-neonatal linked data								
Neonatal adverse outcome indicator (ENAOI)†	16501/318073	5.2	222/2922	7.6	1.50 (1.32,1.72)	<0.001	1.45 (1.27,1.66)	<0.001
Specialist neonatal care	35032/326901	10.7	432/3156	13.7	1.32 (1.04,1.67)	0.02	1.24 (1.02,1.51)	0.03
Neonatal length of stay (3+days)	58410/324665	18.0	857/3104	27.6	1.74 (1.62,1.87)	<0.001	1.61 (1.49,1.75)	<0.001
Neonatal readmission (28-day)	14259/277804	5.1	126/2058	6.1	1.21 (1.01,1.44)	0.04	1.18 (0.98,1.41)	0.08
Maternal-neonatal linked data of deliveries at term (≥ 37 weeks)								
Neonatal adverse outcome indicator (ENAOI)†	9970/298099	3.3	89/2542	3.5	1.05 (0.85,1.29)	0.45	1.03 (0.84,1.27)	0.78
Specialist neonatal care	28002/299456	9.4	294/2555	11.5	1.26 (0.92,1.73)	0.15	1.18 (0.90,1.55)	0.22
Neonatal length of stay (3+days)	43390/297805	14.6	534/2530	21.1	1.56 (1.42,1.74)	<0.001	1.61 (1.49,1.75)	<0.001
Neonatal readmission (28-day)	12749/262437	4.9	106/1802	5.9	1.22 (1.02,1.47)	0.03	1.20 (1.00,1.45)	0.05

†Composite outcome. Birth with any of: birthweight<1500g, gestational age under 32 completed weeks, neonatal death within 28 days, respiratory distress syndrome (RDS), seizure, intraventricular haemorrhage (grade 3 or 4), cerebral infarction, periventricular leukomalacia, birth trauma (intracranial haemorrhage paralysis due to brachial plexus injury, skull or long bone fracture), hypoxic ischaemic encephalopathy, necrotising enterocolitis, sepsis/septicaemia, pneumonia, respiratory disease (respiratory failure, primary atelectasis, chronic respiratory disease originating in the perinatal

period, bacterial meningitis, resuscitation (intubation/chest compression), mechanical ventilation/continuous positive airway pressure/high flow nasal oxygen, central venous or arterial catheter, pneumonthorax requiring intracostal catheter, any intravenous fluids, any body cavity surgical procedure, therapeutic hypothermia
‡Adjusted for maternal age, ethnicity, socioeconomic deprivation measured by IMD, parity, previous Cesarean delivery, diabetes and hypertension

Supplementary Table 1. Definitions of study outcomes and their coding in Hospital Episode Statistics (HES)

Outcome	Numerator / coding	Denominator / coding
Using maternal data:		
Stillbirth (fetal death)	Defined using ICD10 code (Z37.1) OR birth status field (birstat_1=2,3,4) in maternity tail for providers with over 95% data completeness. In the UK stillbirth is defined as birth without signs of life occurring at or after 24+0 completed gestational weeks, based on estimated due date calculated using universally offered ultrasound scan at 11-13 weeks' gestation.	All singleton births This dataset does not contain sufficient information to distinguish between antepartum and intrapartum stillbirth; in England in 2018 (the latest date for which this information is available), nine in every ten stillbirths were antepartum.[1]
Preterm birth	Defined using gestational age field in HES maternity tail (gestat_1<37)	All singleton births, excluding records missing information on gestational age
Small-for-gestational age	Defined as less than the 10th birthweight centile using the WHO-UK charts.[2] Birthweight centiles are calculated using birthweight (birweit_1), gestational age (gestat_1), sex of baby (sexbaby_1) fields in maternity tail	All singleton births, excluding records missing information on gestational age, birthweight or sex of baby
Preeclampsia/eclampsia	Defined using the ICD-10 codes O14 (preeclampsia) and O15 (eclampsia).	All singleton births
Induction of labor	Defined using the delivery onset field (delonset=3,4,5) from the maternity tail. Failed induction (ICD-10 code O61) is also included in the numerator as this represents intention to treat.	All singleton births, excluding elective Cesarean section; and records missing information on delivery onset
Elective Cesarean delivery	ELC is defined using OPCS code R17	All singleton births
Emergency Cesarean delivery	EMCS is defined using OPCS codes R18/R25.1	All singleton births
Instrumental delivery	Instrumental birth is defined using OPCS codes R21/R22	All singleton births
Unassisted delivery	Unassisted birth is defined using OPCS code R23/R24	All singleton births
Maternal length of stay post birth (3 or more days)	Length of stay is defined as the number of days between date of discharge and date of admission for the birth episode.	All singleton births with non-missing date of discharge information and date of delivery before 28th January 2021 (to allow for 3-day follow up)
Maternal readmission (42-days)	Maternal readmission is defined as unplanned, overnight readmission to hospital within 42 days of giving birth, excluding those accompanying an unwell baby. Mothers readmitted with the following admission method codes: 21, 22, 23, 24, 28, 2A, 2B, 2D, 31, 32, 82, 83	All singleton births with non-missing date of discharge information and date of delivery before 19th December 2020 (to allow for six-week follow up). Women who died before discharge or were not discharged within 42 days of delivery were excluded.

[1] Draper ES, Gallimore ID, Smith LK, Fenton AC, Kurinczuk JJ, Smith PW, Boby T, Manktelow BN, on behalf of the MBRRACE-UK Collaboration. MBRRACE-UK Perinatal Mortality Surveillance Report, UK Perinatal Deaths for Births from January to December 2018. Leicester: The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester. 2020.

[2] Cole TJ, Williams AF, Wright CM. Revised birth centiles for weight, length and head circumference in the UK-WHO growth charts. *Ann Hum Biol*. 2010;38(1):7-11. doi:10.3109/03014460.2011.544139

	within 42 days of birth.	

Outcome	Numerator / coding	Denominator / coding
Using maternal-neonatal linked data:		
Neonatal specialist care	Neonatal specialist care is defined using the "neocare" variable in HES, and includes values 1=Special care: care given in a special nursery, transitional care ward or postnatal ward, which provides care and treatment exceeding normal routine care; 2 = Level 2 intensive care (high dependency intensive care); and 3 = Level 1 intensive care (maximal intensive care)	All singleton, term births with non-missing information on neonatal specialist care
Neonatal adverse outcome indicator (ENAOI)	ENAOI is defined as births with any of the following outcomes: birthweight<1500g, gestational age under 32 completed weeks, neonatal death within 28 days, respiratory distress syndrome (RDS), seizure, intraventricular haemorrhage (grade 3 or 4), cerebral infarction, periventricular leukomalacia, birth trauma (intracranial haemorrhage paralysis due to brachial plexus injury, skull or long bone fracture), hypoxic ischaemic encephalopathy, necrotising enterocolitis, sepsis/septicaemia, pneumonia, respiratory disease (respiratory failure, primary atelectasis, chronic respiratory disease originating in the perinatal period, bacterial meningitis, resuscitation (intubation/chest compression), mechanical ventilation/CPAP/high flow nasal oxygen, central venous or arterial catheter, pneumonthorax requiring intracostal catheter, any intravenous fluids, any body cavity surgical procedure, therapeutic hypothermia. Coding of these diagnoses and procedures can be found in Knight et al 2018, Supplementary Table 1.	All liveborn singleton term births with non-missing information on gestational age and birthweight
Neonatal length of stay post birth (3 or more days)	Length of stay is defined as the number of days between date of discharge and date of admission for the birth episode.	All singleton births with non-missing date of discharge information and date of birth before 28th January 2021 (to allow for 3-day follow up)
Neonatal readmission (28-days)	Neonatal readmission is defined as unplanned, overnight readmission to hospital within 28 days of birth, excluding those accompanying an unwell mother. Babies readmitted with the following admission method codes: 21, 22, 23, 24, 28, 2A, 2B, 2D, 31, 32, 82, 83 within 28 days of birth.	All singleton neonates with non-missing date of discharge information and date of birth before 3rd January 2021 (to allow for four-week follow up). Babies who died before discharge or were not discharged within 28 days of birth were excluded.

FIGURE LEGEND

Figure 1. Study flowchart

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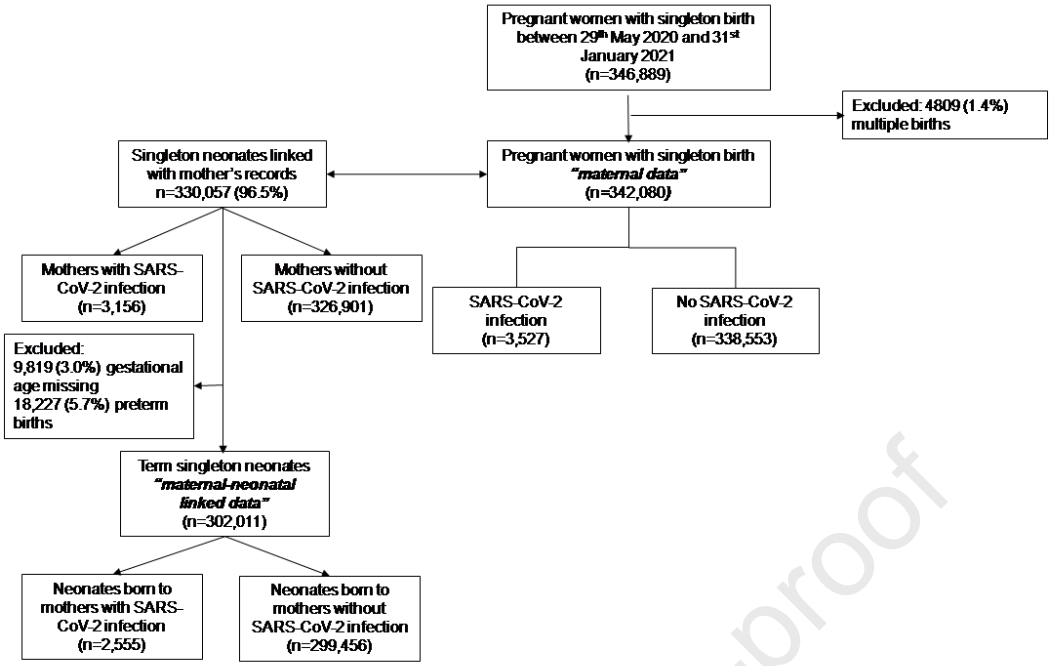

Figure 1