Placental Pathology After SARS-CoV-2 Infection in the Pre-Variant of Concern, Alpha / Gamma, Delta, or Omicron Eras

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Abstract

Objectives. The goal of this study is to describe placental pathology after infection with SARS-CoV-2 before the predominance of variants of concern (pre-VOC) and during eras of predominant transmission of the Alpha & Gamma (co-circulating), Delta, and Omicron variants. Methods. We used county-level variant data to establish population-level variant proportions, SARS-CoV-2 PCR to identify cases, and IgG serology to exclude latent infections from controls and histopathologic examination to identify placental pathology. Results. We report findings in 870 placentas from pregnancies complicated by SARS-CoV-2 including 90 with infection in the Alpha/Gamma era, 60 from the Delta era and 56 from the Omicron era. Features of maternal vascular malperfusion (MVM), including decidual arteriopathy, were significantly more frequent after SARS-CoV-2 infection. The risk of these findings varied over time, with the highest rates in the Delta era. Increased COVID-19 severity and the presence of comorbidities strengthened these associations. Conclusion. MVM is a feature of SARS-CoV-2 infection in pregnancy. Lesion frequency changed with the predominant circulating virus and should be considered with new variants.

Keywords
placenta, SARS-CoV-2, variants of concern, maternal vascular malperfusion, decidual arteriopathy, COVID-19

Introduction

Pregnant patients with SARS-CoV-2 infection have a higher risk of hospitalization, severe disease, and death compared to similarly-aged non-pregnant women with SARS-CoV-2.1 SARS-CoV-2 infection is also associated with adverse pregnancy outcomes, including a possible increased risk of preterm birth and, rarely, vertical transmission or stillbirth.2-8 In utero exposures to infection may have life-long consequences. Rates of adverse outcomes, including stillbirth, have increased with variants of concern (variants), including the Delta variant.9

The placenta is the physiologic interface between maternal and fetal circulation and is responsible for providing a fetus with resources needed for growth and development. As such, it is also in many ways the “black box” of pregnancy – maternal and fetal conditions that impact growth and maturation often leave marks on the placenta which can be diagnosed on pathologic examination after birth. For example, maternal hypertensive disorders, including preeclampsia, are associated with the pathologic finding of maternal vascular malperfusion (MVM) in the placenta.

Pathologic examination of placentas from women with SARS-CoV-2 infection during pregnancy may provide insight into the intrauterine stresses experienced by their fetuses. The first studies of placentas from women infected with SARS-CoV-2 suggested an increased incidence of fetal vascular malperfusion (FVM), sequelae of perturbations of fetal circulation through the placenta, or decidual arteriopathy, damage to maternal decidual vessels.9,10 Subsequent studies have varied from case reports or...
small case series to larger studies of around 100 placentas. While some studies re-demonstrated FVM or MVM, others have not demonstrated any significant placental findings in women with SARS-CoV-2 infection. A meta-analysis conducted in the summer of 2021 reported findings suggestive of placental hypoperfusion and inflammation in pregnancies complicated by SARS-CoV-2 infection, while a more recent meta-analysis suggested that there are no typical placental findings. However, the majority of these studies have looked at broad categories of placental pathology, ie MVM or FVM, rather than at a more granular level, eg components of MVM such as decidual arteriopathy or accelerated villous maturation independently, and most of these studies do not include control groups of placentas without SARS-CoV-2 infection. Additionally, published studies generally do not relate diagnosis frequency to strain or timing within the pandemic. Heterogeneity across viral strains, when analyzed collectively as opposed to sequentially, may mask clinically relevant findings.

We have now collected placentas from SARS-CoV-2 positive pregnant women for nearly two years, including during the waves of the Alpha/Gamma, Delta, and Omicron variants. Given the heterogeneity in prior results that may be informed by sample selection and variant prevalence, our objective was to provide a large, comprehensive, and well controlled study of the impact of SARS-CoV-2 infection in pregnancy on the placenta and to examine the impact of COVID-19 disease severity and presence of comorbidities.

Methods

Patients were included if they delivered between March 18, 2020 and February 14, 2022. Prior to April 30, 2021, we collected specimens on all patients with SARS-CoV-2 delivering at our institution, an academic medical center in a large urban area. Afterward, we transitioned to purposeful recruitment of patients with first or second trimester infection, moderate to critical COVID-19, or infection during a period with high prevalence of variants. Routine testing for SARS-CoV-2 was performed for all admissions to Labor & Delivery during the entire study period.

Placental examination was performed using the Amsterdam Criteria. Individual features of MVM and FVM are reported, as is the frequency of identifying any MFM feature or any FVM features. Accelerated and delayed villous maturation were diagnosed clinically on the basis of villous maturation different from that expected by gestational age in the areas of villous diameter, abundance of syncytial knots, stromal cellularity, stromal density, and position of capillaries. For statistical purposes, we grouped cases where the diagnosis was qualified as “mild”, “patchy”, “regional” or otherwise into the parent diagnosis. Decidual arteriopathy is a parent category diagnosed when mural hypertrophy of membrane arterioles, persistent muscularization of basal plate arterioles (which we consider equivalent to incomplete remodeling of spiral arterioles), atheros or fibrinoid necrosis are present. Formal diagnoses of MVM or FVM are reported separately. Individual practice varies, but members of our section generally render a formal diagnosis when multiple features of MVM or FVM are present; for example, MVM is diagnosed when accelerated villous maturation, decidual arteriopathy, and infarct are all present. Less often, a formal diagnosis is made or suggested when a single feature is extremely prominent, such as a macroscopic focus of avascular villi for FVM.

Histologic slides were imaged on a Leica GT450 scanner at 40× objective magnification. Clinical information was abstracted from the electronic health record and stored in a REDCap database. Comorbidity data were abstracted from the electronic health record using the following ICD9/10 codes. Obesity: 278, E66, O99.21*; Diabetes: 250, 648.0*, E08, E10, E11, O24; Hypertension: 642, 401, 110, O10-15; where * includes any sub-codes. Pre-pregnancy body mass index was not available for most patients; therefore we were reliant on formal diagnosis of obesity.

The trimester of SARS-CoV-2 infection was determined using the gestational age of diagnosis of COVID-19. COVID-19 disease severity was determined using CDC criteria.

Controls were patients without history of vaccination, no history of SARS-CoV-2 infection in pregnancy, and negative SARS-CoV-2 PCRs during routine admission testing. To rule out prior asymptomatic infection we tested for anti-SARS-CoV-2 spike protein IgG and IgM levels similar to that previously described. Positive immunity, defined as signal/cutoff > 1.0 AU/ml, was identified in 21 of 206 patients tested (10.3%). Those patients were excluded as infection could have been during or prior to the current pregnancy, complicating interpretation of their biospecimen.

To characterize proportions of SARS-CoV-2 clades circulating in our patient catchment area, lineage data was downloaded from the GISAID public sequence database for all isolates collected between Jan 1, 2021 and April 1, 2022 and identified as having been isolated from either [our city] or [our county]. Isolates were identified as Alpha if they belonged to pango lineage B.1.1.7 or any Q sublineages (ie Q.1, etc), Gamma if they belonged to lineage P.1 or any sublineages (ie P.1.1, etc), Delta if they belonged to lineage B.1.647.2 or any sublineages (ie AY.1, etc) and Omicron if they belonged to lineage B.1.1.529 or any sublineages (ie BA.1, etc). Of note, our institution is the major contributor to GISAID for our geographic locale, so these data should represent our patient population. The Pre-VOC, Alpha/Gamma, Delta, and Omicron eras were delineated based on the most frequent
variant and shifted to the nearest week. Era boundaries were set by an investigator that was unaware of the placental diagnoses. Of note, some SARS-CoV-2 diagnoses in our population were self-reported without a specific date, therefore not all cases can be definitively assigned to an era. They are excluded from era-specific analyses.

For descriptive values, quantitative values are reported as mean +/- standard deviation. Categorical variables are reported as counts and percentages. Bivariable analyses utilized Student’s t-test for continuous variables or Fisher exact test comparing SARS-CoV-2 or subgroups against the controls only. We used Benjamini and Hochberg’s method to control for multiple comparisons, with corrected P-value based on the number of placental lesions tested for each population with a false discovery rate of 0.05. The study was approved by the institutional review board as STU00212232. Multivariable analyses were performed controlling for birthing person characteristics that significantly differed in bivariable analyses (p < 0.05).

**Results**

**Defining Population Level Variant of Concern Eras**

The Alpha and Gamma variants of SARS-CoV-2 were first identified in our population in the second week of February 2021. These variants rose together in frequency through the week of June 6, 2021 (Figure 1). Delta first appeared the week of April 25 but became dominant in the week of June 27, 2021. Omicron became predominant in the week of December 19, 2021. Based on these estimates, we categorized patients based on the date of their first positive swab as: Pre-VOC: 3/2020–2/2021, Alpha/Gamma: 3/2021–6/2021, Delta: 7/2021–12/18/2021, Omicron: 12/19/2021 – present.

**Patient Demographics and Infection Details**

There were 185 controls and 883 patients with SARS-CoV-2 infection. Of those with SARS-CoV-2 infection, 673 were in the pre-variant of concern era, 90 in the Alpha/Gamma era, 60 in the Delta era, and 56 in the Omicron era. Characteristics of the sample are depicted in Table 1. Patients with SARS-CoV-2 infection were, on average, slightly younger than controls and less likely to be multiparous. The utilization of public insurance differed strikingly between populations: more individuals with SARS-CoV-2 infection utilized public insurance compared to controls. Comorbidity rates were broadly similar, however patients in the Omicron era were more likely to be diagnosed as obese. Individuals with SARS-CoV-2 delivered at earlier gestational ages and were more likely to deliver preterm compared to controls. The incidence of cesarean section was similar between groups. SARS-CoV-2 disease severity was similar between different eras, though Omicron cases were more likely to be symptomatic. Omicron era patients had a preponderance of third trimester infection, possibly reflecting study timing.

**SARS-CoV-2 Infection is Associated with Maternal Vascular Malperfusion and Decidual Arteriopathy**

We tested the association of SARS-CoV-2 infection with different placental lesions and categories of lesions. The strongest association was with the presence of any feature of maternal vascular malperfusion (MVM), which was identified in 87 of 185 controls (47%), as compared to 555 of 883 patients with SARS-CoV-2 infection (63%, OR 1.9, p < .001, Figure 2, Table 2, Supplementary Table 1). MVM describes a constellation of findings associated with hypertensive disorders of pregnancy, fetal growth restriction, preterm delivery, and stillbirth. Among the major findings in MVM, decidual arteriopathy (DA) was identified in 23 of 185 controls (12%) as compared to 227 of 883 patients with SARS-CoV-2 (26%, OR 2.4, p < .001). Decidual arteriopathy includes a group of lesions associated with failure of uterine blood vessels to adapt to pregnancy and resulting injury to those vessels. Among the decidual arteriopathies, the signal is driven by incomplete remodeling of basal plate arterioles (OR 3.8, p < .001). We previously reported an association between infection and atherosclerosis with fibrinoid necrosis, a particularly severe lesion, however the association is not statistically significant in this cohort (p = 0.23). Other features of MVM, such as accelerated villous maturation were also elevated, as was a formal “topline” diagnosis of MVM (Table 2, Supplementary Table 1).

Results from multivariable analyses using logistic regression and controlling for gestational age, insurance type, gravidity, and parity were similar to the bivariable analyses (Supplementary Table 1).

**Associations with Variants of Concern**

SARS-CoV-2 infection in the Alpha / Gamma and Delta eras was associated with MVM features (Figure 2, Table 2, Supplementary Table 1). MVM feature were seen in 87 of 185 controls (47%), as opposed to 59/90 patients in the Alpha / Gamma era (65%, p < .001). Infection in the Delta era had an even higher risk with MVM features seen in 49/56 (82%, p < .001), though Omicron showed a weaker signal, with MVM features in only 31/40 (55%, p = ns). Delta (18/56, 30%, OR 3.0, p < 0.01) and Omicron (18/40, 32%, OR 3.9, p < 0.01) era infections were associated with decidual arteriopathy. Delta era infection was associated with accelerated villous maturation, seen in 10/60 (17%, OR 3.5, p < 0.05). Finally, Delta and Omicron era infections were associated with a formal diagnosis of MVM (10% and 11%, OR 6.7 and 7.3, p < 0.01 and < 0.01, respectively). Associations of Delta and Omicron era infection with decidual arteriopathy and formal diagnosis of MVM and between Delta era infection and MVM features and accelerated...
maturation survived correction for multiple comparison testing (Supplementary Table 2). Placental weights were slightly lower in the Delta era.

FVM and features of FVM have frequently been reported in association with SARS-CoV-2. Among FVM features, delayed villous maturation was observed in 38 controls (21%), as compared to 129 SARS-CoV-2 cases (15%, p=ns) and 109 pre-VOC cases (18%, p=ns). Delayed villous maturation was less frequent in the Delta era with 5 cases (8.3%, OR=0.35, p < 0.05) and the Omicron era with 4 cases (7.1%, OR 0.29, p < 0.05). Other FVM features did not significantly differ with infection (Table 2). A formal diagnosis of FVM was made in 12 controls (6.5%) as opposed to 52 SARS-CoV-2 cases (5.9%, p=ns), 33 pre-VOC cases (4.9%, p=ns), 6 Alpha / Gamma era cases (6.7%, p=ns), 6 Delta cases (10%, p=ns) and 6 Omicron cases (11%, p=ns). Any feature of FVM was identified in 80 controls (43%), 455 SARS-CoV-2 cases (52%), 346 pre-VOC cases (51%), 43 Alpha / Gamma era cases (48%), 32 Delta cases (53%), and 31 Omicron cases (55%).

**Association with Severity**

We tested the association of COVID-19 severity with placentals lesions (Figure 3, Supplementary Table 1). Any MVM feature was present in 87/185 controls (47%) as compared to 142/245 patients with asymptomatic SARS-CoV-2 (58%, OR 1.6, p < 0.05), 290/449 of those with mild COVID-19 (65%, OR 2.1, p < 0.001) and 60/92 of those with moderate to severe disease (65%, p < 0.01). A similar trend was seen for decidual arteriopathy, with decidual arteriopathy in 23/185 controls (12%), as compared with 72/245 with asymptomatic SARS-CoV-2 (29%, OR 2.9, p < 0.001), 100/449 with mild COVID-19 (22%, OR 2.0, p < 0.01), and 33/92 with moderate to severe COVID-19 (36%, OR 3.9, p < 0.001). Similar trends were seen for the component decidual arteriopathies and formal diagnosis of MVM. Interestingly, accelerated villous maturation was sharply and significantly elevated in moderate to severe COVID-19, seen in 26/92 cases (28%) as compared to 10/185 in controls (5.4%, OR 6.9, p < 0.001).

**Association with Comorbidities**

We tested the association of SARS-CoV-2 infection in the presence or absence of comorbidities, defined here as any diagnosis of hypertension in pregnancy, diabetes in pregnancy, or diagnosed obesity (Figure 4). Overall, MVM features were more pronounced with either comorbidities or SARS-CoV-2, and were most pronounced when both were present, however the relatively small number of control patients with comorbidities (34) hampered
Table 1. Patient Characteristics.

|                        | Controls (n = 185) | SARS-CoV-2 (n = 883) | Pre-VOC (n = 673) | Alpha/ Gamma (n = 90) | Delta (n = 60) | Omicron (n = 56) |
|------------------------|--------------------|----------------------|------------------|----------------------|----------------|------------------|
| Maternal age (years)   | 32.8 +/-4.9        | 31.3 +/-5.6          | 31.6 +/-5.7      | 30.9 +/-5.7          | 29.8 +/-5.6    | 29.7 +/-5.1      |
| Gravida                | 2.1 +/-1.4         | 2.5 +/-1.6           | 2.5 +/-1.6       | 2.5 +/-1.7           | 2.5 +/-1.6     | 2.4 +/-1.5       |
| Para                   | 1.6 +/-0.9         | 1.4 +/-1.2           | 1.3 +/-1.1       | 1.4 +/-1.5           | 1.1 +/-1.2     | 0.7 +/-1.2       |
| Multiparous            | 178 (96)           | 635 (72)             | 511 (76)         | 58 (64)              | 38 (63)        | 26 (46%)         |
| Public insurance       | 29 (16)            | 367 (42)             | 263 (39)         | 37 (41)              | 33 (55)        | 32 (58)          |
| Hypertension in pregnancy | 20 (11)           | 131 (15)             | 106 (16)         | 14 (16)              | 8 (13)         | 3 (5.4)          |
| Diabetes in pregnancy  | 12 (6.5)           | 69 (7.8)             | 65 (9.4)         | 2 (2.2)              | 2 (3.3)        | 2 (3.6)          |
| Obesity diagnosis      | 5 (2.7)            | 59 (6.7)             | 43 (6.4)         | 6 (6.7)              | 3 (5)          | 7 (12.5)         |
| Any comorbidity        | 34 (18)            | 210 (24)             | 170 (25)         | 19 (21)              | 11 (18)        | 10 (18)          |
| SARS-CoV-2 disease severity: |               |                      |                  |                      |                |                  |
| Asymptomatic           |                    |                      |                  |                      |                |                  |
| Mild                   | 449 (51)           | 359 (54)             | 40 (44)          | 31 (52)              | 18 (32)        |                  |
| Moderate               | 62 (7)             | 53 (7.9)             | 4 (4.4)          | 4 (6.7)              | 1 (1.8)        |                  |
| Severe                 | 30 (3.4)           | 17 (2.5)             | 6 (6.7)          | 5 (8.3)              | 2 (3.6)        |                  |
| Unknown                | 97 (11)            | 68 (10)              | 12 (13)          | 9 (15)               | 5 (8.9)        |                  |
| Trimester of first positive test: |               |                      |                  |                      |                |                  |
| first                  | 96 (11)            | 82 (12)              | 9 (10)           | 1 (1.7)              | 0 (0)          |                  |
| second                 | 202 (23)           | 170 (25)             | 22 (24)          | 8 (13)               | 2 (3.6)        |                  |
| third                  | 585 (66)           | 421 (63)             | 59 (66)          | 51 (85)              | 54 (96)        |                  |
| Gestational age at delivery (wks) | 38.9 +/-1.6       | 38.4 +/-2.6          | 38.5 +/-1.9      | 38.8 +/-1.9          | 37.6 +/-3.3    | 37.9 +/-3.7      |
| Method of delivery:    |                    |                      |                  |                      |                |                  |
| Vaginal                | 133 (72)           | 639 (72)             | 475 (71)         | 68 (76)              | 48 (80)        | 46 (82)          |
| Cesarean               | 52 (28)            | 244 (28)             | 198 (29)         | 22 (24)              | 12 (20)        | 10 (18)          |
| Placental weight (g, intact singletons, n = 177, 870, 660, 90, 56) | 465 +/-94          | 461 +/-112          | 465 +/-111         | 446 +/-117      | 425 +/-119      | 447 +/-90        |

comparisons. Specifically, any feature of MVM was seen in 69/151 non-comorbid controls and 18/34 comorbid controls (46% vs. 53%, p = ns), as compared to 414/673 patients with SARS-CoV-2 without comorbidities (62%, OR 1.9, p < 0.01 vs. non-comorbid controls) and 141/210 (67%, OR 2.4, p < 0.001 vs. non-comorbid controls). Accelerated villous maturation was seen in 6/151 non-comorbid controls (4.0%) as opposed to 4/34 comorbid controls (12%, p = ns), 64/673 non-comorbid SARS-CoV-2 patients (9.5%, OR 2.5, p < 0.04 vs. non-comorbid controls) and 42/210 comorbid SARS-CoV-2 patients (20%, OR 6.0 p < 0.001 vs. non-comorbid controls and OR 2.4, p < 0.001 vs. non-comorbid SARS-CoV-2 patients). Decidual arteriopathy was seen in 15/151 non-comorbid controls (10%) versus 8/34 comorbid controls (24%, OR 2.8, p = 0.04), 156/673 non-comorbid SARS-CoV-2 patients (23%, OR 2.7, p < 0.001 vs. non-comorbid controls) and 71/210 comorbid controls (34%, OR 4.6, p < 0.001 vs. non-comorbid controls and OR 1.7 p < 0.01 vs. non-comorbid SARS-CoV-2). Delayed villous maturation was seen in 34 of 151 non-comorbid controls versus 4/34 comorbid controls (22% vs. 11%, p = ns), 111 of 673 non-comorbid SARS-CoV-2 patients (16.4%, p = ns) and 18/210 comorbid SARS-CoV-2 patients (8.6%, OR 0.47, p < 0.01).

Changing Lesion Frequency Over the Course of the Pandemic

We determined the frequency of each lesion among patients diagnosed with SARS-CoV-2 in a particular month between March 2020 and February 2022 (Figures 5 and 6 Supplementary Table 2). MVM features waned slightly toward the end of the pre-VOC era, before increasing with Alpha / Gamma and markedly increasing with Delta. Decidual arteriopathy was very frequent in April 2020 but became steadily less common in patients with SARS-CoV-2 over time, before increasing again in the Delta and Omicron eras.
Table 2. Lesions Associated with SARS-CoV-2 and Variant Infection.

| Lesion                                              | Controls (n = 185) | SARS-CoV-2 (n = 883) | Pre-VOC (n = 673) | Alpha / Gamma (n = 90) | Delta (n = 56) | Omicron (n = 40) |
|-----------------------------------------------------|---------------------|-----------------------|-------------------|------------------------|----------------|-----------------|
| **MVM**                                              |                     |                       |                   |                        |                |                 |
| Accelerated villous maturation                       | 10(5.4)             | 106(12)**             | 80(12)**          | 11(12)                 | 10(17)*        | 4(7.1)          |
| Decidual arteriopathy                                | 23(12)              | 227(26)**             | 175(26)**         | 14(16)                 | 18(30)**       | 18(32)**        |
| Atherosis and fibrinoid necrosis                     | 1(0.5)              | 19(2)                 | 14(2)             | 1(0.5)                 | 2(3.4)         | 2(5)            |
| Mural hypertrophy of membrane arterioles             | 17(9)               | 168(17)**             | 114(17)**         | 9(10)                  | 10(17)         | 17(27)**        |
| Persistent muscularization of basal plate arterioles | 5(2.7)              | 84(9.5)**             | 71(11)**          | 8(9)*                  | 3(5)           | 2(3.6)          |
| Formal diagnosis of MVM                              | 3(1.6)              | 55(6)*                | 37(5.5)*          | 5(5.6)                 | 6(10)**        | 6(11)**         |
| Any MVM feature                                      | 87(47)              | 555(63)**             | 413(61)**         | 59(65)**               | 49(82)**       | 31(55)          |
| **FVM**                                              |                     |                       |                   |                        |                |                 |
| Clustered avascular villi                            | 33(18)              | 155(18)               | 127(19)           | 11(12)                 | 11(18)         | 5(8.9)          |
| Villous stromal vascular karyorrhexis                | 12(6.5)             | 77(8.7)               | 57(8.5)           | 10(11)                 | 4(6.7)         | 5(8.9)          |
| Fetal vascular thrombosis or intramural fibrin       | 21(11)              | 128(14)               | 88(13)            | 13(14)                 | 13(22)         | 14(25)**        |
| deposition                                            |                      |                       |                   |                        |                |                 |
| Stem villous obliteration                            | 14(7.6)             | 40(7.6)               | 34(5)             | 2(2.2)                 | 2(3.3)         | 2(3.5)          |
| Delayed villous maturation                           | 38(21)              | 129(15)               | 109(16)           | 10(11)                 | 5(8.3)*        | 4(7.1)*         |
| Abnormal umbilical cord (hypercoiled etc)            | 23(12)              | 168(19)*              | 124(18)           | 14(16)                 | 11(18)         | 18(32)*         |
| Formal diagnosis of FVM                              | 12(6.5)             | 52(5.9)               | 33(4.9)           | 6(6.7)                 | 6(10)          | 6(11)           |
| Any FVM feature                                      | 80(43)              | 455(52)               | 346(51)           | 43(48)                 | 32(53)         | 31(55)          |

Values are frequency(%). FVM: Fetal vascular malperfusion; MVM: Maternal vascular malperfusion. *: uncorrected p < 0.05, **: p < 0.01; ***: p < 0.001.

Figure 2. Histology. Representative H&E images of placental diagnoses. Mural hypertrophy of membrane arterioles (A). Persistent muscularization of basal plate arterioles (B). Accelerated villous maturation at 37 weeks gestation, characterized by lower villous diameter, increased stromal density and syncytial knots (C), versus Delayed villous maturation at 39 weeks gestation characterized by larger villous diameter, looser stroma, increased vascularity, and fewer syncytial knots (D). Objective magnification 10x, scale bar 300 µm.
Discussion

SARS-CoV-2 infection in pregnancy is strongly associated with features of maternal vascular malperfusion, specifically decidual arteriopathy. This association is more pronounced in eras of high-circulation of Alpha/Gamma, Delta, and Omicron variants. MVM and decidual arteriopathy frequency were also increased with more severe COVID-19.

While the present study includes 50-fold more patients with SARS-CoV-2 than the earliest studies, it upholds similar conclusions. Decidual arteriopathy was reported in 7 of 15 patients (47%), representative of the point estimates seen in our study in April 2020 (see Figure 3). Over the course of the pandemic, the frequency of decidual arteriopathy has decreased. Our current findings do not support an association of atherosis and fibrinoid necrosis with SARS-CoV-2 infection.

The same effect of random sampling which caused us early studies to over-estimate the association between SARS-CoV-2 infection and placenta pathologic findings may have impacted other small studies which failed to identify an association of SARS-CoV-2 with MVM features or DA. Some larger studies may have low baseline rates of MVM features or DA, making it more difficult for them to detect changes. Interobserver variability may also drive some disagreement, as agreement for MVM features is low. Studies using pandemic-era controls have not generally performed SARS-CoV-2 serology to exclude possible silent infection in pregnancy. Our findings (see Methods) suggest 10% of such controls could be latent cases, decreasing study power.

MVM represents a constellation of findings that are associated with hypertensive disorders in pregnancy, including pre-eclampsia. Decidual arteriopathy represents a collection of lesions involving failed adaptation of uterine vessels during pregnancy and is considered causative of preeclampsia. The interaction of SARS-CoV-2 infection, COVID-19 severity, and comorbidities, including hypertension in pregnancy, diabetes in pregnancy, and pre-pregnancy obesity is complex. More severe COVID-19 in pregnancy has been associated with comorbidities. Conversely, SARS-CoV-2 infection in pregnancy has been reliably associated with the subsequent development of pre-eclampsia. Our data are agnostic as to

Figure 3. SARS-CoV-2 infection is associated with increased risk of MVM findings, particularly decidual arteriopathy. SARS-CoV-2 infection, or variant of concern other than Omicron, was associated with the presence of at least 1 MVM feature (A). Accelerated villous maturation was increased in SARS-CoV-2 and delta. (B). Decidual arteriopathy was associated with SARS-CoV-2 infection in the pre-VOC era, but the association weakened in the Alpha / Gamma era. It was stronger in the Delta and Omicron (C). Delayed villous maturation was decreased (D). after SARS-CoV-2 infection, significantly so in the Delta and Omicron eras. ***: uncorrected p < 0.001, **: p < 0.01, *: p < 0.05. MVM: maternal vascular malperfusion; pre-VOC: era prior to any predominant variant of concern.
causation, but support that 1) in patients without co-morbidities, SARS-CoV-2 infection is associated with the presence of MVM features including decidual arteriopathy and accelerated villous maturation and 2) among patients with SARS-CoV-2 infection, the presence of comorbidities is associated with increased rates of decidual arteriopathy and accelerated villous maturation.

The changes in lesion frequency over time indicate that placental pathology in response to SARS-CoV-2 is not fixed, but varies by the demographics of the pandemic, treatment, and viral strain. SARS-CoV-2 strains also show regional differences in prevalence over time. Our contemporaneous data allow us to impute the probable viral strain of a larger dataset, suggesting another possible explanation for the discordance between our findings and other, geographically disparate studies.

**Limitations**

This study is subject to several limitations. It is a single center study. Pathology data are largely from clinical examination, where pathologists were generally aware of the patient’s SARS-CoV-2 infection status. SARS-CoV-2 variants were imputed based on population prevalence, rather than testing of the actual patient specimens. This is likely to manifest as imperfect boundaries – for example, patients with infection in July 2021 are extreme outliers in terms of MVM prevalence, possibly representing a mélange of different variants.

**Conclusion**

Examination of placental pathology from patients with SARS-CoV-2 infection in pregnancy showed elevated risk of MVM and DA, particularly with infection in the eras of the Delta or Omicron variants.

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**Figure 4.** Increasing severity of COVID-19 is associated with increased risk of MVM findings. Asymptomatic SARS-CoV-2 infection was associated with the presence of at least 1 MVM feature, with increasing risk in mild or moderate to severe COVID-19 (A). Accelerated villous maturation was markedly increased after moderate to severe COVID-19 (B). Decidual arteriopathy was associated with SARS-CoV-2 infection at all severities, but particularly moderate to severe disease (C). Delayed villous maturation was non-significantly decreased in all severities of COVID-19 (D). ***: uncorrected p < 0.001, **: p < 0.01, *: p < 0.05. MVM: maternal vascular malperfusion.
Figure 5. Impact of comorbidities on MVM in the context of SARS-CoV-2 infection. In a stepwise fashion comorbidities, SARS-CoV-2, and SARS-CoV-2 with comorbidities are associated with increased risk of any feature of MVM (A), particularly, accelerated villous maturation (B) and decidual arteriopathy (C). The risk of abnormally delayed villous maturation is decreased (D). Groups are compared using chi-squared and post-hoc Fisher exact tests. a: significantly different from non-comorbid controls; c: significantly different from non-comorbid SARS-CoV-2. MVM: maternal vascular malperfusion.

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Ethical Approval
The study was approved by the Northwestern University institutional review board as STU00212232.

Informed Consent
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Trial Registration
Not a clinical trial

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Supplemental material
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References
1. Zambrano LD. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy Status — United States, January 22–October 3, 2020. MMWR Morb Mortal Wkly Rep 2020;69. Available at: https://www.cdc.gov/mmwr/volumes/69/wr/mm6944e3.htm. Accessed November 30, 2021.
2. Karasek D, Baer RJ, McLemore MR, et al. The association of COVID-19 infection in pregnancy with preterm birth: a retrospective cohort study in California. Lancet Reg Health – Am 2021;2. Available at: https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00019-3/fulltext. Accessed November 30, 2021.
3. Jering KS, Claggett BL, Cunningham JW, et al. Clinical characteristics and outcomes of hospitalized women giving birth with and without COVID-19. JAMA Intern Med 2021;181:714–717. doi:10.1001/jamainternmed.2020.9241
4. Woodworth KR. Birth and infant outcomes following laboratory-confirmed SARS-CoV-2 infection in pregnancy — SET-NET, 16 jurisdictions, March 29–October 14, 2020. MMWR Morb Mortal Wkly Rep 2020;69(44):1635–1640. doi:10.15585/mmwr.mm6944e2
5. Raschetti R, Vivanti AJ, Vauloup-Fellous C, et al. Synthesis and systematic review of reported neonatal SARS-CoV-2 infections. Nat Commun 2020;11(1):5164. doi:10.1038/s41467-020-18982-9
6. Mullins E, Hudak ML, Banerjee J, et al. Pregnancy and neonatal outcomes of COVID-19: coreporting of common outcomes from PAN-COVID and AAP-SONPM registries. Ultrasound Obstet Gynecol 2021;57(4):573–581. doi:10.1002/uog.23619
7. Schwartz DA, Baldewijns M, Benachi A, et al. Chronic histiocytic intervillositis with trophoblast necrosis is a risk factor associated with placental infection from coronavirus disease 2019 (COVID-19) and intrauterine maternal-fetal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Figure 6. Frequency of selected diagnoses throughout the pandemic. Features of MVM (black line) were identified in 60% of patients with symptomatic SARS-CoV-2 diagnosed in April 2020, but only 29% of patients diagnosed with SARS-CoV-2 in October 2020. Decidual arteriopathy (blue line) rates mirrored those of MVM overall. Note there are only 2 patients in February 2022.
transmission in live-born and stillborn infants. Arch Pathol Lab Med 2021;145(5):517–528. doi:10.5858/arpa.2020-0771-SA
8. DeSisto CL. Risk for stillbirth among women with and without COVID-19 at delivery hospitalization — United States, March 2020–September 2021. MMWR Morb Mortal Wkly Rep 2021;70. Available at: https://www.cdc.gov/mmwr/volumes/70/wr/mm7047e1.htm. Accessed November 30, 2021.
9. Baergen RN, Heller DS. Placental pathology in COVID-19 positive mothers: preliminary findings. Pediatr Dev Pathol 2020;23(3):177–180. doi:10.1177/1093526620925569
10. Shanes ED, Mithal LB, Otero S, et al. Placental pathology in COVID-19. Am J Clin Pathol 2020:aqaa089. doi:10.1093/ajcp/aqaa089
11. Moresi S, Dell’Aquila M, Salvi S, et al. SARS-CoV-2 infection in pregnancy: clinical signs, placental pathology, and neonatal outcome—implications for clinical care. Front Med 2021;8:676870. doi:10.3389/fmed.2021.676870
12. Patberg ET, Adams T, Rekawek P, et al. Coronavirus disease 2019 infection and placental histopathology in women delivering at term. Am J Obstet Gynecol 2021;224:382.e1–382.e18. doi:10.1016/j.ajog.2020.10.020
13. Levitan D, London V, McLaren RA Jr, et al. Histologic and immunohistochemical evaluation of 65 placentas from women with polymerase chain reaction–proven severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Arch Pathol Lab Med 2021;145:648–656. doi:10.5858/arpa.2020-0793-SA
14. Di Girolamo R, Khalil A, Alameddine S, et al. Placental histopathology after SARS-CoV-2 infection in pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM 2021;3(6):100468. doi:10.1016/j.ajogmf.2021.100468
15. Suhren J-T, Meinardus A, Hussein K, et al. Meta-analysis on COVID-19-pregnancy-related placental pathologies shows no specific pattern. Placenta 2022;117:72–77. doi:10.1016/j.placenta.2021.10.010
16. Khong TY, Mooney EE, Ariel I, et al. Sampling and definitions of placental lesions: amsterdam placental workshop group consensus statement. Arch Pathol Lab Med 2016;140:698–713. doi:10.5858/arpa.2015-0225-CC
17. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208. doi:10.1016/j.jbi.2019.103208
18. Anon. Clinical Spectrum of SARS-CoV-2 Infection. COVID-19 Treat Guidel. Available at: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/. Accessed November 30, 2021.
19. Mithal LB, Otero S, Shanes ED, et al. Cord blood antibodies following maternal COVID-19 vaccination during pregnancy. Am J Obstet Gynecol Published online April 1, 2021. doi:10.1016/j.ajog.2021.03.035
20. Romero R, Kim YM, Pacora P, et al. The frequency and type of placental histologic lesions in term pregnancies with normal outcome. J Perinat Med 2018;46(6):613–630. doi:10.1515/jpm-2018-0055
21. Redline RW, Vik T, Heerema-McKenney A, et al. Interobserver reliability for identifying specific patterns of placental injury as defined by the Amsterdam classification. Arch Pathol Lab Med Published online July 9, 2021. doi:10.5858/arpa.2020-0753-OA
22. Metz TD, Clifton RG, Hughes BL, et al. Disease severity and perinatal outcomes of pregnant patients with coronavirus disease 2019 (COVID-19). Obstet Gynecol 2021;137(4):571–580. doi:10.1097/AOG.0000000000004339
23. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. Br Med J. Published online September 1, 2020;m3320. doi:10.1136/bmj.m3320
24. Conde-Agudelo A, Romero R. SARS-CoV-2 infection during pregnancy and risk of preeclampsia: a systematic review and meta-analysis. Am J Obstet Gynecol 2022;226(1):68–89.e3. doi:10.1016/j.ajog.2020.07.009