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Research Article

Maternal First Trimester Gestational COVID-19 Infection is Associated with Increased Placental Maternal Vascular Malperfusion, But Not Clinical Morbidity or Mortality

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Abstract

Maternal COVID-19 infection during pregnancy has been associated with a myriad of pathologic placental changes. Clinically, rare studies have highlighted intrauterine growth restriction (IUGR), pre-term birth, intrauterine fatal demise and stillbirth in association with maternal gestational COVID-19 infection. Third trimester infants should be protected from acquiring COVID-19 infection since there is a paucity of the required angiotensin-converting enzyme (ACE) receptors present in the placenta, and earlier maternal gestational infections theoretically pose higher risk. We reviewed the total of 20 placentas from first trimester maternal COVID-positive pregnancies and clinical outcomes in the Sligo University Hospital catchment area from 2020-2021 to add to the literature of COVID-19 clinical and pathologic findings. Clinical audit was performed on placentas from maternal COVID-positive pregnancies from 2020-2021. Anonymised data from patient pathology reports including maternal and gestational age, clinically provided morbidity and maternal and neonatal outcome data and placental pathologic findings were reviewed. Haematoxylin and eosin-stained slides were available in all cases and reviewed by a consultant pathologist. All variables were compared with known background incidence and a cohort of 20 randomly selected non-COVID cases from the same time period. Maternal age ranged from 20-41 years (m = 31), and gestational age from 25 to 41 weeks (m = 36). All maternal COVID-19 positive results were from first trimester. Placental weights ranged from 312 to 897 grams (m = 594). All cases showed increased peri-villous fibrin deposition with 3 showing extensive fibrin. Ten cases had infarctions and 2 with extensive infarctions (>15% of placenta). Five cases had increased syncytial knotting. Our results support that placental pathology from early maternal gestational COVID-19 infection is associated with maternal procoagulopathic state, not fetal or 'placental' infection.

Keywords: COVID-19; Gestational Infection; Pregnancy; Coagulopathy

Introduction

Maternal COVID-19 infection during pregnancy has been associated with placental pathology including maternal and fetal vascular malperfusion leading to a myriad of pathological placental changes [1]. Clinically, rare studies have reported fatal complications, morbidity and mortality including intrauterine growth restriction (IUGR), pre-term birth, intrauterine fatal demise and stillbirth in association with maternal gestational COVID-19 infection [2-5]. To be infected, host cells require cell membrane angiotensin converting enzyme II (ACE-2) receptors, and facilitation by S protein priming proteases Type II transmembrane serine protease (TMPRSS-2) [1]. Theoretically, third trimester infants should be

protected from acquiring COVID-19 infection since there are almost undetectable quantities of these receptors and proteases present in the pre-term and term placenta [6], and earlier maternal gestational infections theoretically pose higher risk. We reviewed the total of 20 placentas from first trimester maternal COVID-positive pregnancies, including pathologic findings and clinical outcomes in the Sligo University Hospital catchment area, from 2020-2021 to add to the literature of gestational COVID-19 infection.

Clinical audit was performed on placentas from maternal COVID-positive pregnancies from 2020-2021. Anonymised data from patient pathology reports including maternal and gestational age, clinically provided morbidity data, clinically reported maternal and neonatal outcome data and placental pathologic findings were reviewed. Hematoxylin and eosin-stained slides were available in all cases and reviewed by a consultant pathologist. All variables were compared with known background incidence and a cohort of 20 randomly selected non-COVID cases from the same time period. Maternal age ranged from 20-41 years (m = 31), and gestational age from 25 to 41 weeks (m = 36). All maternal COVID-19 positive results were from first trimester. All cases showed increased peri-villous fibrin deposition with 3 showing extensive fibrin. Ten cases had infarctions (5-10% of placenta) and 2 with extensive infarctions (>15%). Five cases had increased syncytial knotting. No post-partum maternal or neonatal sequelae were reported. There were no maternal or neonatal or perinatal deaths.

Materials and Methods

Clinical audit was performed on placentas from maternal reverse transcriptase polymerase chain reaction (RT-PCR) COVID-positive pregnancies from 2020-2021 in the Sligo University Hospital catchment area. Anonymised data from patient pathology reports including maternal and gestational age, clinically provided morbidity data, clinically reported maternal and neonatal outcome data and gross and histologic placental pathologic findings were reviewed. Clinical information was retrieved from the surgical pathology accession sheet, pathology report or directly from clinicians. Mothers had no known history of maternal vascular disease, diabetes, chronic hypertension, thrombophilia, smoking, drug abuse or prior history of pregnancy with intrauterine growth restriction. Due to the infectious nature of the tissue, fixation for 48 hours was performed prior to dissection. Typical sections were fixed in formalin, processed into paraffin blocks, and stained with usual haematoxylin and eosin stains. Hematoxylin and eosin-stained slides were available in all cases and reviewed by consultant pathologist. Testing for COVID-19 was not performed on placental tissue. However, symptomatic mothers were tested via nasal swab RT-PCR during the first trimester and at delivery admission. All variables were compared with known background incidence and a cohort of 20 randomly selected non-COVID cases from the same time period.

Results and Discussion

Maternal age ranged from 20-41 years (m = 31), and gestational age from 25 to 41 weeks (m = 36). All maternal COVID-19 positive results were from first trimester. Placental weights ranged from 312 to 897 grams (m = 594). Umbilical cord length ranged from 24 to 65 cm and number of cord coils from 4 to 22 with 2 cases showing hypercoiling and 1 hypocoiling. Acute funisitis was seen in 1 case. Two cases had circumvallate fetal membrane insertion, 5 showed acute chorioamnionitis and 3 cases had meconium staining. All cases (20/20) showed increased peri-villous fibrin deposition with 3 showing extensive fibrin (Figure 1). Ten cases had infarctions (5-10% of placenta) and 2 showed extensive infarctions (>15%; Figure 2). Five cases had increased syncytial knotting (Figure 3), 4 had chorangiosis and 2 had intervillous thrombi. Two had villous dysmaturation and 1 showed haemorrhagic endovasculitis. One case clinically reported intrauterine growth restriction (IUGR), 1 case had pre-term birth and 1 case foetal distress during labour resulting in C-section. One case reported maternal gestational hypertension and 1 case had maternal antepartum haemorrhage. No post-partum maternal or neonatal sequelae were reported. There were no maternal or neonatal or perinatal deaths. All variables were compared with known background incidence and a cohort of 20 randomly selected, non-COVID cases from the same time period. No differences were found compared with control cases on any variables other than peri- villous fibrin deposition, infarctions, and syncytial knotting (Table 1).

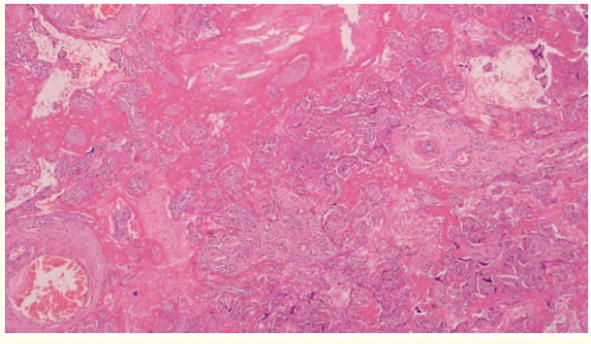

Figure 1: Extensive increased peri-villous fibrin deposition.

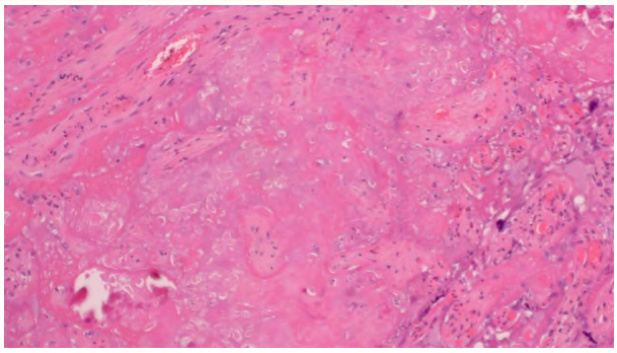

Figure 2: Extensive infarction (>15% of placental tissue).

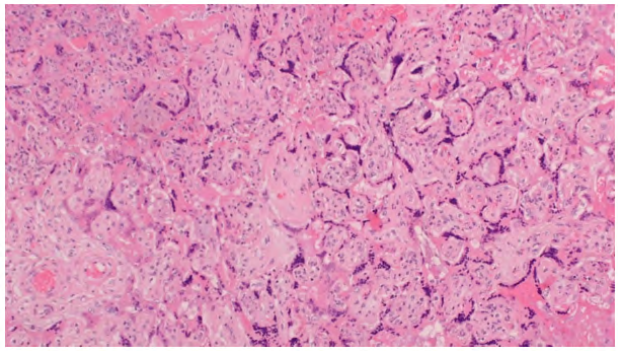

Figure 3: Increased syncytial knots (Tenney-Parker change).

COVID Status	Maternal age, mean years	Gestational age, mean weeks	Placenta weight, mean grams	Increased Peri-villous fibrin	Infarctions	Increased Syncytial knots
COVID +	31	36	594	20/20 (100%)*	10/20 (50%)**	5/20 (25%)
Controls	33	36.5	481	1/20 (5%)	1/20 (5%)	2/20 (10%)

Table 1: Clinical and pathologic variables in COVID-19 positive and control cases.

*3/20 showed extensive fibrin

**2/10 showed extensive infarction (>15% of placental parenchyma).

Maternal COVID-19 infection during pregnancy has been associated with placental pathology including maternal and fetal vascular malperfusion leading to multiple pathological placental changes [1]. Clinically, rare studies have highlighted intrauterine growth restriction (IUGR), pre-term birth, intrauterine foetal demise and stillbirth in association with maternal gestational COVID-19 infection [2-5]. Third trimester infants should be protected from acquiring COVID-19 infection since there is a paucity of the required angiotensin-converting enzyme receptors and transmembrane serine proteases present in the placenta to facilitate infection [6]. Earlier maternal gestational infections theoretically pose higher risk due to the large number of these necessary receptors and proteases present early in placental development. We reviewed the total of 20 placentas from first trimester maternal COVID-positive pregnancies, including gross and histologic pathologic findings and clinical outcomes in the Sligo University Hospital catchment area from 2020-2021, to add to the literature of gestational COVID-19 infection.

Reports on COVID-19 associated illness in general have shown that patients who are severally ill, in addition to acute respiratory distress syndrome (ARDS), often present with coagulopathy and disseminated intravascular coagulation (DIC)-like massive intravascular clot formation and organ dysfunction [7]. Haemorrhagic events are less common [7-9]. It was reported that 71% of non-surviving COVID-19 patients had disseminated intravascular coagulation (DIC), while in contrast, only 0.6% of survivors met DIC criteria [10]. Several reports show that non-survivors initially have higher and increasing D-dimer and fibrinogen degradation product (FDP) levels, longer prothrombin time (PT) and activated partial thromboplastin time (aPTT) compared with survivors [11,12]. The incidence of thrombocytopenia is relatively low in COVID-19 [13]. These findings propose that coagulopathy develops in patients with COVID-19 becoming more severe in critically ill patients. In fact, the frequency of thrombosis and major thromboembolic sequelae in COVID-19 ICU patients is reported to be 20 to 30% 26-28, and as high as nearly 80% [14-16]. COVID-19 directly infects

vascular endothelial cells causing cellular damage and apoptosis and the antithrombotic activity of the luminal surface is remarkably decreased [17].

Reports on COVID-19 in pregnancy have described variable findings. Most studies of COVID infection of term and pre-term third trimester pregnancies report a higher frequency of maternal vascular malperfusion [1], which is a recognized pattern of placental injury related to abnormal uterine perfusion and changes such as accelerated villous maturation, increased perivillous and intervillous fibrin deposition, decidual vasculopathy, increased syncytial knots, villous infarction, and intervillous thrombosis. Second trimester studies have shown increased peri-villous and subchorionic fibrin deposition [14,18]. A similar study to our own of the pathology and clinical information on 20 placentas whose mother tested positive for COVID-19 reported 10 of the 20 cases showed some evidence of fetal vascular malperfusion or fetal vascular thrombosis, primarily in the form of the presence of intramural fibrin deposition, although some increased peri-villous fibrin was also seen [19]. We did not observe intramural fibrin in our sample. One manuscript [20]. describes the placentas from three COVID-19 infected mothers in China. All three placentas were described as having increased peri-villous fibrin. Eleshiva., *et al.* found that compared to controls, third trimester placentas were significantly more likely to show at least one feature of maternal vascular malperfusion, particularly abnormal or injured maternal vessels, and intervillous thrombi [21]. Rates of acute and chronic inflammation were not increased, as they have been in other reports [15,22-24]. Hecht., *et al*. looked at 19 placentas from peripartum COVID-19-positive mothers and found no specific gross or histopathologic findings that differed from control sample background incidence [25]. There were no reports in any of these aforementioned studies of maternal or neonatal death, and neonatal or 'placental infection' appears to be a very rare event. No teratogenic effect of COVID-19 infection in the neonate has been reported, and maternal infection does not equate to placental infection. In the rare event of evidence of placental viral infection intrauterine vertical transmission is not presupposed [26].

In a large review examining over 2500 COVID-19 confirmed pregnancies with over 700 deliveries, maternal critical disease requiring mechanical ventilation was just over 3%, with 0.9% maternal deaths, and 22% preterm birth (primarily iatrogenic) and less than 1% perinatal death [2]. A large matched case-control study of 61 COVID-19 pregnancies reported that adverse outcomes for mother and foetus were 3.4 times and 1.7 times higher among severely ill COVID-19 cases than controls [3]. Maternal advanced age, obesity, Hispanic or Latino origin, and other medical comorbidities, however, were major factors. Other reports of foetal death or demise associated with third-trimester or pre-term/term maternal COVID-19 infection are very uncommon, including a report on the alpha variant being associated with an increased risk of foetal death [4] and two cases of intrauterine foetal demise and one case of severe foetal distress in the setting of maternal infection with Delta-variant [5]. COVID-19 infects target host cells by binding to the cell membrane angiotensin converting enzyme II (ACE-2), facilitated by S protein priming proteases Type II transmembrane serine protease (TMPRSS-2). ACE-2, found in heart, lung, kidney, vasculature, brain, and placenta, is a membrane-bound enzyme that degrades angiotensin I and II which is protective in regulating vascular and heart function. Syncytiotrophoblasts and cytotrophoblasts in chorionic villi, decidual stromal cells, decidual perivascular cells, and endothelial and vascular smooth muscle cells express ACE-2. However, ACE-2 and TMPRSS-2 expression in placenta correlate negatively with gestational age. They are almost undetectable in third trimester preterm and term placenta [6]. Therefore, later stages of pregnancy should be protected, while first trimester pregnancy is theoretically more vulnerable to COVID-19 transplacental transmission, unless other as yet unknown means besides ACE-2/TMPRSS-2-facilitated viral entry exist.

Limitations to our study would be that histopathology was reviewed by a general pathologist as opposed to a perinatal pathologist. Typically, however, histology of maternal vascular malperfusion is easily recognised in general practice. While our study was retrospective, correlation with maternal coagulation studies over the course of pregnancy may also have been useful. Additionally, control cases for comparison with maternal gestational COVID-positive cases were not tested in first trimester as mothers were asymptomatic, but were tested with negative results on delivery admission.

Conclusions

Similar to previous reports, our placentas from maternal COVID-19-positive pregnancies showed evidence of maternal vascular malperfusion, particularly in the form of increased peri-villous fi-

brin deposition and infarctions. Increased syncytial knotting compared to usual background incidence was also seen. In contrast to recent reports, no increased inflammation in umbilical cord, membranes or placenta were identified; and there was no increase in IUGR, pre-term birth, intrauterine foetal demise or stillbirth. As recently proposed, our findings support that placental pathology from early maternal gestational COVID-19 infection is associated with pro-coagulopathic state and a higher frequency of maternal vascular malperfusion, not fetal or 'placental' infection.

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Conflicts of Interest

The authors have nothing to disclose.

Bibliography

1. Wong YP., *et al*. "The Effects of COVID-19 on Placenta and Pregnancy: What Do We Know So Far?" *Diagnostics (Basel)* 11.1 (2021): 94.

2. Brandt JS., *et al.* "Epidemiology of coronavirus disease 2019 in pregnancy: Risk factors and associations with adverse maternal and neonatal outcomes". *American Journal of Obstetrics and Gynecology* 224.4 (2020): 389.

3. Khalil A., *et al.* "SARS-CoV-2 infection in pregnancy: A systematic review and meta-analysis of clinical features and pregnancy outcomes". *E Clinical Medicine* 25 (2020): 100446.

4. Fitzgerald B., *et al.* "Fetal deaths in Ireland due to SARS-CoV-2 placentitis caused by SARS-CoV-2 Alpha". *Archives of Pathology and Laboratory Medicine* 12 (2022).

5. Shook LL., et al. "SARS-CoV-2 placentitis associated with B.1.617.2 (Delta) variant and foetal distress or demise". *The Journal of Infectious Diseases* 13 (2022).

6. Bloise E., *et al.* "Expression of Severe Acute Respiratory Syndrome Coronavirus 2 cell entry genes, angiotensin-converting enzyme 2 and transmembrane protease serine 2, in the placenta across gestation and at the maternal-foetal interface in pregnancies complicated by preterm birth or preeclampsia". *American Journal of Obstetrics and Gynecology* 224.3 (2020): 298.

7. Wu C., *et al.* "Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China". *JAMA Internal Medicine* 180.7 (2020): 934-843.

8. Wong RS., *et al.* "Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis". *BMJ* 326.7403 (2003): 1358-1362.

9. Lee N., *et al.* "A major outbreak of severe acute respiratory syndrome in Hong Kong". *The New England Journal of Medicine* 348.20 (2003): 1986-1994.

10. Tang N., *et al.* "Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia". *Journal of Thrombosis and Haemostasis* 18.4 (2020): 844-847.

11. Huang C., *et al.* "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *Lancet* 395.10223 (2020): 497-506.

12. Zhou F., *et al.* "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study". *Lancet* 395.10229 (2020): 1054-1062.

13. Guan WJ., *et al.* "China Medical Treatment Expert Group for COVID-19. Clinical Characteristics of Coronavirus Disease 2019 in China". *The New England Journal of Medicine* 382.18 (2020): 1708-1720.

14. Cui S., *et al.* "Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia". *Journal of Thrombosis and Haemostasis* 18.6 (2020): 1421-1424.

15. Klok FA., *et al.* "Incidence of thrombotic complications in critically ill ICU patients with COVID-19". *Thrombosis Research* 191 (2020): 145-147.

16. Poissy J., *et al.* "ICU Haemostasis COVID-19 group. Pulmonary Embolism in COVID-19 Patients: Awareness of an Increased Prevalence". *Circulation* 142.2 (2020): 184-186.

17. Toshiaki Iba*., et al.* "The coagulopathy, endotheliopathy, and vasculitis of COVID-19". *Inflammation Research* 69.12 (2020): 1181-1189.

18. Baud D., *et al*. "Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection". *JAMA* 323.21 (2020): 2198-2200.

19. Baergen RN., *et al.* "Placental Pathology in COVID-19 Positive Mothers: Preliminary Findings". *Pediatric and Developmental Pathology* 23.3 (2020): 177-180.

20. Shuo C., *et al.* "Clinical characteristics and pathological analysis of placenta in three cases of pregnant women with novel coronavirus infection". *Chinese Journal of Pathology* 49.5 (2020): 418-423.

21. Shanes ED., *et al.* "Placental Pathology in COVID-19". *American Journal of Clinical Pathology* 154.1 (2020): 23-32.

22. Facchetti F., *et al.* "SARS-CoV-2 vertical transmission with adverse effects on the new born revealed through integrated immunohistochemical, electron microscopy and molecular analyses of placenta". *E Bio Medicine* 59 (2020): 102951.

23. Menter T., *et al.* "Placental pathology findings during and after SARS-CoV-2 infection: Features of villitis and malperfusion". *Pathobiology* 88.1 (2020): 69-77.

24. Lokken EM., *et al.* "Clinical characteristics of 46 pregnant women with a severe acute respiratory syndrome coronavirus 2 infection in Washington state". *American Journal of Obstetrics and Gynecology* 223.6 (2020): 911.

25. Hecht JL., *et al.* "SARS-CoV-2 can infect the placenta and is not associated with specific placental histopathology: a series of 19 placentas from COVID-19-positive mothers". *Modern Pathology* 33.11 (2020): 2092-2103.

26. Robbins JR. *et al.* "Pathogens and the placental fortress". *Current Opinion on Microbiology* 15.1 (2012): 36-43.