



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

Tirso Perez-Medina^{1,2*}, Fátima García-Benasach¹, Ana Royuela¹, Ana Gómez Manrique¹, Pilar Chaves¹, Augusto Pereira¹

¹Department of Obstetrics and Gynecology, University Hospital Puerta de Hierro Majadahonda, Madrid, Spain; ²Department of Obstetrics and Gynecology, Autonomous University of Madrid, Madrid, Spain

ABSTRACT

Background: To find out how COVID-19 infection during pregnancy affects the outcome of the pregnancy.

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.

Results: Placental insufficiency appeared in 38 patients (25%) 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 patients (12.2%) 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 4.852 days is obtained ($p=0.0393$). When neonatal weight between patients with placental insufficiency and those without it are compared, 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 3.203 days is found ($p=0.0919$). When neonatal weight between patients with villitis and those without it are compared, a difference of 242.16 grams is obtained ($p=0.0018$).

Conclusion: COVID-19 infection during pregnancy may produce lower fetal weight and preterm birth.

Keywords: COVID-19; Pregnancy; Placental insufficiency; Preterm birth; Intrauterine growth restriction

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 fetus [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, with limited publications on the impact of its infection on pregnancy itself and the fetuses [4,5].

It is well-established that adverse pregnancy outcomes are related to bacterial infections, such as chorioamnionitis [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 [7]. Additionally, the sequelae of a viral infection can lead to opportunistic infections that can also affect the pregnancy. It has been proposed that viral infections in pregnant women can lead to substantial changes in trophoblast physiology, which can alter the developmental progress of pregnancy, resulting in Preterm Birth (PTB) and intrauterine growth restriction [8,9].

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 fetus 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 [10]. This new concept establishes that a viral

Correspondence to: Tirso Perez-Medina, Department of Obstetrics and Gynecology, University Hospital Puerta de Hierro Majadahonda, Madrid, Spain, E-mail: tirso.perez@uam.es

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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 [11]. 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 preterm birth.

Histopathological analysis of placental tissue can significantly contribute to the study of maternal and fetal health. A variety of fetal infections during pregnancy are associated with specific placental findings, including lymphoplasmacytic villitis with elongated villi and intervillous 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 we present, we analyse how SARS-CoV-2 infection affects pregnant women regarding two common obstetric syndromes, which are Placental Insufficiency (PI) and Preterm Birth (PTB).

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.

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). Anatomopathological study of the placentas of both groups were compared to detect the presence or absence of pathological alterations of the placenta. The risk factor is a positive PCR for SARS-CoV-2, and the expected effect is the presence of PI or villitis.

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].

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, in spite of 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 maternal infection on the placenta implies clinical effect in the outcome of the pregnancy, namely days of length of the pregnancy and weight of newborn.

Statistical analysis

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

To assess differences between the COVID-19 and non-COVID-19 mothers in terms of gestational age and neonatal birth weight, the t-Student test has been employed. To contrast differences between the group and the presence of placental abnormalities, the Pearson's χ^2 test has been used.

Similarly, t-Student and χ^2 tests have been used to contrast these same variables in terms of the trimesters of pregnancy in which the SARS-CoV-2 infection occurred and mothers COVID-19 (-); and placental abnormalities with gestational age and neonatal birth weight.

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.).

RESULTS

The study group consists of 166 pregnant women with a positive PCR for SARS-CoV-2 at some point during pregnancy who deliver 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 comprises 128 pregnant women who had a 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 of study participants.

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

In addition to these findings, approximately 30% of patients with threat of premature birth have placental lesions consistent with PI, and a similar number show a failure in the physiological transformation of the myometrial segment of the spiral arteries, which has been defined as PI, as we have seen before.

When the presence of PI between the study group and the control group are compared, PI is present in 38 women (24%) in the COVID-19 group and 17 (14.2%) in the control group, with a p-value of 0.016.

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).

When gestational age between patients with placental insufficiency and those without it are compared, a difference of 4.852 days (SD: 2.1) (95% CI: 0.218-8.552) 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.

When neonatal weight (in grams) between patients with placental insufficiency and those without it are compared, a difference of 406.4 (95% CI: 245.77-566.981) 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.

When gestational age between patients with villitis and those without it are compared, a difference of 3.203 days (95% CI: -0.527-6.933) 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.

When neonatal weight between patients with villitis and those without it are compared, a difference of 242.16 grams (95% CI: 91.176-393.159) 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).

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

PI normal	COVID group	Control group	Total	OR	95% CI	p
PI between study group and control group						
Normal	116 (75.32%)	111 (86.72%)	227 (80.5%)	0.46752	0.249417-0.876345	0.016
PI	38 (24.68%)	17 (13.28%)	55 (19.5%)	-	-	-
Total	154 (100%)	128 (100%)	282 (100%)	-	-	-
Presence of villitis between the control group and the study group						
Normal	116 (69.88%)	111 (87.40%)	227 (77.47%)	0.334414	0.179861-0.621775	0
Villitis	50 (30.12%)	16 (12.60%)	66 (22.53%)	-	-	-
Total	166 (100%)	127 (100%)	293 (100%)	-	-	-

Note: OR: Odds Ratio; 95% CI: 95% Confidence Interval; PI: Placental Insufficiency.

Table 3: Correlation between gestational age and neonatal birth weight with presence of placental abnormalities.

Group	N	Mean	Std. Err.	Std. Dv.	95% CI	p
Pregnancy length (days) in COVID-19 positive patients, related to PI						
Normal	116	276.5431	0.965941	10.4035	274.6298-278.456	-
PI	38	272.1579	2.215787	13.65903	267.6683-276.6475	-
Combined	154	275.461	0.919017	11.4047	273.6454-277.2766	-
Diff	-	4.385209	2.108902	-	0.2186635-8.55174	0.0393
Weight of newborns (grams) in COVID-19 positive patients, related to PI						
Normal	116	3359.328	41.37328	445.6039	3277.375-3441.28	-
PI	38	2952.947	64.85655	399.8027	2821.536-3084.359	-
Combined	154	3259.052	37.69294	467.757	3184.586-3333.518	-
Diff	-	406.3802	-	81.28834	245.7793-566.9811	0
Pregnancy length (days) in COVID-19 positive patients, related to the presence of villitis						
Normal	116	276.5431	0.965941	10.4035	274.6298-278.4564	-

Villitis	50	273.34	1.807379	12.7801	269.7079-276.9721	-
Combined	166	275.5783	0.871614	11.22996	273.8574-277.2993	-
Diff	-	3.203103	1.889143	-	-7.46036	0.0919

Weight of newborns (grams) in COVID-19 positive patients, related to the presence of villitis

Normal	116	3359.328	41.37328	445.6039	445.6039-3277.375	-
Villitis	50	3117.16	66.001	466.6975	2984.526-3249.794	-
Combined	166	3286.386	36.02983	464.2119	3215.247-3357.524	-
Diff	-	242.1676	76.46937	-	91.17618-393.159	0.0018

Note: N: Number of Patients; Std. Err.; Standard Error; Std. Dv: Standard Deviation; 95% CI: 95% Confidence Interval; PI: Placental Insufficiency; Diff: Difference.

DISCUSSION

When studying our cases, increased rates of inflammatory placental response and intervillous thrombosis is found, suggesting a common theme of abnormal maternal circulation as an IP consequence. These findings provide a possible mechanism for the observed epidemiological associations between COVID-19 during pregnancy and adverse perinatal outcomes [14,15]. PI has been associated with oligohydramnios, fetal growth restriction, preterm birth, and fetal death. The most significant pathophysiological phenomenon in PI is chronic vasoconstriction of tertiary villi due to inadequate trophoblastic invasion by maternal spiral arteries.

In the PCR analysis of our placentas, there were no positives, which corroborates the existing evidence that vertical transmission of the virus is infrequent and suggests that placental changes, if caused by COVID-19, are related to maternal infection and inflammation rather than fetal infection. The spectrum of placental abnormalities is vast, and many anomalies are commonly seen through pathological examination for a variety of indications, which increases the need for appropriate controls. Collectively, these findings suggest that increased monitoring is necessary for pregnant women infected with SARS-CoV-2. Given that placentas of women with SARS-CoV-2 show reproducible histopathological abnormalities, this suggests that women with COVID-19 require closer gestational monitoring. Updated recommendations are currently available for the obstetric management of SARS-CoV-2 in pregnant women [16].

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 (IT) 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. In the early weeks of gestation, the intermediate trophoblast invades the spiral arteries' decidual segment, replacing the endothelium and the muscular and elastic tissue of the arterial's medial layer.

In normal conditions, maternal endothelium is replaced, and the medial layer of the arterial wall is destroyed to achieve marked vascular dilation. Between the 14th and 20th week, intravascular trophoblast extends from the decidual portion to the myometrial portion of the spiral arteries, which are also remodelled. 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. The remodelled spiral arteries in this process undergo progressive dilation, increasing blood flow from 100 ml/min to 500 ml/min in a full-term pregnancy [17].

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 relatively low. This incomplete physiological vascular remodelling of spiral arteries undoubtedly hinders uteroplacental flow, with abundant evidence that endothelial dysfunction is the common final pathway. 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 [18]. Subsequent PI causes a reduction in placental and fetal growth. In more advanced cases, accelerated villous maturation occurs. Additionally, areas of severe ischemia develop, leading to infarcts, which are areas of ischemic necrosis produced by the obstruction of blood flow in spiral arteries by thrombi. Acute atherosclerosis is a lesion limited to vessels that have not been remodelled in the normal adaptation process for implantation, specifically the myometrial segments of spiral arteries in the placental bed that have not had physiological adaptation [19].

This decreased uteroplacental flow and its effect on the placenta can be attributed to pathological abnormalities that occur in the spiral arteries at the implantation site. These arteries differ from normal ones in two ways- First, the normal adaptive physiological remodelling of placental vessels is reduced in degree and extent. The second wave of intravascular trophoblastic migration does not occur. Intramyometrial segments of spiral arteries retain their muscular layer and do not dilate. Therefore, normal vascular changes during pregnancy are incomplete. Furthermore, spiral arteries in women with PI have a characteristic arteriopathy, acute atherosclerosis, resulting in thrombosis and infarcts. As a consequence of this PI and subsequent placental insufficiency, there is theorizing about the possible development of Intrauterine Growth Restriction (IUGR). This theoretical problem has already been described with other SARS infections. However, there is very little specific COVID-19 data on fetal growth following maternal infection [20,21].

Although these placental histopathological changes do not occur in all patients, suboptimal fetal growth due to PI is plausible because maternal COVID-19 infection has been associated with PI, including acute and chronic intervillous inflammation, focal avascular villi, and thrombosis in large fetal vessels in the chorionic plate and stem villi [22]. These lesions 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 [23,24].

These data shed light on an area of pregnancy that was once considered pure and pristine: The maternal-fetal interface and the placenta. The immune effects of interactions between different microorganisms can lead to adverse perinatal outcomes such as preterm birth [25]. Armed with this new information about the microbial environment and potential pregnancy-related effects associated with viruses and bacteria, new strategies are needed to detect these microorganisms even in asymptomatic women. Romero et al., approach the problem from a new pathophysiological perspective, a polymicrobial etiology, recently examining the role of infection in the pathophysiology of pre-term birth [26]. Unlike multiple studies that have focused on a single organism as the etiology of preterm birth, they investigated a different approach by infecting mouse placentas with herpes virus and characterizing the subsequent response to bacteria, demonstrating that the simultaneous presence of viral and bacterial infection resulted in preterm birth in 100% of the mice. Based on these findings, they propose that viral infection of the placenta during pregnancy (the first hit) can affect the normal interaction with local bacteria (the second hit), leading to a “proinflammatory cytokine storm” that results in pre-term birth. Consequently, infection leading to preterm birth is a polymicrobial pathology. This model illustrates how a viral infection during pregnancy leads to an exaggerated response to a low bacterial insult, resulting in preterm birth [27].

Understanding this polymicrobial disease mechanism can lead to treatment and prevention strategies to reduce the incidence of preterm birth. Identifying the “first hit” in the cascade can offer opportunities for intervention and potential preterm birth prevention [28]. Only then can this devastating obstetric problem be controlled and neonatal outcomes improved.

Rates of preterm birth and caesarean section have increased in many studies, although there are some exceptions [29,30]. Fever and hypoxemia can increase the risk of premature birth, membrane rupture, and altered fetal heart tracings, but preterm birth also occurs in patients without SARS. Most third-trimester cases appear to be elective c-sections due to maternal illness which is expected to improve after birth; however, this hypothesis is unconfirmed. A systematic review including more than 11,000 pregnant women, and more recently pregnant women with COVID-19, reported that 17% gave birth before 37 weeks, and 65% gave birth by caesarean section [31]. Most premature birth cases were iatrogenic, with only 6% being spontaneous. In the COVID-19-Associated Hospitalization Surveillance Network study described above, the prevalence of preterm birth among 598 pregnant women hospitalized for COVID-19 was 12.6%, higher than the 10% observed in the general US population in 2018 [32]. Symptomatic patients have a threefold increase in preterm birth compared to asymptomatic ones (23% versus 8%). The overall C-section rate was 33% (rates in symptomatic and asymptomatic cases: 42% and 29%, respectively). It is important to emphasize that these data reflect a range of disease severity, with a disproportionate number of symptomatic women with COVID-19 [33,34]. In a study specifically reporting outcomes by disease severity, 32 of 64 pregnant women hospitalized for severe or critical COVID-19 gave birth during infection; 9 of 44 women with severe disease and 13 of the 20 women with critical disease gave birth due to maternal status, and only 3 due to fetal status [35]. Premature birth occurred in 9% of women with severe disease and 75% with critical disease.

One strength of our study is the use of a control group. In this control group, placentas were only sent for pathological examination when there was an obstetric indication, typically pregnancy-related diseases or complications during childbirth. Patients who had a caesarean delivery were excluded from the analysis to favor group homogeneity. Similarly, patients with twin pregnancies were also excluded from the analysis.

When we tried to detect placental alterations based in the trimester in which infection was acquired, the resulting subgroups are too small to detect differences.

CONCLUSION

Placentas of women infected with SARS-CoV-2 have higher rates of placental insufficiency and villitis compared to the controls. Placental insufficiency is associated with a notable reduction in gestational age and neonatal weight. Villitis also correlates with decreased neonatal weight, although its impact on gestational age is less significant. These findings indicate that COVID-19 infection during pregnancy may contribute to adverse outcomes such as reduced fetal weight and preterm birth, highlighting the necessity for vigilant monitoring and management of these pregnancies.

AUTHORS CONTRIBUTIONS

Tirso Perez-Medina designed the project; Ana Gómez Manrique, Pilar Chaves, Fátima García-Benasach investigation and data curation; Tirso Perez-Medina and Ana Royuela analyzed the data; Augusto Pereira wrote the manuscript draft; Tirso Perez-Medina and Augusto Pereira 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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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: A systematic review and meta-analysis. *Am J Obstet Gynecol MFM*. 2020;2(2):100107.
2. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. *Am J Obstet Gynecol*. 2004;191(1):292-297.
3. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA*. 2020;323(18):1843-1844.
4. Kwon JY, Romero R, Mor G. New insights into the relationship between viral infection and pregnancy complications. *Am J Reprod Immunol*. 2014;71(5):387-390.
5. Breslin N, Baptiste C, Miller R, Fuchs K, Goffman D, Gyamfi-Bannerman C, et al. Coronavirus disease 2019 in pregnancy: Early lessons. *Am J Obstet Gynecol MFM*. 2020;2(2):100111.
6. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. *N Engl J Med*. 2014;370(23):2211-2218.

7. Romero R, Espinoza J, Gonçalves LF, Kusanovic JP, Friel L, Hassan S. The role of inflammation and infection in preterm birth. *Semin Reprod Med.* 2007;25(1):021-039.
8. Kelly R, Holzman C, Senagore P, Wang J, Tian Y, Rahbar MH, et al. Placental vascular pathology findings and pathways to preterm delivery. *Am J Epidemiol.* 2009;170(2):148-158.
9. Zeitlin J, Ancel PY, Saurel-Cubizolles MJ, Papiernik E. The relationship between intrauterine growth restriction and preterm delivery: An empirical approach using data from a European case-control study. *BJOG: Int J Obstet Gynaecol.* 2000;107(6):750-758.
10. Gravett MG, Novy MJ, Rosenfeld RG, Reddy AP, Jacob T, Turner M, et al. Diagnosis of intra-amniotic infection by proteomic profiling and identification of novel biomarkers. *JAMA.* 2004;292(4):462-469.
11. Miyake K. Innate immune sensing of pathogens and danger signals by cell surface Toll-like receptors. *Semin Immunol.* 2007;19(1):3-10.
12. Ng WF, Wong SF, Lam A, Mak YF, Yao H, Lee KC, et al. The placentas of patients with severe acute respiratory syndrome: A pathophysiological evaluation. *Pathology.* 2006;38(3):210-218.
13. Gersell DJ, Kraus FT. Diseases of the placenta. In Blaustein's pathology of the female genital tract. New York, NY: Springer. 1994;975-1048.
14. Smith ER, Oakley E, Grandner GW, Ferguson K, Farooq F, Afshar Y, et al. Adverse maternal, fetal, and newborn outcomes among pregnant women with SARS-CoV-2 infection: An individual participant data meta-analysis. *BMJ Glob Health.* 2023;8(1):e009495.
15. Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: A systematic review and meta-analysis. *CMAJ.* 2021;193(16):E540-E548.
16. Sutton D, Fuchs K, D'alton M, Goffman D. Universal screening for SARS-CoV-2 in women admitted for delivery. *N Engl J Med.* 2020;382(22):2163-2164.
17. Gulersen M, Prasannan L, Tam HT, Metz CN, Rochelson B, Meirowitz N, et al. Histopathologic evaluation of placentas after diagnosis of maternal severe acute respiratory syndrome coronavirus 2 infection. *Am J Obstet Gynecol MFM.* 2020;2(4):100211.
18. Smithgall MC, Liu-Jarin X, Hamele-Bena D, Cimic A, Mourad M, Debelenko L, et al. Third-trimester placentas of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive women: Histomorphology, including viral immunohistochemistry and *in-situ* hybridization. *Histopathology.* 2020;77(6):994-999.
19. Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA. Placental pathology in COVID-19. *Am J Clin Pathol.* 2020;154(1):23-32.
20. Pereira A, Cruz-Melguizo S, Adrien M, Fuentes L, Marin E, Perez-Medina T. Clinical course of coronavirus disease-2019 in pregnancy. *Acta Obstet Gynecol Scand.* 2020;99(7):839-847.
21. Elshafeey F, Magdi R, Hindi N, Elshebiny M, Farrag N, Mahdy S, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth. *Int J Gynaecol Obstet.* 2020;150(1):47-52.
22. Yan J, Guo J, Fan C, Juan J, Yu X, Li J, et al. Coronavirus disease 2019 in pregnant women: A report based on 116 cases. *Am J Obstet Gynecol.* 2020;223(1):111-e1.
23. Mullins E, Evans D, Viner RM, O'Brien P, Morris E. Coronavirus in pregnancy and delivery: Rapid review. *Ultrasound Obstet Gynecol.* 2020;55(5):586-592.
24. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: National population based cohort study. *BMJ.* 2020;369.
25. Hughes BL, Sandoval GJ, Metz TD, Clifton RG, Grobman WA, Saade GR, et al. First-or second-trimester SARS-CoV-2 infection and subsequent pregnancy outcomes. *Am J Obstet Gynecol.* 2023;228(2):226-e1.
26. Romero R, Miranda J, Chaiworapongsa T, Korzeniewski SJ, Chaemsaihong P, Gotsch F, et al. Prevalence and clinical significance of sterile intra-amniotic inflammation in patients with preterm labor and intact membranes. *Am J Reprod Immunol.* 2014;72(5):458-474.
27. Khalil A, Von Dadelszen P, Draycott T, Ugwumadu A, O'Brien P, Magee L. Change in the incidence of stillbirth and preterm delivery during the COVID-19 pandemic. *JAMA.* 2020;324(7):705-706.
28. Prabhu M, Cagino K, Matthews KC, Friedlander RL, Glynn SM, Kubiak JM, et al. Pregnancy and postpartum outcomes in a universally tested population for SARS-CoV-2 in New York City: A prospective cohort study. *BJOG: Int J Obstet Gynaecol.* 2020;127(12):1548-1556.
29. Ahlberg M, Neovius M, Saltvedt S, Soderling J, Pettersson K, Brandkvist C, et al. Association of SARS-CoV-2 test status and pregnancy outcomes. *JAMA.* 2020;324(17):1782-1785.
30. Delahoy MJ, Whitaker M, O'Halloran A, Chai SJ, Kirley PD, Alden N, et al. Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed COVID-19-COVID-NET, 13 States, March 1-August 22, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69.
31. Allotey J, Chatterjee S, Kew T, Gaetano A, Stallings E, Fernandez-Garcia S, et al. SARS-CoV-2 positivity in offspring and timing of mother-to-child transmission: Living systematic review and meta-analysis. *BMJ.* 2022;376:e067696.
32. Juan J, Gil MM, Rong Z, Zhang Y, Yang H, Poon LC. Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review. *Ultrasound Obstet Gynecol.* 2020;56(1):15-27.
33. Woodworth KR, Olsen EO, Neelam V, Lewis EL, Galang RR, Oduyeyo T, et al. 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.
34. Allotey J, Stallings E, Bonet M. Update to living systematic review on COVID-19 in pregnancy. *BMJ.* 2021;372:n615.
35. Jering KS, Claggett BL, Cunningham JW, Rosenthal N, Vardeny O, Greene MF, et al. Clinical characteristics and outcomes of hospitalized women giving birth with and without COVID-19. *JAMA Intern Med.* 2021;181(5):714-717.