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Haematological parameters and coagulation in umbilical cord blood following COVID-19 infection in pregnancy

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ABSTRACT

Objective: The aim of this study was to evaluate infants, born to women with SARS-CoV-2 detected during pregnancy, for evidence of haematological abnormalities or hypercoagulability in umbilical cord blood.

Study design: This was a prospective observational case-control study of infants born to women who had SARS-CoV-2 RNA detected by PCR at any time during their pregnancy (n = 15). The study was carried out in a Tertiary University Maternity Hospital (8,500 deliveries/year) in Ireland. This study was approved by the Hospital Research Ethics Committee and written consent was obtained. Umbilical cord blood samples were collected at delivery, full blood count and Calibrated Automated Thrombography were performed. Demographics and clinical outcomes were recorded. Healthy term infants, previously recruited as controls to a larger study prior to the outbreak of COVID-19, were the historical control population (n = 10).

Results: Infants born to women with SARS-CoV-2 had similar growth parameters (birth weight 3600 g v 3680 g, p = 0.83) and clinical outcomes to healthy controls, such as need for resuscitation at birth (2 (13.3%) v 1 (10%), p = 1.0) and NICU admission (1 (6.7%) v 2 (20%), p = 0.54). Haematological parameters (Haemoglobin, platelet, white cell and lymphocyte counts) in the COVID-19 group were all within normal neonatal reference ranges. Calibrated Automated Thrombography revealed no differences in any thrombin generation parameters (lag time (p = 0.92), endogenous thrombin potential (p = 0.24), peak thrombin (p = 0.44), time to peak thrombin (p = 0.94)) between the two groups.

Conclusion: In this prospective study including eligible cases in a very large population of approximately

Abbreviations: CAT, Calibrated automated thrombography; EDTA, Ethylenediaminetetraacetic acid; ETP, Endogenous thrombin potential; FBC, Full blood count; IQR, Interquartile range; PPP, platelet poor plasma; TTP, Time to peak thrombin; UCB, Umbilical cord blood.

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1500 women, there was no evidence of derangement of the haematological parameters or hypercoagulability in umbilical cord blood due to COVID-19. Further research is required to investigate the pathological placental changes, particularly COVID-19 placentitis and the impact of different strains of SARS-CoV-2 (particularly the B.1.1.7 and the emerging Delta variant) and the severity and timing of infection on the developing fetus.

Background

COVID-19, an illness caused by the SARS-CoV-2 virus, typically manifests as a viral pneumonia, but has also been characterised by a high incidence of thrombo-embolic complications [1]. Elevated markers of coagulation activation and endothelial dysfunction appear to be a hallmark of COVID-19, and persistent hypercoagulability has been reported for months following infection [2,3]. Children infected with SARS-CoV-2 have also demonstrated hypercoagulability, albeit without evidence of clinical thromboembolic complications [4]. Adult COVID-19 infection (including pregnant women) is commonly associated with lymphopenia, leukopenia and thrombocytopaenia [5–7].

Women infected with SARS-CoV-2 during pregnancy usually experience mild-to-moderate disease [8]. However, pregnant women are at greater risk of severe COVID-19 illness [9].

Evidence suggests that the vertical transmission of COVID-19 is possible [10], although the mother to child transmission rate is low [11]. Neonatal COVID-19 infection is rare, and most infants are mildly affected [12]. However, there is growing concern about the effect of maternal SARS-CoV-2 infection on the placenta and developing fetus. Numerous studies have described an increased rate of preterm birth, low birth weight infants and neonatal unit admission following a COVID-19 infection during pregnancy [7,13]. It is unclear whether these findings are due to placental pathology or the increased incidence of preterm birth.

Pathological evidence of maternal and fetal vascular malperfusion and thrombosis of larger fetal vessels have been demonstrated in placentas of pregnancies affected by COVID-19 [14–18]. These findings occur in the absence of inflammatory changes or confirmed placental infection, suggesting the placental changes may be a result of a maternal systemic hypercoagulable or hyperinflammatory state following a COVID-19 infection.

Concerningly, there are reports of COVID-19 placentitis, resulting from direct placental COVID-19 infection. The features of COVID-19 placentitis include positive SARS-CoV-2 staining with chronic histiocytic intervillositis and necrosis of the syncitiotrophoblast [19,20]. In April 2021, reports of six stillbirths and one second trimester miscarriage caused by SARS-CoV-2 placentitis were reported in Ireland, a country with variant B.1.1.7 dominance [21].

Several viruses, including Human Immunodeficiency Virus and Cytomegalovirus, cause hypercoagulability and thrombotic complications [22–26]. Moreover, maternal infections with Cytomegalovirus, Parvovirus B-19 and Rubella are associated with haematological abnormalities including thrombocytopenia and anaemia in the fetus [27–29]. Placental insufficiency can independently cause fetal thrombocytopenia, neutropenia and polycythaemia [30,31]. We aimed to assess if maternal COVID-19 infection during pregnancy caused derangement of haematological parameters or increased thrombin generation in the fetal circulation, measured in umbilical cord blood (UCB) at birth, compared with controls without antenatal COVID-19 exposure.

Methods

Patient recruitment

This was a prospective observational case-control study carried out in a tertiary university maternity hospital and neonatal intensive care unit (8,500 deliveries/year). Women who had SARS-CoV-2 RNA detected at any time during pregnancy were eligible for recruitment. Women less than 18 years of age, those with a personal history of coagulation disorder, major fetal abnormality, those who did not speak English and those who could not be contacted were excluded. Women were contacted by phone about this study, prior to presentation to hospital for delivery and were provided with a Patient Information Leaflet. Ethical approval was granted by the Hospital Research Ethics Committee (REC-2020-022) and written consent was obtained for each participant. All infants were delivered between January and March 2021.

A group of healthy full-term infants, with no major congenital anomalies or family history of coagulation disorders, recruited to a larger study prior to 1st March 2020 (before the COVID-19 outbreak in Ireland) were the historical control group (n = 10).

Maternal demographics, antenatal history, details of the COVID-19 infection and neonatal outcomes were recorded from the electronic patient record.

Sample collection

Following routine delayed cord clamping, a sample of umbilical cord blood was collected using a 10 ml syringe and a 21 gauge needle. Blood was collected in sodium citrate 3.2% (3 × 3mls) and ethylenediaminetetraacetic acid (EDTA) (1 × 2.5mls). All samples were manually checked for clot and excluded if detected.

Full blood count

A full blood count (FBC) was performed on the EDTA sample using the "CELL-DYN Sapphire Hematology Analyzer" (Abbott). Results were compared to local neonatal reference ranges.

Preparation of platelet poor plasma

UCB samples were transported directly to the laboratory and processed within one hour of collection. Platelet poor plasma (PPP) was prepared by double centrifugation of the citrated blood at 3000 RPM for six minutes. PPP was aliquoted and stored at −80 C.

Calibrated Automated Thrombography (CAT)

Calibrated Automated Thrombography (CAT) is a global coagulation assay which evaluates both the pro- and anti-coagulant pathways, and is used to evaluate thrombin generation [32]. CAT has been used extensively as a research tool to evaluate for both hypercoagulability [33–35] and hypocoagulability [36,37].

CAT was performed using the Fluoroskan Ascent (ThermoFisher Scientific, Waltham Massachusetts) plate reader and Thrombinoscope BV (Stago, Asnieres sur Seine, France) software. All reagents were obtained from Thrombinoscope BV. Frozen PPP was thawed in a water bath at 37 °C for 10 min. Briefly, 80μL of PPP was incubated with 20μL of "PPP reagent LOW" (contains 1 pM tissue factor and 4μMphospholipid) or "Thrombin calibrator". To initiate the reaction, 20μL of FluCa (fluorogenic Z-Gly-Gly-Arg-AMC.HCl substrate and 100 mM $CaCl_2$) was added to each well (final concentrations, Z-Gly-Gly-Arg-AMC.HCl, 0.42 mM and CaCl2, 16.67 mM). Thrombin generation was performed in duplicate over 60 min and the thrombin generation curve was analysed.

The CAT parameters include "lag time", the time from the beginning of the experiment until 10 nM of thrombin is produced [38]. "Peak thrombin" indicates the maximum amount of thrombin produced and "time to peak thrombin" (TTP) represents the propagation phase of the coagulation cascade. The "endogenous thrombin potential" (ETP) represents the total amount of thrombin produced during the clotting process. A shortened lag time and increased peak thrombin/ETP suggest a hypercoagulable state.

Statistical analysis

Data was collected from both the COVID-19 and control groups and entered into an MS Excel spreadsheet. Descriptive analysis of continuous data included medians and interquartile ranges (25th-75th percentile) (IQR), and frequency (percentages) for categorical data. For some categorical data, the values were combined to ensure sufficient numbers available for analysis. Comparisons between the COVID-19 and control groups were performed using Fisher's exact test for categorical variables and non-parametric Mann Whitney *U* test for continuous variables. Significance was assumed at two-sided $p < 0.05$. Stata (version 16.0) was used for statistical analysis and R (version 4.0.2) was used for graphical representation of the data.

Results

Clinical demographics

Recruitment began on 4th January 2021 and was completed on 6th March 2021. During this period, 1449 infants were delivered in this hospital (Fig. 1). The charts of 142 women with a SARS-CoV-2 diagnosis were screened. Thirty-three patients met inclusion criteria and were contacted about the study. Written consent was obtained from 23 patients and fifteen patients were ultimately recruited. The maternal demographics and details of the SARS-CoV-2 diagnosis are described in Table 1.

The maternal SARS-CoV-2 diagnosis occurred between September 2020 and February 2021 (12 occurred between December 2020 and February 2021). Fourteen participants (93%) were diagnosed on PCR testing in the community. All of the women had mild to moderate disease and none required hospitalisation for symptoms of COVID-19 and were managed conservatively. The neonatal outcomes are described in Table 2. All infants in the COVID-19 group were born at full term (37 – 42 weeks gestation). All infants were singletons, had an Apgar score greater than 7 at five minutes and no baby in either group was small for gestational age (<10th centile). As per hospital policy (and national recommendations) infants in the COVID-19 group roomed in with their mothers unless there was a clinical indication for admission to the NICU [39]. Breastfeeding was encouraged regardless of maternal COVID-19 status at delivery and 9 (60%) infants in the COVID-19 group received breast milk during their hospital stay. The median

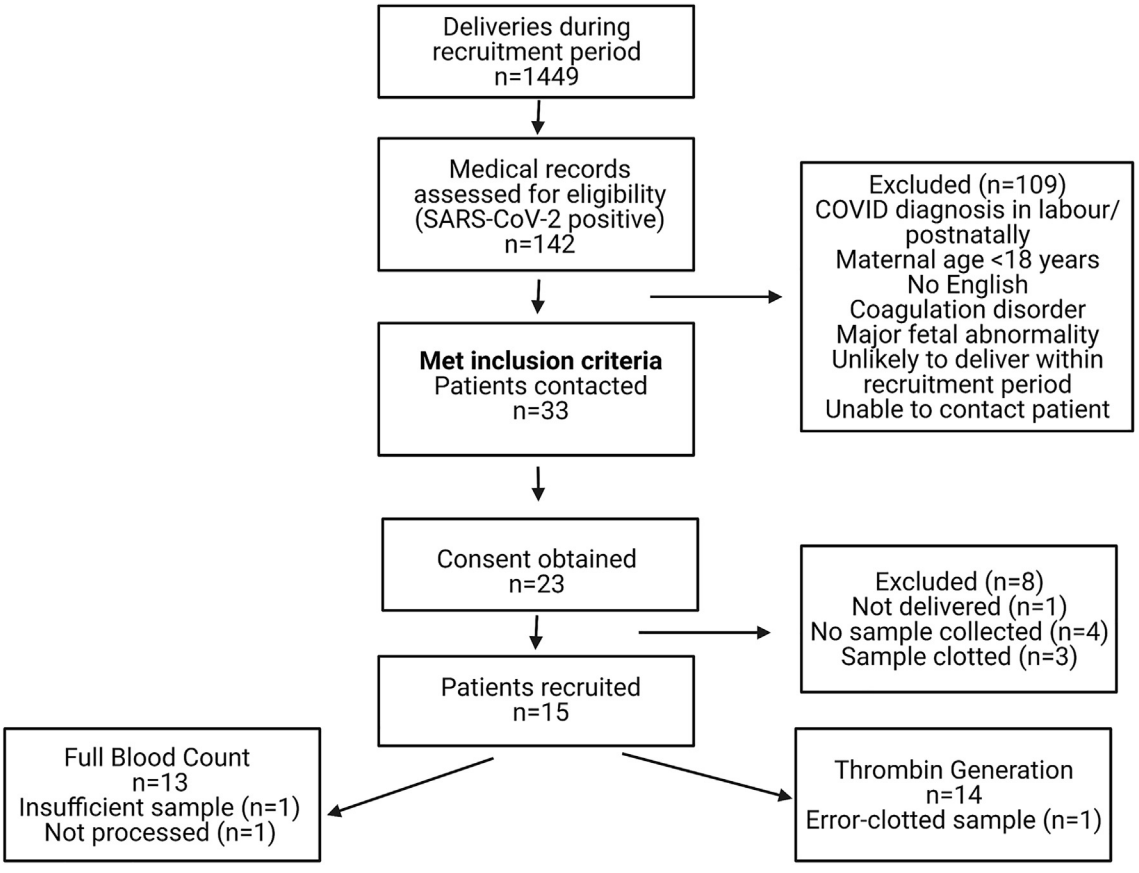

Fig. 1. Cohort flow diagram of the COVID-19 group (image created with *BioRender.com*).

Table 1
Maternal and antenatal demographic details, including SARS-CoV-2 diagnosis.

Clinical outcome	COVID-19 N = 15	Controls N = 10	*p*-value
Maternal Demographics			
Maternal age (years) (IQR)	30 (28 – 35)	34.5 (34 – 37)	0.01[a*]
BMI (kg/m2) (IQR)	23.8 (22.9 – 26.7)	26 (24.9 – 27.8)	0.24[a]
Caucasian (%)	14 (93.3)	9 (90)	1.0[b]
Nulliparous (%)	10 (66.7)	2 (20)	0.04[b*]
Any underlying medical diagnosis (%)	5 (33.3)	4 (40)	1.0[b]
Tobacco use in pregnancy (%)	1 (6.7)	0 (0)	1.0[b]
Antenatal History			
Gestation at booking (weeks) (IQR)	12.9 (12.3 – 13.3)	12.6 (12.1 – 13.7)	0.92[a]
Aspirin use in pregnancy (%)	0 (0)	2 (20)	0.15[b]
Thrombocytopenia (platelet count ever < 150 × 10^9/L) (%)	1 (6.7)	1(10)	1.0[b]
Pre-eclampsia (%)	1 (6.7)	0 (0)	1.0[b]
Gestational diabetes (%)	1 (6.7)	0 (0)	1.0[b]
SARS-CoV-2 Diagnosis			
Gestation at SARS-CoV-2 diagnosis (weeks) (IQR)	34.7 (31.6 – 36.1)		
Trimester at time of diagnosis			
1st trimester	0 (0)		
2nd trimester	2 (13.3)		
3rd trimester	13 (86.7)		
Any symptoms of COVID-19 (%)	14 (93.3)		
Maternal hospitalisation with COVID-19 symptoms (%)	0 (0)		
Time from diagnosis to delivery (days) (IQR)	36 (21 – 58)		
Delivery within 10 days of diagnosis (%)	1 (6.7)		

*p < 0.05, [a]Mann Whitney *U* test, [b]Fisher's exact test.

Table 2
Birth and neonatal outcomes between COVID-19 and control groups.

Clinical Outcome	COVID-19 N = 15	Control N = 10	*p*-value
Onset of labour			
Spontaneous/ Induced labour (%)	11 (73.3)	2 (20)	0.015[b*]
Pre-labour (%)	4 (26.7)	8 (80)	
Method of Delivery			
Spontaneous/ operative vaginal delivery (%)	8 (53.3)	1 (10)	0.04[b*]
Caesarean section (%)	7 (46.7)	9 (90)	
Male (%)	10 (66.7)	6 (60)	1.0[b]
Gestational age (weeks) (IQR)	39.3 (38.9 – 40.3)	39.4 (39.1 – 39.7)	0.75[a]
Birth weight (g) (IQR)	3600 (3270 – 4040)	3680 (3290 – 4120)	0.83[a]
Chorioamnionitis (%)	1 (6.7)	0(0)	1.0[b]
Need for resuscitation (%)	2 (13.3)	1 (10)	1.0[b]
Admission to NICU	1 (6.7)	2 (20)	0.54[b]
Congenital anomaly	2 (13.3)	1 (10)	1.0[b]
Tested for SARS-CoV-2	0 (0)		

*p < 0.05, [a]Mann Whitney *U* test, [b]Fisher's exact test.

day of life at discharge was Day 4 in the COVID group, and Day 4.5 in the control group. No infant developed clinical evidence of haemorrhage or thrombosis and there were no neonatal deaths.

Haematological parameters

UCB full blood counts were available for 13 infants in the COVID group (insufficient sample = 1, not processed = 1). All had haematological parameters within the local normal neonatal reference ranges (Table 3).

Calibrated automated thrombography

CAT was performed in PPP from the COVID-19 group (n = 15) and the control group (n = 10). One patient in the COVID-19 group was excluded from CAT analysis due to an erroneous thrombogram, suggestive of a clotted sample. There was no difference between the COVID-19 group and control group in any thrombin generation parameter (Table 4). The ETP results are displayed in Fig. 2.

Table 3
Hematological parameters in UCB in the COVID-19 group: Median (IQR) and local neonatal reference ranges displayed.

Median values	COVID-19 N = 13	Neonatal reference ranges
Haemoglobin (g/L)	15.7 (14.7 – 16.4)	13.5 – 19.5
Haematocrit (L/L)	0.47 (0.44 – 0.51)	0.42 – 0.6
Platelet count (× 10^9/L)	260 (214 – 281)	150 – 450
White cell count (× 10^9/L)	16.5 (16.2 – 18.9)	9–30
Lymphocyte count (× 10^9/L)	5.62 (4.69 – 7.17)	2–11

Table 4
CAT Parameters of plasma thrombin generation in PPP in the COVID-19 group compared with controls; Median values (IQR).

CAT Parameter	COVID-19 N = 14	Control N = 10	*p*-value
Lag Time (mins)	2.84 (2.67 – 3)	2.84 (2.67–3.33)	0.92[a]
Peak thrombin (nM)	136.7 (130.7–156.1)	133.9 (129.2–149.5)	0.44[a]
ETP (nM.min)	967.8 (869–1055.6)	861 (826.3 – 980)	0.24[a]
Time to peak (mins)	6.4 (6.0–7.0)	6.3 (5.7–7.3)	0.94[a]

*p < 0.05, [a]Mann Whitney *U* test, [b]Fisher's exact test.

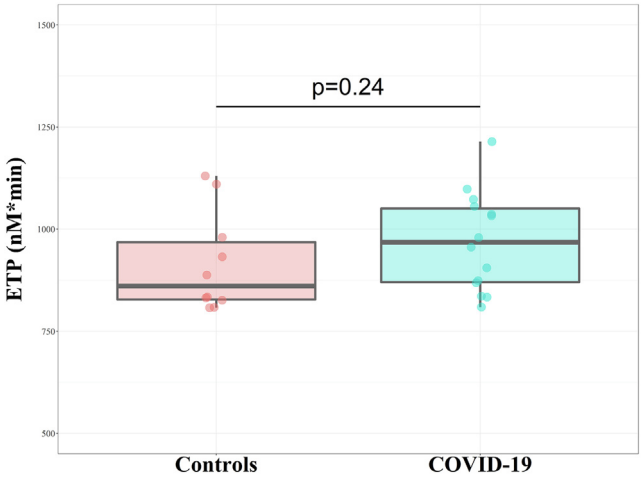

Fig. 2. Box plot of the Endogenous Thrombin Potential in controls versus those born to women with SARS-CoV-2 during pregnancy.

Discussion

In this prospective observational study, including eligible cases from a large population of approximately 1500 women, the neonatal clinical outcomes following a maternal COVID-19 infection were reassuring and similar to controls. The haematological parameters in UCB in the COVID-19 group were all within normal neonatal ranges; we did not identify any of the haematological abnormalities typically associated with COVID-19 infection in adults or placental insufficiency in the fetus [5,30,31]. Moreover, a maternal COVID-19 infection did not result in hypercoagulability in the fetal circulation, measured by CAT in UCB.

In this study, the neonatal outcomes differed from the adverse perinatal outcomes reported in the literature [7]. Infants in the COVID-19 group were born at full term, appropriately grown and none were small for gestational age (<10th centile). While two infants (13.3%) did require initial resuscitation, this was brief, and all infants had Apgar scores of $\geq$ 9 by five minutes. Approximately 10% of infants are expected to require some initial resuscitation at birth [40]. The incidence of admission to NICU (6.7%) did not exceed the control group (20%) or 2019 hospital incidence (15%) [41]. The congenital anomalies in the COVID-19 group were mild to moderate genitourinary anomalies. In both cases, the diagnosis of SARS-CoV-2 occurred after 35 weeks and was unlikely to have caused these anomalies. The incidence of routine postnatal neonatal complications in the COVID group were low; jaundice requiring phototherapy (n = 1), neonatal hypoglycaemia (n = 0), greater than 10% weight loss (n = 0). As per local and national policy at the time this study was completed, routine SARS-CoV-2 testing was not recommended for infants born to women with SARS-CoV-2, unless there were symptoms suggestive of COVID-19; none of these infants met the criteria for testing [39].

Few studies have described the haematological parameters in asymptomatic/SARS-CoV-2 negative infants born to women with COVID-19. Zeng *et al.* and Zhu *et al.* reported haematological parameters in infants, born to mothers with COVID-19, who tested negative for SARS-CoV-2 during the initial outbreak in China (n = 30 and n = 9 respectively) [42,43]. Several infants had abnormal white cell, lymphocyte and platelet counts, however both of these studies included preterm infants and described high rates of symptomatic infants, unlike our group. The FBC findings in our study (n = 13) are supported by other small studies, describing normal haematological parameters in infants born to women with SARS-CoV-2 detected during pregnancy (n = 5, n = 3) [44,45].

CAT parameters were similar between groups and there was no evidence of hypercoagulability in the COVID-19 group. While COVID-19 infection causes hypercoagulability in adults [46], and there may be evidence of thrombosis on the fetal and maternal aspects of the placenta [14], this does not appear to result in hypercoagulability in the fetus. Pre-eclampsia (PET) is a placental pathology involving endothelial dysfunction [47]. Increased microparticle procoagulant activity in UCB, has been demonstrated in infants born to women with PET compared with healthy controls [48]. However, no hypercoagulability was identified in this group of infants exposed to COVID-19 during pregnancy.

The absence of haematological abnormalities or hypercoagulability in UCB in COVID-19 is a positive finding, suggesting that the fetus is somehow protected from the maternal systemic infection and inflammatory response. "Immunothrombosis" is the interaction between the immune system and coagulation, and forms part of the innate defence mechanism against pathogens [49]. However, the hyperinflammation seen in COVID-19 can result in severe and pathological hypercoagulation and thrombosis in adults [50] and may result in pathological findings, including possible thrombosis, seen in the placenta, even in the absence of placental infection. The placenta is a complex regulator of immunological function and acts as both a physical and immunological barrier to infection of the fetus [51,52].

To our knowledge, this is the first study to evaluate for fetal hypercoagulability in UCB following a maternal SARS-CoV-2 diagnosis in pregnancy. CAT, a global coagulation assay was performed to evaluate thrombin generation, as standard clotting tests are of limited use in neonates and do not evaluate for hypercoagulability [53]. UCB was the source of blood, given our interest in evaluating placental hypercoagulability and the ethical restrictions to collecting peripheral blood from healthy neonates for research purposes only. UCB is a reliable substitute for peripheral FBCs in neonates [54,55].

There are several limitations to this study, including the small number of participants in each group. There were demographic differences between the COVID-19 and control groups. Control infants were generally recruited prior to elective caesarean sections (often elective repeat). It is therefore unsurprising that the mothers are older, fewer are nulliparous, and there are more pre-labour deliveries by caesarean section in the control group. However, given the high incidence of asymptomatic COVID-19 infections (which may have been undiagnosed) and the inaccessibility of SARS-CoV-2 testing for symptomatic patients/close contacts in Ireland during certain periods over the last year, a historical control group was chosen, albeit with some demographic differences, to exclude the possibility of undetected COVID-19 infection. This is important as evidence suggests that maternal symptom status does not influence the adverse perinatal outcomes of COVID-19 [56].

Only one of the COVID-19 group delivered during the acute infectious period (<10 days after diagnosis), the remainder were diagnosed with SARS-CoV-2 between 16 and 172 days prior to delivery. There were several reasons for this. Firstly, due to ethical considerations, parents had to be provided adequate time to consider this study and could not be approached for the first time about this study when they presented in labour. Secondly, we aimed to evaluate whether there was an ongoing risk of hypercoagulability following a COVID-19 infection, as many infections occur weeks before delivery. This was important to evaluate for a possible cause of the adverse perinatal outcomes reported in the literature [7]. Finally, many patients diagnosed with SARS-CoV-2 within ten days of delivery in this hospital, were diagnosed on asymptomatic pre-admission screening swabs, with very high cycle threshold values, suggestive of a low viral load. Following further testing, many had serology results suggestive of an infection in the previous months, and would therefore not have been truly acute COVID-19 infections. Placental histopathological analysis was not part of this study and routine SARS-CoV-2 testing was not performed in infants, in keeping with National Irish Guidelines [39]. FBC results were not available in the control group, as ethical approval at that time did not allow it. However, all FBC parameters in the COVID group were within the local neonatal reference ranges.

Conclusions

Infants born to women with SARS-CoV-2, in this prospective study, had normal growth and neonatal outcomes compared with healthy controls. There was no evidence of haematological abnormalities or evidence of hypercoagulability in UCB. This study provides some reassurance regarding the haematological outcomes of infants exposed to COVID-19 in utero.

Further research is required to investigate the adverse perinatal outcomes and pathological placental changes, particularly COVID-19 placentitis, seen in some pregnancies and the relative impact of different strains of SARS-CoV-2 (particularly the B.1.1.7. and the

emerging Delta variant) and the severity and timing of infection on the developing fetus.

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Declaration of Competing Interest

Prof. Fionnuala NíAinle has received research funding (paid to the University) from Bayer and Sanofi (unrelated to this study). The remaining authors report no conflicts of interest.

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