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Investigating Placental Pathologies in Pregnant Women with and Without SARS-Cov-2: A Systematic Review

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Abstract

An investigation into placental pathologies, with respect to SARS-CoV-2 in pregnant women and their neonates or infants, requires critical attention. The aim of this systematic review is to assess the rate of placental pathologies among pregnant women who test positive for SARS-CoV-2, in comparison to pregnant women without SARS-CoV-2.

Records were sourced from MEDLINE, Embase, Cochrane Covid-19 study register, and the WHO Covid-19 Collection. Studies followed the PRISMA guidelines. Primary outcomes included the presence of any placental pathologies as defined by the Amsterdam Consensus. Using a random effects model, proportions of study endpoints were pooled.

Sixteen observational studies were included, in which 593 pregnant women were tested positive for SARS-CoV-2 on RT-PCR testing and 21 716 were controls. Results loosely suggest that the percentage of maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), chronic inflammation, and acute chorioamnionitis appeared slightly higher in cases than controls, although the majority of pathologies were similar in proportion.

There is an increase rate of MVM and FVM diagnosis, and chronic inflammation in positive pregnant women in SARS-CoV-2 positive versus negative pregnant women, although the reason remains unclear. Future studies of robust sample sizes with adequate blinding and control procedures are needed.

INTRODUCTION

The maternal-placental-fetal interface (MPFI) is critical for communication between the placenta, uterine mucosa, and fetal chorioamniotic membranes [1]. In particular, the placenta is a crucial organ of fetal origin, providing oxygen and nutrients, enabling the fetus to develop and function during pregnancy [1]. Immune tolerance is important throughout pregnancy, and is a mechanism enabling embryo implantation [2].

Pregnant women are vulnerable to viral infections, resulting from altered adaptive immune response, which can affect self-tolerance and may dysregulate circulating cytokines [3-5]. As such, viral infections may have detrimental consequences for mother and baby, like tissue damage, fetal demise, and infection-induced fetal tolerance disruptions [6].

At present, obstetrical and neonatal outcomes are linked to the severity of COVID-19 and maternal disease. Maternal diseases, include pulmonary problems, hypertensive disorders, obesity, inflammation and clotting activity, and diabetes predispose pregnant women with SARS-CoV-2 to severe adverse outcomes, such as needing advanced oxygen support, ICU admission, and maternal death [7-10]. In fact, a greater percentage of pregnant women who tested positive for SARS-CoV-2 with severe maternal diseases underwent a caesarean section, delivered preterm, and gave birth to newborns requiring admission into the neonatal intensive care unit (NICU) [7,11]. Overall, adverse perinatal outcomes are more prevalent in pregnant women exhibiting severe COVID-19 symptoms versus mild-moderate COVID-19 or pregnant women who are asymptomatic [11,12]. Moreover, rates of stillbirth/neonatal deaths appear higher in SARS-CoV-2 infected pregnant women than controls [13-15]. Preterm birth (i.e., <37 weeks' gestation) is also a prevalent, detrimental outcome of pregnancy [16], occurring in 41.1% of SARS-CoV-2 positive cases [17].

One systematic review determined that the pooled proportion of perinatal death was 7% (2/41, 95% CI, 1.4–16.3), 43% of fetuses (12/30, 95% CI, 15.3–73.4) with fetal distress, and 8.7% of newborns (1/10, 95% CI, 0.01–31.4) were admitted to the NICU. Though one study reported no signs of vertical transmission among any newborn during the follow-up period [17], recent literature suggests the possibility of vertical transmission in 3-6% of third-trimester pregnancies [18,19].

With respect to pregnancy outcomes, another systematic review and meta-analysis determined that SARS-CoV-2 is

correlated with preeclampsia (OR 1.33, 95% CI 1.03 to 1.73) [20]. Compared with mild COVID-19, severe COVID-19 had higher risk of preeclampsia (OR 4.16, 95% CI 1.55 to 11.15), gestational diabetes (OR 1.99, 95% CI 1.09 to 3.64), and low birth weight (OR 1.89, 95% CI 1.14 to 3.12) [20]. Pooled proportion analysis demonstrated that pregnant women with SARS-CoV-2 experience premature rupture of membranes [18.8% (5 of 31, 95% CI, 0.8–33.5)], caesarean delivery [91% (38 of 41, 95% CI, 81.0–97.6)] [17], and are more frequently admitted to the intensive care unit and hospitalized in comparison to SARS-CoV-2 negative women [21,22].

A systematic investigation of placental pathology in SARS-CoV-2 pregnancies is still limited, and studies differ by ascertainment, evaluation methods, and whether results are adjusted for known confounders. A 2022 systematic review supports that there is no evidence of a COVID-19 placental lesion and that nonspecific placental changes occur equally in non-COVID-19 pregnancies [23]. Furthermore , certain evidence suggests that vertical transmission is rare [24-28], with a couple of reports having demonstrated direct placental infection [29,30]. In contrast, other studies documented increased frequencies maternal vascular malperfusion (MVM) features, intervillous thrombi [31], fetal vascular malperfusion (FVM) or fetal vascular thrombosis [32,33], and increased perivillous fibrin deposition and intervillositis, in placentas at third trimester, versus controls [34]. This evidence is further supported by Patberg et al. In fact, SARS-CoV-2 cases were more likely to show mural fibrin deposition [32.5% (25/77) vs. 3.6% (2/56), p<0.0001], and villitis of unknown etiology (VUE) [20.8% (16/77) vs. 7.1% (4/56)], p=0.030] than controls. Their multivariable models (controlling for maternal age, ethnicity, mode of delivery, oligohydramnios, preeclampsia, and fetal growth restriction) demonstrated higher odds of FVM [OR 12.63 (2.40, 66.40)] and VUE [OR 2.11 (0.50, 8.97) among cases [35].

Opposingly, He et al., reported no significant changes in gross or microscopic pathological attributes [36]. Furthermore, Gulersen et al found that decidual vasculopathy was not detected in any third trimester placentas with severe SARS-CoV-2 infection, and there was no statistical difference in placental histopathological characteristics between cases and controls [37].

The impact of placental pathologies in SARS-CoV-2 pregnant women, and their neonates, is of keen interest to pathologists and obstetricians worldwide. Thus, the aim of this systematic review is to determine the prevalence of placental pathologies among pregnant women who test positive for SARS-CoV-2 versus pregnant women without SARS-CoV-2.

MATERIALS AND METHODS

This review followed the Cochrane Methodology to identify and select the studies [38] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [39].

Search Strategy and Selection Criteria

A systematic search for relevant studies was performed between January 1st 2020 to November 17th 2020 using these databases: MEDLINE including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Embase. Our review thus only includes literature captured during the first and second waves of the pandemic mainly from the USA and Italy, followed by Brazil and Switzerland. All studies were captured before COVID-19 vaccination was made available internationally. Two specialized COVID-19 resources were also searched on November 18, 2020; Cochrane Covid-19 study register, and the WHO Covid-19 Collection, as well as MedRxiv, OSF Preprints, and database for Disaster Medicine and Public Health (Supplemental Material 1).

A librarian experienced in systematic reviews developed and conducted the searches [40]. The study protocol has been registered in Open Science Framework (10.31219/osf.io/e5tns). Duplicates were deleted online, and studies collected by the electronic search were imported into a systematic review software InsightScope [(www.insightscope.ca)] for title, abstract, and full text review. Three reviewers (IO, DM, JT) screened at title/abstract level and full text review stages. Studies were omitted if at least two reviewers agreed to exclude. Any discrepancies were resolved by the corresponding author (DD).

Inclusion Criteria

Case series, case-control and cohort studies written in English or French of asymptomatic and symptomatic pregnant women, who tested positive for SARS-CoV-2 on admission, as validated by laboratory confirmed positive antibody testing or using real-time reverse-transcriptase-polymerase chain reaction (rRT-PCR) were considered. Control groups were differentiated into: controls recruited before the pandemic (historical prior to January 2020), controls recruited during the pandemic period who screened negative after rRT-PCR testing, or negative based on a clinical diagnosis (absence of presenting symptoms during initial screening).

Exclusion Criteria

Studies were excluded if non-pregnant women or non-human trials were examined, could not be accessed online, and written in a language other than English or French. We excluded conference abstracts, literature and systematic reviews, and editorials or commentaries.

Data extraction and Outcomes

Three authors (DM, JT, and IO) extracted frequencies and percentages using a pre-constructed and piloted data abstraction sheet in REDCap (Research Electronic Data Capture), a secure, third-party web server [41,42]. The extracted information included: title; year of publication; study location and design; publishing journal; maternal age; gestational age; maternal chronic or gestational hypertension; chronic or gestational diabetes; preeclampsia; trimester of pregnancy (1st- conception to 12 weeks, 2nd- week 13 to 27, and 3rd- week 28 to birth); mode of delivery (vaginal, elective caesarean, emergency caesarean); and placental weight (small defined as below the 10th percentile, appropriate 10-90th percentile, or large >90th percentile for that gestational age). To approximate placental weight categories in case series studies, the reference weights for trimmed singleton placentas were used with corresponding gestational age (weeks) [43].

The primary endpoints were frequency or percent of any placental pathology syndromes (i.e., any individual feature) in cases vs controls, as outlined in the Amsterdam placental workshop group consensus statement (Supplemental Table 2) [44]. If the authors of the included studies did not provide any individual feature, the study team followed the Amsterdam criteria and advice from an experienced pathologist (DD), to determine a diagnosis of MVM and FVM, respectively. A diagnosis of MVM was made if accelerated villous maturation (AVM), and/or decidual arteriopathy (DA), was present, regardless if other features were present. The presence of fetal thrombosis or avascular villi without chronic villitis was indicative of FVM. If the study did not report chronic deciduitis and villitis separately, but chronic inflammation overall was provided, then this frequency was collected. Acute chorioamnionitis included stages 1 and 2 of chorioamionitis.

As defined by the included studies, our secondary, clinical endpoints referred to frequency or percent of preterm birth (34 weeks or less gestation), small-for-gestational age (SGA) (birth weight < 10^{th} percentile), large-for-gestational age (LGA) (birth weight > 10^{th} percentile), abortions (< 24 weeks of pregnancy), and stillbirths (mortality after 24 completed weeks of pregnancy).

Assessment of Risk of Bias (ROB) within studies

DM and JT independently assessed risk of bias using the Ottawa-Newcastle Scale to evaluate the quality of nonrandomized studies in meta-analyses [45,46]. To score the quality of the included studies, three factors were assessed: (1) selection, such as representativeness of the exposed cohort, selection of the non-exposed cohort, exposure ascertainment, and evidence that the outcome of interest was not present at study initiation; (2) comparability in the study design and analysis, including methods of controlling important confounding variables (hypertensive diseases like preeclampsia, chronic and gestational hypertension, and diabetes); and (3) outcome, including the follow-up period, cohort retention, and possibility of independent blind assessment. We rated the quality of the studies (good, fair and poor) by awarding points in each domain following the guidelines of the Ottawa-Newcastle Scale. A "good" quality score implied 3 or 4 points in selection, 1 or 2 points in comparability, and 2 or 3 points in outcomes. A "fair" quality score referred to 2 points in selection, 1 or 2 points in comparability, and 2 or 3 points in outcomes. A "poor" quality score reflected 0 or 1 point(s) in selection, or 0 points in comparability, or 0 or 1 point(s) in outcomes. The scale was slightly modified to correspond to the appropriate study design and in the context of placental pathology, where placentas are typically dissected immediately after birth. Under the outcomes section, length and adequacy of follow-up may not have been applicable; as such, certain studies were not penalized for this.

Statistical analysis

The R statistical programming language Version 4.0.3 was used for all statistical analysis [47]. Frequencies and percentages represented the categorical variables. Using a random effects model, proportions with 95% Confidence intervals (CI) of the study endpoints were pooled for each study design and for positive pregnant women and negative women separately.

RESULTS AND DISCUSSION

Study Selection

Figure 1 depicts the results of the search strategy, which yielded 627 studies. After level I screening, 440 studies were excluded because they did not meet the inclusion criteria. Overall, 16 studies were included in the systematic review (Figure 1).

Study characteristics and individual results

Seven studies (44%) were case controls, 5 (31%) case series, and 4 (25%) were cohort studies, and 12/16 (75%), were conducted in the United States of America (Table 1). Five hundred and ninety-three pregnant women tested positive for SARS-CoV-2 on RT-PCR testing and 21 716 controls (including historical, RT-PCR negative, and abnormal controls).

Risk of bias across studies

A detailed quality appraisal of case-control, cohort, and case series studies is summarized in the Supplemental Table 3. After formally assessing risk of bias for all studies based on limitations in their study design (Table 2), we rated fifteen studies as "poor " and one study [35] as "good". Due to poor study quality, a meta-analysis of the association between positive test for SARS-CoV-2 and outcomes of interest was not performed. One case-control study did not describe how the non-exposed cohort was derived [48], in addition to two case series studies [32,49]. There was no description of statistical adjustment for known confounders of placental pathology like preeclampsia, chronic and gestational hypertension and diabetes or non-hypertensive factors such as maternal age in fourteen studies [31,32,53-56,33,36,37,48-52], apart from Patberg et al., 2020 [35]. The authors were able to produce multivariable logistic regression models adjusting for variables that could be on the causative pathway of MVM and villitis of unknown etiology (preeclampsia, fetal growth restriction etc.), despite their inability to examine pre-existing and gestational diabetes, due to insufficient sample size [35]. Twelve studies did not provide a description as to whether pathologists were independently blinded to SARS-CoV-2 exposure before evaluating placental specimens [31,32,56,57,33,36,37,50,52-55], excluding Facchetti et al., 2020 [51], and Richtmann et al., 2020 [49]. Follow-up periods were not applicable to the majority of study designs as the assessment of placental histopathology occurs immediately after delivery, without prospective follow-up. Such studies were not penalized.

Demographic characteristics

Table 2 summarizes the demographic characteristics by study design of SARS-CoV-2 positive versus women who tested negative, where appropriate. Results were divided by study design to enable direct comparisons between the studies consistently. Maternal age for positive and negative women ranged from 29.1 to 32.4 years. Prevalent hypertensive diseases for both study groups included chronic hypertension, diabetes, and preeclampsia. However, the percentage of chronic hypertension in case control studies was elevated in SARS-CoV-2 positive pregnant women vs SARS-CoV-2 negative women [7.1% (1.0%, 16.3%) vs 5.9% (1.3%, 12.7%)], respectively. In cohort studies, the percentage of chronic hypertension [10.5% (0.1%,

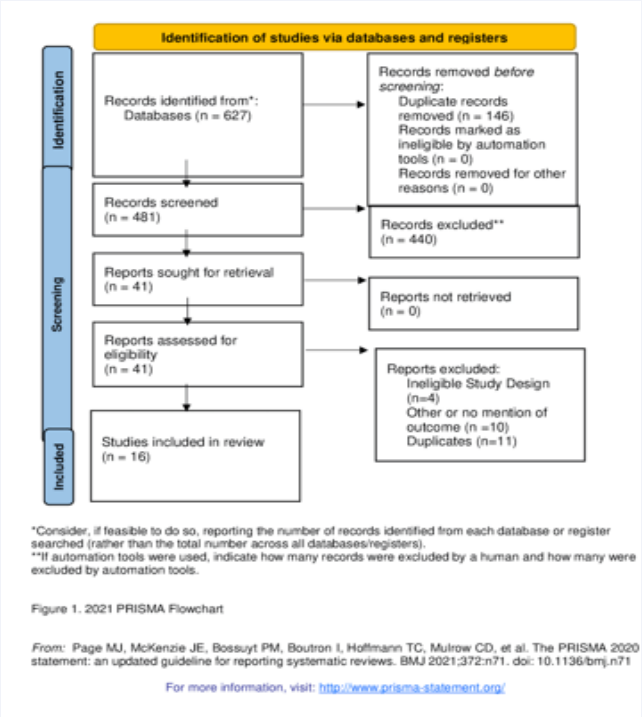

Figure 1 2021 PRISMA Flowchart.

Table 1: Study Characteristics.

Author, year	Study design	Location	SARS-CoV-2 positive pregnant women with placental pathology assessed (cases, N)[a]	SARS-CoV-2 negative pregnant women with placental pathology assessed (controls, N)
Baergen & Heller, 2020[32]	Case series	USA	20	N/A[b]
Shanes et al., 2020[31]	Case Control	USA	15	Historical controls: 17,479 Melanoma: 215
Prabhu et al., 2020[50]	Prospective Cohort	USA	29	106
Cribiu et al., 2020[53]	Case series	Italy	9	N/A
Richtmann et al., 2020[49]	Case series	Brazil	5	N/A
Facchetti et al., 2020[51]	Case control	Italy	15	PCR controls: 34 'Not determinate': 52
Zhang & Salafia et al., 2020[52]	Case control	USA	74	290
Gulersen et al., 2020[37]	Cohort	USA	50	50
Menter et al., 2020[48]	Case series	Switzerland	5	N/A
He et al., 2020[36]	Case control	USA	21	20
Patberg et al., 2020[35]	Retrospective Cohort	USA	77	56
Adhikari et al., 2020[83]	Cohort	USA	187	Not clear how many controls underwent placental pathological examination
Schwartz et al.,2020[56]	Case series	USA	11	N/A
Hecht et al., 2020[54]	Case control	USA	19	COVID-19 mothers before pandemic or with negative tests: 10 Historical: 122 "Abnormal" with HIE[c]: 130
Smithgall et al., 2020[55]	Case control	USA	51	25
Mulvey et al., 2020[33]	Case control	USA	5	5

aValidated by laboratory confirmed positive antibody testing or using real-time reverse-transcriptase-polymerase chain reaction (rRT-PCR).
bNot applicable based on study design.
cHypoxic ischemic encephalopathy (HIE).

Table 2: Demographic Characteristics.

Characteristic	# of studies for positive women[a]	SARS-CoV-2 positive pregnant women (Percentage, 95% CI)	# of studies for negative women	SARS-CoV-2 negative pregnant women (Percentage, 95% CI)
Case control studies				
Maternal age (years), mean	6	31.0 (28.3,33.6)	4	29.1 (26.3,31.9)
Gestational age (weeks), mean	5	38.1 (37.1,39.0)	3	36.5 (35.6,37.4)
Hypertensive diseases				
Chronic hypertension	3	7.1 (1.0, 16.3)	2	5.9 (1.3, 12.7)
Gestational hypertension	5	5.8 (0.8, 13.5)	2	5.3 (0.1, 15.2)
Diabetes	6	5.1 (1.5, 10.1)	3	6.9 (4.2, 10.1)
Preeclampsia	6	3.1 (0.3, 7.4)	3	12.0 (6.5, 18.7)
Trimester of pregnancy				
First trimester[b]	5	0.0 (0.0, 2.4)	2	0.0 (0.0, 0.9)
Second trimester[c]	6	5.6 (0.1, 16.0)	3	3.9 (0.0, 13.3)
Third trimester[d]	6	94.4 (84.0, 99.9)	3	96.1 (86.7, 100.0)
Mode of delivery				
Vaginal	5	55.3 (37.9, 72.1)	2	52.5 (33.0, 71.6)
Elective caesarean	0	N/A	0	N/A
Emergency caesarean	0	N/A	0	N/A
Cohort studies				
Maternal age (years), mean	4	29.1 (26.3,31.9)	4	31.0 (26.6,35.4)
Gestational age (weeks), mean	3	39.1 (38.6,39.7)	3	39.2 (38.8,39.6)
Hypertensive diseases				
Chronic hypertension	2	10.5 (0.1, 30.8)	2	3.9 (1.7, 6.9)
Gestational hypertension	1	6.0 (0.8, 14.7)	1	2.0 (0.0, 8.4)
Diabetes	4	6.0 (3.6, 8.9)	4	7.3 (2.8, 13.5)
Preeclampsia	3	9.7 (6.5, 13.3)	3	6.9 (0.6, 18.4)
Trimester of pregnancy				
First trimester[b]	2	0.0 (0.0, 0.6)	2	0.0 (0.0, 0.0)
Second trimester[c]	2	1.7 (0.0, 6.8)	2	1.9 (0.0, 7.1)
Third trimester[d]	2	98.3 (93.2, 100.0)	2	98.1 (92.7, 100.0)
Mode of delivery				
Vaginal	4	71.2 (64.8, 77.1)	4	54.5 (38.9, 69.7)
Elective caesarean	0	N/A	0	N/A
Emergency caesarean	0	N/A	0	N/A
Case series studies				
Maternal age (years), mean	5	32.4 (31.1,33.7)		
Gestational age (weeks), mean	5	36.9 (32.3,41.5)		
Hypertensive diseases				
Chronic hypertension	1	5.0 (0.0, 20.2)		
Gestational hypertension	1	0.0 (0.0 , 0.4)		
Diabetes	3	16.6 (0.4, 43.4)		
Preeclampsia	3	9.9 (1.0, 23.6)		
Trimester of pregnancy				
First trimester[b]	5	0.0 (0.0, 3.4)		
Second trimester[c]	5	4.6 (0.0, 21.0)		
Third trimester[d]	5	95.4 (79.0, 100.0)		
Mode of delivery				
Vaginal	4	69.2 (52.8, 83.8)		
Elective caesarean	0			
Emergency caesarean	2	23.9 (4.4, 49.8)		

[a]Number of studies that captured a particular variable
[b]Conception to 12 weeks
[c]Week 13 to 27
[d]Week 28 to birth

30.8%) vs 3.9% (1.7%, 6.9%)], gestational hypertension [6.0% (0.8%, 14.7%) vs 2.0% (0.0%, 8.4%)] and preeclampsia [9.7% (6.5%, 13.3%) vs 6.9% (0.6%, 18.4%)] was also increased, relative to the SARS-CoV-2 negative cohorts. The overwhelming majority of women were in their final trimester of pregnancy and delivered vaginally (Table 2).

Overall, the percentage of symptomatic cases on admission ranged from 13% to 81.8%, similar to the percent range of asymptomatic cases (9.1% to 80%), indicating that mothers may have been asymptomatic initially and then tested positive during pregnancy or presented with common, documented COVID-19 symptoms (cough, fever, myalgia, difficulty breathing, chest pain) upon admission. For data available in SARS-CoV-2 positive women (N=593), there were 52 (8.8%) ICU admissions in women with severe COVID-19 or obstetric complications (preeclampsia, diabetes, preterm labour), 22 had pneumonia (3.7%), 5 women had hypoxia (0.8%), and there were 25 cases of severe or critical COVID-19 illness (4.2%). No maternal deaths were reported.

Primary endpoints: Placental Pathology Syndromes

Table 3 provides a detailed overview of the distribution of placental pathologies. Briefly, prevalent syndromes documented across all study designs included any feature of MVM or FVM, chronic inflammation, and acute or chronic chorioamnionitis, among SARS-CoV-2 positive and negative pregnant women. In case controls, prevalence of retroplacental hematoma, MVM and FVM diagnosis, and placental villous edema was higher in positive pregnant women than controls. Apart from edema, the same findings were reported in cohort studies. In general, there is no indication that placental weight was lower (<10th Percentile) or higher (>90th Percentile) in SARS-CoV-2 positive women compared to negative (Table 3).

Secondary endpoints: Perinatal outcomes

Table 4 succinctly demonstrates the clinical endpoints of interest. Overall, SARS-CoV-2 positive pregnant women gave birth to more SGA babies than negative pregnant women in case control and cohort studies. Interestingly, the percent of LGA babies was higher among SARS-CoV-2 negative controls than cases. Percentages of prematurity, abortion, and stillbirth were relatively similar in case control and cohort studies. Despite this, a high percent of stillbirth was documented in case series studies with SARS-CoV-2 [76.9% (95% CI (13.1%, 100.0%)] but was not evident in cohort and case control studies (Table 4).

The aim of this systematic review was to identify and quantify any differences in placental pathologies and clinical endpoints in pregnant women who test positive for SARS-CoV-2 versus pregnant women without SARS-CoV-2. Along with the structured review by Sharps et al 2020 [58], our study is one of the first, current reviews of its kind to comprehensively quantify placental pathologies, including any individual feature of MVM and FVM, via the structured and detailed assessment of the Amsterdam Consensus. Previous systematic reviews have either investigated pathologies from SARS-CoV-2 positive biopsies from other parts of the body, including the lungs, liver, and skin [59,60], or provide only a general overview of the placental abnormalities examined [61]. Our systematic review aligns with findings reported in Sharps et al 2020, where 35.5% of cases had evidence of FVM, 46% of MVM, and details of chronic inflammation ranged between 5.3% to 8.7% of cases, in their study [58].

Interestingly, only one of our included studies documented the rare association of diffuse synctiotrophoblast necrosis with histiocytic intervillositis in 5 stillborn, and liveborn infants, who acquired SARS-CoV-2 infection before delivery [62]. These findings suggest potential of placental fetal infection [62], which are echoed in case reports [63-66], or recently published communications [67,68]. However, the true prevalence of trophoblast necrosis with histiocytic intervillositis may be underreported, since we excluded case reports in our review and more literature has been generated since the end date of our capture period.

A systematic review conducted by Peiris et al determined that 11/19 (57.9%) of SARS-CoV-2 placentas showed microthrombi and 1 (5.3%) inflammation [59]. Further, AbdelMassih et al showed evidence of placental infarction and vascular villi compromise in 64% of SARS-CoV-2 positive placentas [61]. Thrombotic tendency in villous apparatus was evident, as well as multiple organizing intervillous hemorrhage/thrombi/avascular villi/fibrosis [61]. Lastly, Polak et al. [60], cited inflammatory infiltrates in the placenta [24], while three other women had no placental abnormalities [26].

Interestingly, our review shows that the percentage of MVM is similar between cases and controls. We do know that maternal hypertensive diseases of pregnancy can predispose pregnant women to severe COVID-19 [7,10,11]. Since the percentage of chronic hypertension, gestational hypertension, and preeclampsia was higher relative to SARS-CoV-2 negative cohorts, MVM placental changes may not be driven by COVID-19 itself. Rather, maternal risk factors might elevate the risk of developing severe COVID-19. MVM features are usually seen in women with hypertensive diseases of pregnancy [69,70], or coincident infarctions [71,72]. Therefore, the presence of MVM in SARS-CoV-2 cases could be driven by maternal risk factors or thrombi deposition in response to the virus [73–75]. Baud et al described focal perivillous fibrin and syncytial knots as features of MVM in SARS-CoV-2 pregnant women [24], but other authors argue that these findings are more due to intrauterine fetal demise [54], or features of a coagulopathic process [25], rather than SARS-CoV-2.

Our review noted greater percentage of FVM in SARS-CoV-2 pregnant women than controls. This finding suggests that FVM is distinctly different in its distribution between the two groups. Coagulopathy and inflammation has been reported in the lung, heart, and kidney of COVID-19 patients [35,76-78]. As such, SARS-CoV-2 may induce FVM pathology due to changes in coagulopathy leading to microthrombi and/or avascular villi in the fetal vessels. In COVID-19 placentas, most FVM lesions showed global distribution, which could suggest partial obstruction in umbilical blood flow [35]. Hence, endothelial damage in COVID-19 placental cases could represent varying blood flow to the fetus [35].

Despite our findings, studies show similar prevalence of chronic inflammation in both groups [31,52,54]. Chronic inflammatory pathologies are typically expected with Ribonucleic

Table 3: Placental pathologies in SARS-CoV-2 positive versus SARS-CoV-2 negative pregnant women.

Pathologies	Number of studies for positive women[a]	SARS-CoV-2 positive pregnant women (Percentage, 95% CI)	Number of studies for negative women	SARS-CoV-2 negative pregnant women (Percentage, 95% CI)
Case control studies				
Placental weight				
Small placental weight (<10th percentile)	4	30.5 (7.9, 59.0)	0	
Appropriate placental weight (10-90th percentile)	4	39.2 (14.6, 66.7)	0	
Large placental weight (>90th percentile)	4	5.6 (0.2, 15.1)	0	
Placental pathologies				
Retroplacental hematoma or placental abruption	3	5.4 (0.9, 12.4)	5	2.2 (0.9, 4.0)
Maternal vascular malperfusion (MVM)[b]	5	43.3 (22.7, 65.0)	9	33.2 (21.0, 46.6)
Diagnosis of MVM[c]	5	15.9 (5.6, 29.3)	5	9.3 (1.5, 21.4)
Fetal vascular malperfusion (FVM)[b]	7	41.5 (18.5, 66.4)	11	19.6 (5.5, 38.6)
Diagnosis of FVM[c]	6	15.9 (2.1, 36.5)	6	2.7 (0.2, 6.9)
Chronic plasma cell deciduitis	4	12.3 (4.9, 21.7)	4	12.4 (4.2, 23.4)
Chronic villitis	6	9.0 (2.8, 17.6)	7	9.9 (5.5, 15.3)
Chronic inflammation[d]	4	13.7 (6.0, 23.5)	7	21.9 (12.4, 33.1)
Acute chorioamnionitis[e]	3	14.2 (2.0, 32.4)	2	14.2 (2.0, 32.4)
Chronic chorioamnionitis	0		0	
Undifferentiated chorioamnionitis	1	64.9 (53.6, 75.4)	1	65.9 (60.3, 71.2)
Placental villous edema	3	13.8 (5.3, 24.9)	2	7.5 (7.1, 7.9)
Normal pathology	1	6.7 (0.0, 26.4)	0	
Cohort studies				
Placental weight				
Small placental weight (<10th percentile)	2	10.8 (5.8, 17.0)	2	16.1 (9.5, 24.0)
Appropriate placental weight (10-90th percentile)	2	85.6 (75.0, 93.8)	2	76.5 (67.8, 84.2)
Large placental weight (>90th percentile)	2	3.0 (0.0, 9.1)	2	7.5 (3.0, 13.5)
Placental pathologies				
Retroplacental hematoma or placental abruption	3	6.5 (0.0, 31.2)	3	3.7 (0.0, 16.5)
Maternal vascular malperfusion (MVM)[b]	3	27.0 (11.8, 45.4)	2	25.2 (13.8, 38.7)
Diagnosis of MVM[c]	2	8.4 (0.0, 50.8)	2	13.6 (0.0, 51.5)
Fetal vascular malperfusion (FVM)[b]	3	31.2 (17.2, 47.2)	2	7.6 (1.9, 16.5)
Diagnosis of FVM[c]	3	25.5 (7.6, 48.9)	3	7.8 (2.2, 15.9)
Chronic plasma cell deciduitis	2	10.4 (0.0, 34.7)	0	
Chronic villitis	4	12.5 (1.3, 31.4)	3	3.6 (0.0, 14.0)
Chronic inflammation[d]	2	37.9 (12.4, 67.7)	1	7.5 (1.9, 15.9)
Acute chorioamnionitis[e]	2	23.6 (16.5, 31.5)	2	17.9 (11.0, 25.9)
Chronic chorioamnionitis	2	1.1 (0.0, 5.0)	0	
Undifferentiated chorioamnionitis	1	6.9 (0.1, 19.7)	1	6.6 (2.5, 12.2)
Placental villous edema	1	5.9 (2.9, 9.8)	0	
Normal pathology	3	32.2 (1.3, 77.5)	2	72.1 (26.0, 99.7)
Case series studies				
Placental weight				
Small placental weight (<10th percentile)	2	14.7 (0.0, 57.8)		
Appropriate placental weight (10-90th percentile)	2	64.7 (36.1, 89.3)		

Large placental weight (>90th percentile)	2	13.6 (0.0, 39.3)	
Placental pathologies			
Retroplacental hematoma or placental abruption	2	0.0 (0.0, 5.9)	
Maternal vascular malperfusion (MVM)[b]	4	35.1 (4.7, 73.2)	
Diagnosis of MVM[c]	4	21.4 (7.5, 38.8)	
Fetal vascular malperfusion (FVM)[b]	4	34.8 (13.3, 59.4)	
Diagnosis of FVM[c]	4	17.8 (6.1, 32.8)	
Chronic plasma cell deciduitis	2	40.0 (9.7, 74.1)	
Chronic villitis	3	25.0 (9.3, 43.9)	
Chronic inflammation[d]	3	47.8 (10.0, 86.8)	
Acute chorioamnionitis[e]	2	51.5 (0.0, 100.0)	
Chronic chorioamnionitis	0		
Undifferentiated chorioamnionitis	1	20.0 (0.0, 67.5)	
Placental villous edema	1	0.0 (0.0, 31.7)	
Normal pathology	1	0.0 (0.0, 15.1)	

[a]Number of studies that captured a particular variable
[b]Any individual feature
[c]Using Amsterdam Consensus guidelines or advice from co-investigator and pediatric pathologist (DD)
[d]If study did not report indicators of chronic inflammation separately, the frequency of pregnant women with chronic deciduitis and villitis were reported together
[e]Includes stage 1 and 2 of chorionitis (mild acute chorioamnionitis)

Table 4: Adverse perinatal outcomes.

Perinatal outcome	Number of studies positive women[a]	SARS-CoV-2 positive pregnant women (Percentage, 95% CI)	Number of studies negative women	SARS-CoV-2 negative pregnant women (Percentage, 95% CI)
Case control studies				
Small-for-gestational age (SGA)[b]	2	50.9 (19.6, 81.8)	2	32.4 (18.7, 47.8)
Large-for-gestational age (LGA)[c]	2	1.5 (0.0, 12.5)	2	7.3 (6.9, 7.7)
Preterm[d]	4	15.1 (8.2, 23.4)	3	12.7 (0.8, 32.9)
Abortion[e]	1	0.0 (0.0, 3.3)	1	0.0 (0.0, 6.8)
Stillbirth[f]	3	0.2 (0.0, 4.1)	3	1.6 (0.0, 5.8)
Cohort studies				
Small-for-gestational age (SGA)[b]	1	16.6 (11.6, 22.3)	1	10.0 (9.0, 11.1)
Large-for-gestational age (LGA)[c]	1	16.0 (11.1, 21.7)	0	
Preterm[d]	4	3.0 (0.0, 10.5)	2	3.3 (0.0, 18.0)
Abortion[e]	1	3.2 (1.1, 6.3)	1	3.0 (2.4, 3.6)
Stillbirth[f]	1	0.0 (0.0, 0.4)	2	0.4 (0.2, 0.7)
Case series studies				
Small-for-gestational age (SGA)[b]	3	11.3 (0.9, 27.7)		
Large-for-gestational age (LGA)[c]	2	6.6 (0.0, 36.0)		
Preterm[d]	2	2.2 (0.0, 15.1)		
Abortion[e]	0			
Stillbirth[f]	2	76.9 (13.1, 100.0)		

[a]Number of studies that captured a particular variable
[b]Small-for-gestational age (SGA) defined as birth weight < 10th percentile
[c]Large-for-gestational age (LGA) defined as birth weight > 10th percentile
[d]Preterm defined as 34 weeks or less gestation
[e]Abortion occurring at 24 weeks or less of pregnancy
[f]Stillbirth defined as mortality after 24 weeks of pregnancy

acid (RNA) viruses [54,79]. Regression results indicate that the risk of chronic villitis of unknown etiology (VUE) varies seasonally; in fact the risk of VUE is 16% to 17% higher in the fall and winter versus summer (fall relative risk [RR]: 1.17, 95% CI (1.06, 1.29); winter RR: 1.16, 95% CI (1.05, 1.29)] [80]. Although chronic inflammation may manifest because of the SARS-CoV-2 virus, seasonality might also contribute to causing infection or loss of organism tolerance [31]. Therefore, chronic inflammation may be similar between cases and controls, partly due to seasonal variations, not only because of SARS-CoV-2. Case reports have identified chronic inflammatory processes, including histiocytic intervillositis [25,29,30]. Two cases had massive intervillous fibrin deposition with mixed intervillositis and villitis, and prominent neutrophil and lymphocyte infiltration [49]. Chronic villitis has been described in placentitis due to STORCH (Syphilis, Toxoplasmosis, Other Agents, Rubella, Cytomegalovirus, and Herpes Simplex), and other viral infections, indicating heightened maternal immune response [31,32]. The presence of VUE in healthy patients without SARS-CoV-2 might be explained by its development as sequelae after harboring the virus, in healthy patients with normal placental weights in the third trimester [35]. Authors suspect that the presence of chronic villitis might be a direct or indirect effect of viral infection, from a heightened systemic immune response (i.e., cytokine storm) characteristic of other respiratory viral infections [81].

Results from this review demonstrate that having an SGA baby is more prevalent in SARS-CoV-2 positive pregnant women than negative pregnant women. Percentages of prematurity, abortion, and stillbirth remained unchanged between SARS-CoV-2 positive versus negative pregnant women. These findings are in contrast with a previous systematic review, showing higher preterm birth rate in pregnant women with COVID-19 (15.9%), than uninfected women (6.1%) [82]. However, caution should be exercised when generalizing these findings, since the sample size from this review were small, included only case series, and preprints were not peer reviewed [83]. Although we did not explicitly measure intrauterine fetal demise (<23 weeks), previous literature of SARS-CoV-2 deliveries often show low-stage inflammation and negative bacteria, without showing mildly increased perivillous fibrin and acute subchorionitis /acute chorioamnionitis [84,85].

Overall, many of the studies included in this review differed by ascertainment of placental changes, sample size, and whether results were adjusted for known confounders. There is a potential for misclassification bias when we extracted chorioamnionitis, if authors did not explicitly differentiate acute versus chronic. There is also possible overlap of cases, since three studies included data from New York Presbyterian Hospital [32,50,52], and two collected data from the University of Brescia, Italy during similar periods [51,56] , which may inflate the placental pathologies observed. There is also wide variability in the number of and minimal individual features needed for a diagnosis of MVM [51], making it difficult to discern if authors across studies followed the Amsterdam Criteria consistently. Further exacerbating this difficulty is the lack of standardized definitions for control groups. Certain studies did not have comparable control groups [31,54], which further limits the placental pathology findings among controls who test negative for SARS-CoV-2 during the pandemic period, historical controls, or pregnant women with underlying issues such as melanoma and hypoxic ischemic encephalopathy.

We did not exclusively examine the relationship between COVID-19 severity to pregnancy outcomes, yet we did collect adverse maternal outcomes like ICU admission, pneumonia, and mortality, when COVID-19 severity (severe or critical) was reported. A statistical investigation into the percentage of pregnant women with hypertensive diseases of pregnancy and certain placental findings, like MVM or FVM, was also not performed. However, we did capture important differences in the distribution of hypertensive diseases vs placental findings between SARS-CoV-2 positive and negative women, to describe this relationship narratively.

CONCLUSIONS

Results from the sixteen studies included in our review suggest that there are differences in placental pathologies between SARS-CoV-2 positive versus negative pregnant women during the first and second waves of the pandemic, although we were unable to test for statistical differences to validate this claim. Notably, percent of any individual feature of MVM, FVM, and chronic inflammation appeared slightly higher in cases than controls. Presence of SARS-CoV-2 RNA in placentas is rare [48]. Importantly, no significant placental histopathologic changes were reported after the diagnosis of SARS-CoV-2 in women in their final trimester of pregnancy, versus a gestational-age matched historical control group [37].

In the future, there is a need for high caliber evidence (with robust sample sizes, adequate blinding, statistical adjustment for known confounders, and identical control populations) to determine if any conclusive link exists between SARS-CoV-2 and the development of placental pathologies in pregnant women. Future studies can explore placental pathologies during different phases of the pandemic, including among vaccinated vs. unvaccinated pregnant women, to consider the potential role of the delta or omicron variants on placental pathology. Moreover, future studies can investigate changes in placental pathologies in the first vs. second and third trimester, different modes of possible transmission, or the possible impact of maternal stress precipitating adverse, perinatal outcomes. Acute vs. chronic placental phenotypic pathologies in relation to SARS-CoV-2 pregnancies, is warranted. Specifically, we could examine correlations to different SARS-CoV-2 variants and placental findings, in the context of maternal infection relative to delivery.

AUTHOR CONTRIBUTIONS

All Authors accept responsibility for the entirety of this manuscript and approve its submission.

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