# The Effect of COVID-19 Infection During Pregnancy; Evaluating Neonatal Outcomes and the Impact of the B.1.1.7. Variant

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**Background:** Coronavirus disease 2019 (COVID-19) infection during pregnancy has been associated with adverse perinatal outcomes. We aim to evaluate the neonatal outcomes including the incidence of preterm birth, admission to the neonatal unit and incidence of congenital anomalies in this cohort. We will also describe these outcomes in the context of the B.1.1.7. variant outbreak, the dominant variant in Ireland since January 2021, which has had a greater impact on pregnant patients.

**Methods:** This was a retrospective study of liveborn infants, delivered between 1st March 2020 and 1st March 2021, to women with a severe acute respiratory syndrome coronavirus 2 diagnosis during pregnancy, in a tertiary maternity hospital (8,500 deliveries/year). Clinical data were collected, and analyses were performed to evaluate the impact of maternal symptom status, time from diagnosis to delivery and the B.1.1.7. variant on neonatal outcome.

**Results:** In total 133 infants (1.6%) were born to women with severe acute respiratory syndrome coronavirus 2 identified during pregnancy. The median birth weight was 3.45 kg and gestational age at birth was 39.3 weeks. 14 infants (10.5%) were preterm. 22 infants (16.5%) required admission to the neonatal unit and 7 (5.3%) were small for gestational age. There was no difference in growth, preterm birth or neonatal unit admission based on maternal symptom status or infection after the outbreak of B.1.1.7. as the dominant strain.

**Conclusions:** Following a COVID-19 infection in pregnancy, there was no increase in the incidence of preterm birth or neonatal intensive care unit admission compared with 5-year hospital data. Maternal symptom status did not influence neonatal outcomes. Further studies to evaluate the impact of COVID-19 in early pregnancy, the variants of concern, particularly the emerging Delta variant and COVID-19 placentitis are required.

**Key Words:** SARS-CoV-2, fetus, growth, preterm, congenital

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## BACKGROUND

Coronavirus disease 2019 (COVID-19), an infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, rapidly developed into a global pandemic in 2020. In adults, COVID-19 typically causes respiratory illness[1] and is commonly associated with thromboembolic complications.[2] While most people experience mild to moderate disease, COVID-19 can cause severe disease or death, particularly in high-risk patients such as the elderly and those with underlying medical conditions.[3]

Pregnant women with COVID-19 usually display mild to moderate symptoms.[4] However, they are at higher risk of developing severe disease requiring respiratory support and admission to intensive care compared with nonpregnant women of the same age and risk factor profile.[5,6]

The SARS-CoV-2 virus can be transmitted from the mother to the newborn, although this rarely occurs.[7–9] While there have been rare reports of suspected vertical transmission of COVID-19,[10,11] mother-to-child transmission typically occurs by postnatal exposure and infection. Moreover, neonates with COVID-19 typically have a mild illness.[12,13]

There is concern regarding the perinatal outcomes of COVID-19 infection in pregnancy. In October 2020, this group published an initial review of neonatal outcomes following maternal SARS-CoV-2 diagnosis during pregnancy.[14] An increased rate of preterm birth was described (23%), similar to that reported by other studies at the time (17%–26%).[7,15] Maternal COVID-19 infection during pregnancy has been associated with increased rates of preterm birth, admission to the neonatal intensive care unit (NICU), low birth weight and fetal distress.[8,9] Neonates with SARS-CoV-2 usually present with fever, poor feeding or respiratory distress[12] but there have been rare individual case reports of white matter injury and persistent pulmonary hypertension in infants born to women with SARS-CoV-2 and neonates infected with SARS-CoV-2.[16,17]

The first reported case of COVID-19 in the Republic of Ireland occurred on 29th February 2020.[18] Since then, there have been 3 waves of infection, the most significant of which occurred following the emergence of the B.1.1.7 variant (UK variant) as the dominant circulating strain in this country in January 2021.[19] There is growing concern regarding the B.1.1.7 variant, particularly in relation to the severity of maternal COVID-19 illness in pregnancy[6] and COVID-19 placentitis.[20,21] In April 2021, 6 cases of stillbirth associated with COVID-19 placentitis were reported in Ireland, however, this was outside the data collection period for this study.[22]

In this study, we aim to evaluate the neonatal clinical outcomes following a maternal SARS-CoV-2 diagnosis at any time during pregnancy, over the 12-month period since the outbreak of COVID-19 in Ireland. Analysis of the impact of maternal symptom status, time from diagnosis to delivery and the B.1.1.7 variant as the dominant strain in Ireland on neonatal outcomes were also evaluated.

## METHODS

This was a retrospective observational study performed in an Irish Tertiary University Maternity Hospital and Neonatal Intensive Care Unit. All liveborn infants, of women with SARS-CoV-2 ribonucleic acid (RNA) detected at any time during pregnancy (and

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up to 24 h postnatally), delivered between 1st March 2020 and 1st March 2021 were included. Ethical approval was obtained from the Hospital Research Ethics Committee (RAG-2021-001).

Patients were identified from the central hospital COVID-19 notification system (n = 131) and 2 were identified by the neonatal unit (maternal SARS-CoV-2 test performed prior to booking in this hospital). If an individual had 2 dates of SARS-CoV-2 diagnosis, the first confirmed infection was selected, as the second test likely represented asymptomatic shedding. If only the month of diagnosis was known, the 15th of that month was arbitrarily assigned as the date of diagnosis (n = 1). For multiple births, maternal data were recorded once, whereas infant data were considered independently as the number of multiple births was small (n = 3). Neonatal outcomes, including mode of delivery, gestational age birth weight, preterm birth, NICU admission, congenital anomalies, small for gestational age, breast-feeding, common postnatal complications, SARS-CoV-2 diagnosis, length of stay and outpatient follow-up were recorded.

Data were extracted from the Electronic Patient Record and anonymous data were collected in Microsoft Excel. Descriptive statistics were performed. Stata SE (Version 16.0) was used for statistical analysis. For continuous variables, the mean [standard deviation (SD)] and median [25th–75th percentile, interquartile range(IQR)] are described for normal and non-normal distribution, respectively. For categorical variables, frequency (percentages) are described.

Historical hospital data, describing annual pregnancy outcomes for all patients attending the same center, was available for some variables (maternal age, parity, mode of delivery, birth weight gestational age, NICU admission and preterm birth). For comparison of categorical variables with annual hospital data, the $\chi^2$ test was used.

Analysis was performed, comparing neonatal outcomes [gestational age, birth weight, preterm birth, NICU admission and small for gestational age (<10th centile)] of infants born to women infected before the emergence of variant B.1.1.7 (1st March 2020–31st December 2020) and after the emergence of variant B.1.1.7 as the dominant circulating strain (1st January 2021–1st March 2021). Further analyses comparing neonatal outcomes by maternal symptom status (presence or absence of symptoms) and the time from diagnosis to delivery (greater than or less than 10 days) were also performed. Univariate comparisons between these groups were performed using the $\chi^2$ test for categorical variables and the Mann-Whitney *U* test (nonparametric) or independent samples *t*-test (parametric) for continuous variables. Significance was assumed at 2-sided $P < 0.05$.

## RESULTS

During this 12-month period, 8,313 infants (liveborn and stillborn) were delivered in this hospital. In total 133 liveborn infants of 130 women with SARS-CoV-2 detected during pregnancy, were identified (1.6 %).

### Maternal Demographics

Table 1 describes the maternal demographic details. The mean maternal age was 30.9 years (SD ± 5.8 years). A large proportion of women [n = 38 (29.2%)] had an underlying medical illness, which included thyroid disease [n = 15 (11.5%)], renal, liver and respiratory disease.

### Maternal SARS-CoV-2 diagnosis

The indication for SARS-CoV-2 testing included symptomatic patients [n = 61 (46.9%)], close contacts [n = 17 (13.1%)], preadmission screening [n = 41 (31.5%)] and in 11 (8.5%) cases the indication was not described. The symptoms for which SARS-CoV-2 testing was indicated, both tests performed in this hospital and in the community, were in accordance with the Irish Health Service Executive recommendations.[23] The criteria for testing of symptomatic patients did change over the course of the 12 months, in line with the emerging evidence and the availability of testing. The major symptoms indicating SARS-CoV-2 testing included fever, cough, shortness of breath and a change or loss of taste or smell and are supported by the local[24] and international literature.[1,25] Preadmission SARS-CoV-2 screening was performed prior to elective cesarean sections and induction of labor since June 2020 and all nonelective admissions to hospital from the 28th of December 2020.

A majority of patients [n = 79 (60.8%)] reported at least 1 symptom of COVID-19 whereas 43 (33.1%) reported no symptoms and in 8 (6.2%) cases the symptom status was not documented. In total, 78 (60%) SARS-CoV-2 diagnosis were made in the hospital, while the remainder were diagnosed in the community. The median gestational age at diagnosis of SARS-CoV-2 was 36.4 weeks (IQR 32.6–39 weeks). The majority [116 (89.2%)] of diagnosis occurred in the 3rd trimester.

The median time from diagnosis of SARS-CoV-2 to delivery was 15 days (IQR 1–39). Four women (3.1%) required escalation of care to a high dependency unit or transfer to an acute adult hospital for symptoms related to COVID-19.

### Neonatal Outcomes

The neonatal characteristics and outcomes of liveborn infants to women with SARS-CoV-2 diagnosed at any time during pregnancy are described in Table 2.

### Neonatal COVID-19

As per Irish National Guidelines, infants were not routinely tested for SARS-CoV-2, and only screened if they developed symptoms suggestive of COVID-19, or had common neonatal pathologies (such as transient tachypnea of the newborn) which did not resolve in the expected time frame.[26] In total 5 infants were tested for SARS-CoV-2, 2 were performed before transfer/re-admission;

**TABLE 1.** Maternal Characteristics of Women with SARS-CoV-2 Detected During Pregnancy Compared with Historical Hospital Data

| | COVID-19 Group N (%) | |
|---|---|---|
| Characteristic | N = 130 | Hospital Data |
| Nulliparous | 73 (56.2) | 41%–44%* |
| Ethnicity | | |
| Caucasian | 88 (67.7) | 81.4%† |
| African | 11 (8.5) | 2.1%† |
| Asian | 18 (13.9) | 4.9%† |
| Members of Ireland's Roma Community and Irish travelers | 10 (7.7) | 1.8%† |
| Other | 3 (2.3) | 9.7%† |
| Underlying medical illness | 38 (29.2) | |
| Gestational diabetes | 17 (13.1) | 9.3 %–14.3%* |
| Pre-eclampsia/pregnancy induced hypertension | 7 (5.4) | |
| Smoking during pregnancy | 10 (7.7) | |
| Thrombocytopaenia in pregnancy (<150 × $10^9$/L) | 24 (18.5) | |

*Hospital data 2015–2019.
†Hospital data 2020.

**TABLE 2.** Characteristics and Neonatal Outcomes of Infants Born to Women with SARS-CoV-2 Detected During Pregnancy Compared with Hospital Data

| | COVID-19 | |
|---|---|---|
| | N = 133 | Hospital Data |
| Mode of delivery N (%) | | |
| Spontaneous vaginal delivery | 63 (47.4) | 49%–51%* |
| Operative vaginal delivery | 18 (13.5) | 16%–17%* |
| Cesarean section | 52 (39.1) | 29%–35%* |
| Male gender N (%) | 68 (51.1) | 50.6%–51.7%* |
| Gestational age, weeks median (IQR) | 39.3 (38.4–40.3) | 39* |
| Birth weight, kg median (IQR) | 3.45 (3.01–3.84) | 3.39–3.41* |
| Preterm N (%) | 14 (10.5) | 6.3%–7.9%* |
| SGA (weight <10th centile) N (%) | 7 (5.3) | |
| Admission to NICU N (%) | 22 (16.5) | 13.1%–15.5%* |
| Congenital anomaly N (%) | 12 (9) | |
| Neonatal death N (%) | 1 (0.75) | |
| Received any breast milk N (%) | 92 (69.2) | |
| Weight loss >10% N (%) | 4 (3) | |
| Hypoglycemia <2.6 N (%) | 6 (4.5) | |
| Jaundice requiring phototherapy N (%) | 13 (9.8) | |
| Neonate ever tested for SARS-CoV-2 N (%) | 5 (3.8) | |
| Sars-CoV-2 detected N (%) | 0 (0) | |
| Day of life at discharge median (IQR) | 3 (2–4) | |
| Discharge location N (%) | | |
| Home | 129 (97.7) | |
| Other hospital | 1 (0.8) | |
| Isolation facility | 2 (1.5) | |
| Any outpatient follow-up N (%) | 77 (57.9) | 55%–60%* |

*Hospital data 2015–2019.
SGA, small for gestational age; NICU, neonatal intensive care unit.
Infants in multiple births (n = 3) were considered independently.

the remainder for symptoms which could have been attributable to COVID-19. SARS-CoV-2 RNA polymerase chain reaction was not detected in any of the 5 infants tested.

## NICU Admission and Congenital Anomalies

22 (16.5%) infants in this cohort were admitted to the Neonatal Unit. 6 were preterm and were admitted for complications of prematurity (respiratory distress, hypoglycemia, birth weight <2 kg). Of the 16 term infants, the most common indication for admission was jaundice requiring phototherapy and other indications included skin infections, hypoglycemia and congenital anomalies. Of note, 4 infants [4/133, (3%)] were critically unwell and required mechanical ventilation (respiratory distress syndrome, neonatal encephalopathy and persistent pulmonary hypertension). The neonatal death was not caused by SARS-CoV-2 infection. The most common congenital anomalies included genitourinary anomalies (n = 5) and neurological abnormalities [eg, microcephaly (OFC <10th centile)], head and neck, respiratory and musculoskeletal malformations accounted for the remainder (n = 7). Five anomalies were diagnosed antenatally and the remainder were diagnosed postnatally.

## Preterm Birth

14 infants (10.6%) were born preterm (<37 weeks) in this 12-month cohort. 12 (85.7%) were late preterm (34–36 weeks). The median birth weight of preterm infants was 2.45 kg (IQR 2.24–2.68kg) and median gestation was 36.6 weeks (IQR 34.3–36.6 weeks). The cause of preterm birth was also evaluated. Prematurity was due to preterm labor/chorioamnionitis (n = 4 (28.6%)), intrauterine growth restriction [n = 4 (28.6%)], pre-eclampsia [n = 3 (21.4%)] and preterm prelabor rupture of the membranes [n = 3 (21.4%)]. Unsurprisingly, preterm infants were more likely to require admission to NICU than term infants [6/14 (42.9%) vs. 16/119 (13.5%), $P = 0.005$].

## Maternal Infection Pre and Post B.1.1.7 Variant Dominance

The SARS-CoV-2 variant of concern (VOC) B.1.1.7 was first detected in Ireland in December 2020 and has been the dominant circulating variant in this country since January 2021.[19] In this cohort, 66 (49.6%) infants were born following a maternal SARS-CoV-2 diagnosis after 1st January 2021, following the outbreak of the B.1.1.7. variant. Table 3 compares the neonatal outcomes by maternal SARS-CoV-2 diagnosis before and after the emergence of variant B.1.1.7 as the dominant circulating variant.

## Neonatal Outcomes Based on Maternal Symptom Status

Neonatal outcomes are compared in Table 4 between women with and without symptoms of COVID-19 (the 8 patients with unknown symptom status were excluded from the analysis).

## Perinatal Outcomes by Time from Diagnosis of SARS-CoV-2 to Delivery

In Ireland, patients are considered infectious for 10 days following the onset of symptoms of a confirmed SARS-CoV-2 diagnosis. The neonatal outcomes by the timing of infection (number of days prior to delivery) were evaluated in Table 5 and key neonatal outcomes (preterm birth, NICU admission and birth weight) were similar between the 2 groups (diagnosis <10 days or >10 days prior to delivery).

In view of the trend towards a reduced birth weight in the group diagnosed with SARS-CoV2 more than 10 days before delivery, we further interrogated these findings. When asymptomatic patients, diagnosed on a preadmission swab were excluded from the analysis (many had high cycle thresholds, suggestive of previous infection and therefore the true timing of their infection was unclear), the median birth weight in those diagnosed less than 10 days from delivery was 3.54 kg (IQR 3.23–3.86 kg) and 3.35 kg (IQR 2.99–3.72kg) in those diagnosed more than 10 days before delivery. However, there was no significant association between birth weight and time diagnosed to delivery ($P = 0.22$).

# DISCUSSION

In this study, 133 infants were born to 130 women with SARS-CoV-2 during pregnancy over a 12-month period in a large maternity unit. The neonatal clinical outcomes included an incidence of preterm birth of 10.5%, a NICU admission rate of 16.5% and only 5.3% were small for gestational age (<10th percentile). There were no differences in the neonatal clinical outcomes based on maternal infection before or after the outbreak of VOC B.1.1.7. or maternal symptom status.

It has previously been demonstrated that pregnant women with co-morbidities (eg, diabetes and asthma) were more likely to require hospitalization with COVID-19.[6] There was a high incidence of underlying maternal illness in this cohort (29.2%), although the overall number of women requiring admission to a high dependency unit or an acute adult hospital during this period, with symptoms related to COVID-19 was low (3.1%).

Certain ethnicities were over-represented in the COVID-19 group. 1.8% of pregnant women attending this hospital in 2020

**TABLE 3.** Neonatal Outcomes by Maternal SARS-CoV-2 Diagnosis Before and After the Emergence of Variant B.1.1.7

| | Pre-B.1.1.7 Emergence N = 67 | Post B.1.1.7 Emergence N = 66 | *P* value |
|---|---|---|---|
| Time of maternal SARS-CoV-2 diagnosis | 1st March 2020 to 31st December 2020 | 1st January 2021 to 1st March 2021 | |
| Gestational age at diagnosis, weeks median (IQR) | 34.9 (30–38.9) | 37.7 (5–39) | 0.002*† |
| Gestational age at birth, weeks median (IQR) | 39.6 (38.6–40.3) | 39.3 (38.3–40.4) | 0.57* |
| Birth weight, kg median (IQR) | 3.46 (3.05–3.84) | 3.39 (2.97–3.82) | 0.91* |
| Preterm birth N (%) | 7 (10.5%) | 7 (10.6%) | 0.98‡ |
| NICU admission N (%) | 11 (16.4%) | 11 (16.7%) | 0.97‡ |
| Small for gestational age (<10$^{th}$ centile) N(%) | 4 (6%) | 3 (4.6%) | 0.71‡ |

*Mann Whitney U test.
†$P < 0.05$.
‡$\chi^2$ test.
NICU, neonatal intensive care unit.

were members of the Irish Traveler or Ireland's Roma Community, yet they accounted for 7.7% (10/130) of the COVID-19 group ($P < 0.001$). Minority communities have been disproportionately affected by COVID-19, both in Ireland and internationally.[27,28] Similarly, patients of Asian [18 (13.8%) vs. 4.9%, $P < 0.001$] and African ethnicity [11 (8.5%) vs. 2.1%, $P < 0.001$] were over-represented in the COVID-19 group compared with the hospital population. This high incidence of COVID-19 in pregnancy in African and Asian ethnicities is similar to that described in a UK study.[7]

The incidence of gestational diabetes (GDM) (both requiring and not requiring insulin) was 13.1%. This did not differ significantly from the hospital incidence of GDM over the last 5 years (11.7%, $P = 0.63$). The incidence of pre-eclampsia and pregnancy-induced hypertension was 5.4%, similar to the reported incidence in the literature.[29] The incidence of thrombocytopenia during pregnancy (any platelet count $<150 \times 10^9$/L) was 18.5% and is higher than typically described during pregnancy (6.6–11.6%).[30–33] However, thrombocytopenia is a common finding in adults (both pregnant and non-pregnant) with COVID-19 infection[1,9] and may explain this increased incidence of thrombocytopenia seen in this cohort.

An increased incidence of preterm birth following a maternal COVID-19 infection has been described in several studies.[7,8,15,34] In this study, the incidence of preterm birth was slightly higher in the COVID-19 exposed infants (10.5%) than the prepandemic hospital incidence (2015–2019) (6.3–7.9%), although this was not statistically significant ($P = 0.13$). A majority were born late preterm, a cohort less likely to experience severe neonatal morbidity and mortality. This propensity towards late preterm birth is similar to that described in other studies.[15] As discussed previously, there were several indications for preterm birth, not one unifying cause.

The incidence of preterm birth was lower in this 12-month review (10.5%), than in our previous report (23%).[14] There are several possible explanations for this. First, this report includes 133 infants born over a 12-month period, (compared with 26 over a 4-month period). The larger numbers in this study are more likely to reflect the true incidence of preterm birth following a COVID-19 infection during pregnancy. Second, vulnerable groups such as Members of the Traveling Community, Ireland's Roma Community, the homeless and asylum seekers, have been disproportionately affected by COVID-19 in Ireland, particularly during the first wave.[35] These groups typically have worse perinatal outcomes[36–39] and this may have confounded our previous findings. Finally, it has been suggested that societal lockdowns, introduced in many countries, including Ireland, after the outbreak of COVID-19, may have resulted in reductions in the overall incidence of preterm birth, although the evidence for this is not conclusive.[40–43]

Several studies have reported increased rates of NICU admission in infants born to women with COVID-19 (10–76.9%).[5,9] While admission rates in other countries do appear to be higher in infants exposed to COVID-19 perinatally, the large variations may have been explained by the high rates of preterm birth described in some studies, and hospital policies stipulating that infants were transferred directly to the neonatal unit after delivery. In this hospital, infants born to women with SARS-CoV-2 roomed-in with their mother on the postnatal ward/COVID ward with the necessary precautions, unless there was a clinical indication for admission to the neonatal unit (eg, preterm < 34 weeks, respiratory support).[26] The

**TABLE 4.** Neonatal Outcomes Based on Maternal Symptom Status [Patients with Unknown Symptom Status were Excluded (n = 8)]

| | Symptomatic | Asymptomatic | |
|---|---|---|---|
| | N = 80 | N = 45 | *P* value |
| Gestational age at diagnosis (weeks) median (IQR) | 35 (31.8–38) | 39 (36.1–40) | <0.001*† |
| Time from diagnosis to delivery, days median (IQR) | 22.5 (10–48.5) | 2 (1–8) | <0.001*† |
| Gestational age at birth, weeks median (IQR) | 39.1 (38.4–40.2) | 39.6 (38.1–40.9) | 0.17* |
| Birth weight, kg median (IQR) | 3.47 (3–3.82) | 3.48 (3.05–3.91) | 0.51* |
| Preterm birth N (%) | 9 (11.3%) | 5 (11.1%) | 0.98‡ |
| NICU admission N (%) | 13 (16.3%) | 7 (15.6%) | 0.91‡ |
| Small for gestational age (<10* centile) N (%) | 4 (5%) | 3 (6.7) | 0.7‡ |

*Mann Whitney U test.
†$P < 0.05$.
‡$\chi^2$ test.
NICU, neonatal intensive care unit.

**TABLE 5.** Neonatal Outcomes Based on the Number of Days From Maternal Diagnosis of SARS-CoV-2 to Delivery (Includes both Symptomatic and Asymptomatic Women)

| | Diagnosis <10 Days Before Delivery | Diagnosis >10 Days Before Delivery | |
|---|---|---|---|
| | N = 58 | N = 75 | *P* value |
| Diagnosis to delivery, days median (IQR) | 1 (0–3) | 36 (21–58) | |
| Gestational age at birth, weeks median (IQR) | 39.5 (38.1–40.6) | 39.3 (38.4–40.3) | 0.46* |
| Birth weight, kg median (IQR) | 3.61 (3.12–3.91) | 3.33 (2.99–3.72) | 0.07* |
| Preterm birth N (%) | 7 (12.1 %) | 7 (9.3%) | 0.61† |
| NICU admission N (%) | 9 (15.5%) | 13 (17.3%) | 0.78† |
| Small for gestational age (<10th centile) N (%) | 3 (5.2%) | 4 (5.33%) | 0.97† |

*Mann Whitney U test.
†$\chi^2$ test.
NICU, neonatal intensive care unit.

NICU admission rate in the COVID-19 exposed infants (16.5%) was similar to the hospital admission rate over the 5-year period, 2015–2019 (13.1%–15.5%) (*P* =0.49). Among the term infants, there was a variety of indications for admission, described previously. However, 4 infants (3%) were critically unwell and required intensive care supports.

High rates of low birth weight (LBW) (<2500 g) infants have been described in some studies (7.8%–47.4%),[9] although this is confounded by a high incidence of preterm birth. In this study, 10 (7.5%) infants were LBW, of which, 7 were preterm (<37 weeks) and the remaining 3 were full-term. To further analyze the effect of COVID-19 on fetal growth, the number of infants that were small for gestational age (SGA) was found to be 7 (5.3%) and is likely a more accurate marker than LBW. A trend towards a lower birth weight was seen in women diagnosed with SARS-CoV-2 remote from delivery, although this trend did not persist when asymptomatic patients diagnosed on preadmission screening were removed. Given the concerns regarding an increased incidence of placental pathology seen following COVID-19 infection in pregnancy, even in the absence of direct placental infection,[44,45] it is plausible that an earlier infection could impair placental function and fetal growth. This should be investigated in larger studies in the context of the timing of SARS-CoV-2 infection.

The effect, if any, of COVID-19 exposure during pregnancy on congenital malformations is not yet known.[46] The European Surveillance of Congenital Anomalies network describe a prevalence of major congenital anomalies of 2.4% in the general population.[47] In this study, 9% of infants had a congenital anomaly diagnosed. Although this is higher than expected, this figure includes both major and minor anomalies. In each of these 12 cases, maternal SARS-CoV-2 was diagnosed after 24 weeks gestation, making it unlikely to have caused these malformations. All women attending this hospital are offered an anomaly scan between 18 and 22 weeks gestation. Women diagnosed with SARS-CoV-2 were offered an additional growth scan to ensure fetal wellbeing and follow-up of SGA infants was as recommended by the Institute of Obstetricians and Gynecologists national guideline. 3rd-trimester growth scans have previously been shown to increase the antenatal diagnosis of incidental anomalies, particularly renal anomalies.[48] Moreover, this hospital is 1 of only 4 tertiary maternity units in Ireland, and is a national referral center for fetal abnormalities so it would be expected to see a higher-than-average number of congenital anomalies. However, further studies are required to evaluate the incidence of congenital anomalies following perinatal COVID-19 exposure, particularly after 1st-trimester infection.

The SARS-CoV-2 VOC B.1.1.7. (UK variant) has been associated with poorer maternal outcomes,[6] and has also been associated with COVID-19 placentitis resulting in intrauterine death in a number of cases.[22] When the neonatal outcomes (birth weight, preterm birth, NICU admission and SGA) were evaluated in maternal infections that occurred before and after VOC B.1.1.7. dominance, no differences were identified. It is unsurprising that the gestation at diagnosis was higher in the B.1.1.7. group, as these women were diagnosed after 1st January 2021 and delivered by 1st March, suggesting that most would be over 32 weeks at the time of diagnosis. Women diagnosed with SARS-CoV-2 after 1st January 2021 but not delivered by 1st March 2021 are not described in this cohort.

Severe COVID-19 can result in hypoxia,[49] activation of the coagulation system and endothelial dysfunction.[50,51] Several studies have described pathological evidence of fetal and maternal vascular malperfusion and large-vessel thrombosis within the placentas of women with SARS-CoV-2.[44,52,53] These findings have occurred in the absence of direct placental SARS-CoV-2 infection, suggestive of a maternal hyperinflammatory or hypercoagulable state. Pneumonia during pregnancy has previously been associated with adverse neonatal outcomes, particularly an increased incidence of preterm birth and low birth weight,[54] in addition to other conditions resulting in maternal hypoxia, such as cyanotic heart disease, or placental malperfusion, such as pre-eclampsia.[55–57] It could therefore be hypothesized that a more severe maternal COVID-19 infection may be associated with worse outcomes than an asymptomatic infection. However, no differences in the neonatal outcomes were found between women with and without symptoms of COVID-19. These findings are supported by another study which found that maternal symptom status did not impact the incidence of preterm birth.[34] This highlights the importance of pregnant women taking precautions to avoid exposure to COVID-19.

The strengths of this study include the large number of infants included over a 12-month period at Ireland's largest maternity hospital and the detailed analysis of the cause of preterm birth, the indication for NICU admission and the assessment of growth and congenital anomalies. The analysis pre and post the VOC B.1.1.7 outbreak, provides a useful comparison of neonatal outcomes, given the growing concern regarding the effects of B.1.1.7 infection in pregnancy.

There are several limitations to this study, including its retrospective nature, where confounding and other biases are inherent. Only univariate analyses were conducted without adjustment in multivariable regression due to the limited study size and unmeasured confounding factors. The central COVID-19 notification system included all hospital diagnosis of SARS-CoV-2 and

community diagnosis which were either self-reported by patients or their healthcare team to the helpline. It is likely that some community diagnoses were not identified or declared, particularly those in the 1st trimester, before the patient had booked the pregnancy which may have introduced bias. For this reason, we have not been able to evaluate the impact of 1st-trimester infections. This study was not designed to evaluate maternal outcomes of COVID-19 infection or disease severity. We do not have access to the individual SARS-CoV-2 variants detected and have had to rely on the dominant strains within the community as reported by the Health Protection Surveillance Centre.[19] This study was not designed to evaluate mother-to-child transmission and neonatal SARS-CoV-2 testing was only performed if clinically indicated.[26] The study is retrospective in nature and so, these findings may not be generalizable outside of this setting, particularly in the context of emerging variants of SARS-CoV-2.

## CONCLUSIONS

In this retrospective study of neonatal outcomes, following a maternal COVID-19 infection during pregnancy, the incidence of preterm birth and NICU admission did not differ from the prepandemic hospital incidence. The neonatal outcomes were comparable before and after the emergence of VOC B.1.1.7. as the dominant strain. Maternal symptom status did not impact the neonatal outcomes. Further analysis of the effects of variants of concern, particularly the emerging Delta variant, associated with more severe maternal illness and adverse pregnancy outcomes,[58] COVID-19 placentitis and infection in the 1st trimester are required, to further expand our understanding of SARS-CoV-2 on the placenta and the growing fetus.

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