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Article

COVID-19 Disease during Pregnancy. Gestational Duration and Fetal Weight: Two Understudied Adverse Outcomes

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Abstract: (1) Background: to find out how COVID-19 infection during pregnancy affects the outcome of the pregnancy; (2) Methods: 166 SARS-CoV-2-positive pregnant women formed the study group. 128 SARS-CoV-2-negative pregnant women formed the control group. Anatomopathological study of the placenta was performed in all cases; (3) Results: Placental insufficiency appeared in 38 patients (22.9%) of the study group and in 17 patients (13.2%) in the control group ($p=0.016$). Villitis appeared in 50 patients (30.1%) of the study group and in 16 (12.6%) in the control group ($p=0.000$). 166 COVID-19 positive patients were further subdivided, into those with anatomopathological affection of the placenta, and those without. When gestational age between patients with placental insufficiency and those without it are compared, a difference of 4.38 days is obtained ($p=0.0393$). If we compare neonatal weight between patients with placental insufficiency and those without it, a difference of 406.4 grams is obtained ($p=0.0000$). When gestational age between patients with villitis and those without it are compared, a difference of 3.2 days is found ($p=0.0919$). When neonatal weight between patients with villitis and those without it are compared, a difference of 242.2 grams is obtained ($p=0.0018$). (4) Conclusions: COVID-19 infection during pregnancy may produce lower fetal weight and shorter gestational length.

Keywords: COVID-19; pregnancy; placental insufficiency; villitis; fetal weight; pregnancy length

1. Introduction

Viral infections during pregnancy have long been considered low risk. However, the importance of understanding their role becomes more relevant as data shows that viral infections, especially respiratory viruses, can significantly alter the prognosis of both mother and foetus [1]. Pandemics like influenza, Ebola, and the recent epidemics of coronaviruses (SARS-CoV, MERS, and SARS-CoV-2) demonstrate that pregnant women suffer worse consequences (ARDS, maternal death, thromboembolism) than the general population and non-pregnant women [2,3].

The impact of SARS-CoV-2 infection and its associated disease, COVID-19, on fetuses is of particular interest [4], with limited publications on the impact of its infection on pregnancy itself and the foetuses [5].

It is well-established that adverse pregnancy outcomes are related to bacterial infections, such as chorioamnionitis and pyelonephritis [6]. In contrast, viral infections are generally considered benign, with a few exceptions. Clinically, pregnant women with a cold or an upper respiratory tract viral infection are treated symptomatically, and it is usually assumed that there are no harmful effects on pregnancy. However, there can be adverse pregnancy effects resulting from these infections. It has been proposed that viral infections of the placenta can lead to substantial changes in trophoblast physiology, which can alter the developmental progress of pregnancy, resulting in preterm birth and intrauterine growth restriction [7,8].

What is a viral infection of the placenta? The placenta has the ability to modulate the maternal immune system, interact with maternal blood vessels, and protect the foetus from additional infections. Viral infections modulate the trophoblast's ability to release increased levels of inflammatory mediators such as IL-6, G-CSF, and MCP-1 [9]. This new concept establishes that a viral infection in the placenta triggers an exaggerated immune response to bacteria due to increased sensitivity to viral infections, resulting from changes in the modulatory role of the trophoblast's immune system [10]. Clinical evidence outlining the relationship between viral infections and adverse perinatal outcomes emphasizes that, although the virus itself may not be harmful, it can put the pregnancy at risk of complications like placental insufficiency (PI) and preterm birth [11].

Histopathological analysis of placental tissue can significantly contribute to the study of maternal and foetal health. A variety of foetal infections during pregnancy are associated with specific placental findings, including lymphoplasmacytic villitis with elongated villi and intravillous hemosiderin deposits. While there are no specific placental findings associated with the most common coronaviruses, Ng et al. reported placental pathology in 7 women with SARS infection in Hong Kong [12]. Since SARS-CoV-2 is a virus, it is expected to provoke inflammation. Chronic inflammatory pathology, particularly chronic villitis, can be directly caused by some viral diseases.

In this paper, how SARS-CoV-2 infection affects pregnant women is analysed regarding two common obstetric syndromes, which are PI and preterm birth.

The objective is to determine if there is a higher rate of PI and villitis in women infected with SARS-CoV-2, (study group) compared to uninfected women (control group) and compare gestational age and birth weight in the study group (COVID-19 positive) related to different placental findings: villitis, PI, and none.

The hypothesis of the study is: in women infected with the SARS-CoV-2 virus, both gestational age (in days) at birth and birth weight (in grams) are lower if there is placental compromise.

2. Materials and Methods

This is a prospective cohort study conducted on pregnant women tested for COVID-19 infection during the pregnancy. PCR COVID-19 test was performed prospectively along the pregnancy in the first, second and third trimester of the pregnancy. The study group was formed with patients with a positive PCR for SARS-CoV-2 test (166 patients) and the control group was formed with patients with a negative PCR for SARS-CoV-2 test (128 patients). The presence of anatomopathological alterations of the placenta (PI or villitis) is studied.

The second part of the study was limited to those patients with positive PCR COVID-19 test (166 patients). We aim to compare patients with anatomopathological alterations of the placenta with those that do not have placental alterations, despite a positive test. Outcome of the pregnancy, related to gestational length and weight of the newborn were compared between the groups to assess if the presence of pathological alterations on the placenta implies clinical effect in the outcome of the pregnancy, namely days of length of the pregnancy and weight of newborn.

PI is defined as three or more of the following: decidual arteriopathy including atherosclerosis and fibrinoid necrosis, as well as mural hypertrophy of arteriolar membranes with syncytial nodules, accelerated villous maturation, and intervillous fibrin accumulation, which are findings defined in pathological reports as PI [13].

Chronic villitis is defined as an increase in stromal cellularity in terminal villi at the expense of mononuclear inflammatory cells (lymphocytes, plasma cells, and histiocytes), without granulomatous component or neutrophilic or plasmacytic involvement, in which inflammatory cellularity that partially destroys villi extends to the intervillous space and adjacent villi [13].

Statistical Analysis

Mean and standard deviation for numerical variables is presented once normality assumptions have been evaluated. Categorical variables are represented by absolute and relative frequencies.

To assess differences between the COVID-19 and non-COVID-19 mothers the *t*-Student test has been employed. To contrast differences in the study group and the presence or absence of placental

abnormalities, regarding gestational age and neonatal birth weight, the Pearson’s X^2 test has been used.

The significance level has been set at 0.05. The statistical package used was Stata/IC v16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.).

3. Results

The study group consists of 166 pregnant women with a positive PCR for SARS-CoV-2 at some point during pregnancy who delivered at our hospital and for whom we have a placental histopathological report. Express permission was obtained from these patients. Recruitment started in the third week of March 2020 and ended in September of the same year. The control group was formed by 128 pregnant women who had pregnancy follow up and delivery at our hospital during the same period, with a negative PCR for SARS-CoV-2 and for whom we have placental pathological reports. Patients were included from the third week of March 2020 to December of the same year (Table 1).

Table 1. Clinical characteristics.

Characteristic (SARS-CoV-2)	Negative (N=128)	Positive (N=166)	p
Age (years)	33,9 (5,4)	31,6 (5,6)	NS
Weight gain (Kg)	11,2 (9,1-13,2)	10,2 (8,7-11)	NS
Parity (median, range)	2 (1-3)	3 (2-4)	NS

When the presence of PI between the study group and the control group are compared, PI is present in 38 women (22.9%) in the COVID-19 group and 17 (13.2%) in the control group, with a p-value of 0.016 (Table 2).

Table 1. Clinical characteristics.

Characteristic (SARS-CoV-2)	Negative (N=128)	Positive (N=166)	p
Age (years)	33,9 (5,4)	31,6 (5,6)	NS
Weight gain (Kg)	11,2 (9,1-13,2)	10,2 (8,7-11)	NS
Parity (median, range)	2 (1-3)	3 (2-4)	NS

When the presence of villitis between the study group and the control group are compared, villitis is present in 50 women (30.1%) in the COVID-19 group and 16 (12.6%) in the control group, with a p-value of 0.000 (Table 2).

Table 2. Statistical analysis between groups and presence of placental abnormalities.

PI	COVID group	Control group	Total	OR	95% CI	p
normal						
PI between study group and control group.						
Normal	128 (77.1%)	111 (85.9%)	239 (81.3%)	0.47	0,25-0,88	0.016
PI	38 (22.9%)	17 (13.2%)	55 (18.7%)			
Total	166 (100%)	128 (100%)	294 (100%)			
Presence of villitis between the study group and the control group						
Normal	116 (69.88%)	112 (87.40%)	228 (77.5%)	0.33	0,17-0,62	0.000
Villitis	50 (30.1%)	16 (12.6%)	66 (22.5%)			
Total	166 (100%)	128 (100%)	294 (100%)			

Abbreviations: OR: Odds Ratio; 95% CI: 95% confidence interval; PI: placental insufficiency.

When gestational age between patients with PI and those without it are compared, a difference of 4.38 days (95% CI 0.22-8.55) is obtained (p=0.0393). This means that among all COVID-19-positive patients, those with PI give birth 4.4 days earlier than those without it (Table 3).

Table 3. Correlation between the presence of placental abnormalities (PI and villitis) and adverse pregnancy outcome (gestational age and neonatal birth weight).

Pregnancy length (days) in COVID-19 positive patients, related to PI					
Group	N	Mean	Std. Dv.	95% CI	p
Normal	128	276.54	10.4035	274. 63 -278.56	0.0393
PI	38	272.16	13.659	267.66-276.64	
Combined	166	275.46	11.4047	273.64-277.27	
Diff		4.38		0.2186-8.5517	
Weight of newborns (grams) in COVID-19 positive patients, related to PI					
Group	N	Mean	Std. Dv.	95% CI	p
Normal	128	3359.32	445.604	3277.37-3441.28	0
PI	38	2952.95	399.803	2821.53-3084.36	
Combined	166	3259.05	467.757	3184.58-3333.52	
Diff		406.4		245.77-566.98	
Pregnancy length (days) in COVID-19 positive patients, related to the presence of villitis					
Group	N	Mean	Std. Dv.	95% CI	p
Normal	116	276.54	10.4035	274.63-278.45	0.0919
Villitis	50	273.34	12.7801	269.71-276.97	
Combined	166	275.57	11.2299	273.85-277.29	
Diff		3.2		-0.52-6.93	
Weight of newborns (grams) in COVID-19 positive patients, related to the presence of villitis					
Group	N	Mean	Std. Dv.	95% CI	p
Normal	116	3359.33	445.604	445.60-3277.37	0.0018
Villits	50	3117.16	466.698	2984.52-3249.79	
Combined	166	3286.39	464.212	3215.24-3357.52	
Diff		242.2		91.17-393.15	

Abbreviations: N: number of patients; Std. Dv: standard deviation.; 95% CI: 95% confidence interval; PI: placental insufficiency; Diff: difference.

When neonatal weight (in grams) between patients with PI and those without it are compared, a difference of 406.4 grams (95% CI 245.77-566.98) is obtained (p=0.0000). This means that among all COVID-19-positive patients, those who develop PI have new-borns whose weight is 406.4 grams less than those who do not have it (Table 3).

When gestational age between patients with villitis and those without it are compared, a difference of 3.21 days (95% CI -0.53-6.93) is found (p=0.0919). This means that among all COVID-19-positive patients, those with villitis give birth 3.2 days earlier than those without it (Table 3).

When neonatal weight between patients with villitis and those without it are compared, a difference of 242.2 grams (95% CI 91.17-393.16) is obtained (p=0.0018). This means that among all COVID-19-positive patients, those who develop villitis have neonates whose weight is 242.16 grams less than those who do not have it (Table 3).

4. Discussion

Our results show how the presence of placental affection (PI or villitis) in 22.9% of our patients is higher in patients with COVID-19 positive test than in the COVID-19 negative group in which the frequency of alterations was 13.2%, a statistically significant difference.

PI has been associated with preeclampsia, oligohydramnios, foetal growth restriction, preterm birth, and foetal death [14,15]. Wei et al [16] in a meta-analysis including 438,548 pregnant women conclude that compared with no SARS-CoV-2 infection in pregnancy, COVID-19 was associated with preeclampsia (OR 1.33, 95% CI 1.03 to 1.73), preterm birth (OR 1.82, 95% CI 1.38 to 2.39) and stillbirth (OR 2.11, 95% CI 1.14 to 3.90). Compared with mild COVID-19, severe COVID-19 was strongly associated with preeclampsia (OR 4.16, 95% CI 1.55 to 11.15), preterm birth (OR 4.29, 95% CI 2.41 to 7.63), 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).

In a recent meta-analysis by Smith et al [17], pregnant women with SARS-CoV-2 infection, compared with uninfected pregnant women, were at significantly increased risk of maternal morbidity and neonates born to women with SARS-CoV-2 infection were more likely to be admitted to a neonatal care unit after birth, be born preterm and to be born low birth weight.

Conde-Agudelo et al [18], including 15,524 pregnant women diagnosed with SARS-CoV-2 infection found that the odds of developing preeclampsia were significantly higher among pregnant women with SARS-CoV-2 infection than among those without SARS-CoV-2 infection (7.0% vs 4.8%; pooled odds ratio, 1.62; 95% confidence interval, 1.45-1.82; $P < .00001$; $I^2 = 17\%$; 26 studies; 95% prediction interval of the odds ratio, 1.28-2.05).

Our results are consistent with these studies. Our 38 patients with PI in placental histology were further compared with the 128 COVID-19 positive patients without PI. Related to newborn weight, a significant difference of 406.4 grams in the newborn weight was found. This means that among all COVID-19 positive patients, those who develop PI have new-borns whose weight is 406.4 grams less than those who do not have it. Similarly, related to pregnancy length, a significant difference of 4.4 days is found. This means that among all COVID-19-positive patients, those with PI give birth 4.4 days earlier than those without it.

The most significant pathophysiological phenomenon in PI is chronic vasoconstriction of tertiary villi due to inadequate trophoblastic invasion by maternal spiral arteries [19]. The potential mechanism to explain these clinical observations may be attributed to the virus's effect on the trophoblast, leading to suboptimal trophoblastic invasion.

In normal placentation, the intermediate trophoblast that infiltrates the decidua and myometrium at the implantation site is responsible for physiological structural modifications in spiral arteries, essential for increasing blood flow to the placenta. During a normal pregnancy, cytotrophoblastic invasion physiologically transforms the uterine spiral arteries, turning small, high-resistance vessels into large, low-resistance vessels that perfuse the chorionic villi of the placenta. When physiological changes do not progress adequately, the smooth muscle of the arterial medial layer persists, the lumen does not expand, and uteroplacental flow is low. Spiral arteries develop a distinctive lesion, acute atherosclerosis, characterized by eosinophilic necrosis and the presence of lipid-laden cells in the vascular wall. Vascular lumens narrow or occlude completely [20]. Subsequent PI causes a reduction in placental and foetal growth. In more advanced cases, accelerated villous maturation occurs [21].

Although these placental histopathological changes do not occur in all patients, suboptimal foetal growth due to PI is plausible because maternal COVID-19 infection has been associated with PI. These problems could be caused by COVID-19-associated coagulopathy, placental hypoxia during maternal acute illness, viral infection of the placenta, or, more likely, a combination of these factors [22].

The immune effects of interactions between different microorganisms can lead to adverse perinatal outcomes such as preterm birth. Rates of preterm birth are increased. Symptomatic patients have a threefold increase in preterm birth compared to asymptomatic ones (23% versus 8%).

Rates of low-birth-weight infants (8.7% vs. 7.4%; $p = 0.03$) and spontaneous preterm deliveries (2.6% vs. 1.7%; $p = 0.01$), particularly spontaneous moderate-to-late preterm delivery (32-36 weeks) (1.9% vs. 1.2%; $p = 0.01$) were significantly higher during COVID-19 [23].

The meta-analysis suggested that reporting data from 3158 pregnancies: with 1900 symptomatic and 1258 asymptomatic pregnant women. The odds of preterm birth (< 37 weeks) (OR:2.10;95%CI:1.04 to 4.23) was higher amongst symptomatic pregnant women [24].

Among 6012 pregnant individuals with SARS-CoV-2, the risk of preterm birth was significantly elevated among SARS-CoV-2-affected pregnancies (11.05% vs 6.76%; relative risk, 1.63 [95% CI, 1.52-1.76]), even in cases of milder disease not requiring hospitalization, compared with unaffected pregnancies during the same time period [25].

In our study, the 50 patients with villitis in placental histology were further compared with the 116 COVID-19 positive patients without villitis. Related to newborn weight, a significant difference of 242.2 grams in the newborn weight was found. This means that among all COVID-19 positive patients, those who develop villitis have new-borns whose weight is 242 grams less than those who do not have it. Similarly, related to pregnancy length, a significant difference of 3.2 days is found. This means that among all COVID-19-positive patients, those with villitis give birth 3.2 days earlier than those without it.

Romero et al. [26] suggest a polymicrobial aetiology. They propose that viral infection of the placenta during pregnancy can affect the normal interaction with local bacteria, leading to a proinflammatory cytokine storm that results in preterm birth, showing how a viral infection during pregnancy can lead to an exaggerated response to a low bacterial insult, resulting in preterm birth.

Given that placentas of women with SARS-CoV-2 show reproducible histopathological abnormalities, this suggests that women with COVID-19 require closer gestational monitoring. These findings suggest that increased monitoring is necessary for pregnant women infected with SARS-CoV-2. Updated recommendations are currently available for the obstetric management of SARS-CoV-2 in pregnant women [27,28].

Based in other studies [29], we hypothesized that PI was more frequent when infection occurred during the second trimester, in the process of placentation and that villitis was more frequent when infection occurred during the third trimester affecting the contractility and producing shorter pregnancy length. We tried to detect differences concerning the trimester in which the infection occurred but, unfortunately, when segmentation was performed, the results were not interpretable.

In the PCR analysis of our placentas, there were no positive cases, which corroborates the existing evidence that vertical transmission of the virus is very infrequent and suggests that placental changes, if caused by COVID-19, are related to maternal infection and inflammation rather than foetal infection.

5. Conclusions

Placentas of women infected with SARS-CoV-2 have higher rates of PI and villitis.

Author Contributions: T.P.-M. designed the project; A.G.M., P.CH., F.G.-B. investigation and data curation. T.P.-M. and A.R. analyzed the data; M.G.C. and A.P. wrote the manuscript draft; T.P.-M. and A.P. revised and prepared the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Medical Ethics Committee of Puerta de Hierro University Hospital in Madrid, Spain (approval code: PI_78/20, approved on 14 April 2020).

Conflicts of Interest: The authors declare no conflict of interest.

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