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Placental histological differences between COVID19 infected and non-infected mothers during third trimester of pregnancy: a retrospective cohort study

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Abstract

Background Covid-19 infection was revealed to be associated with higher risk of maternal and fetal morbidity and mortality. Knowing that Covid-19 virus can infect the placenta, the aim of this study is to investigate placental histological differences between Covid-19 uncomplicated pregnancies and Covid-19 infected mothers in the 3rd trimester or intrapartum.

Methods This was a retrospective cohort study conducted between the 28th of January 2021 and the 31st of June of the same year at Saint George University Medical Hospital, Beirut-Lebanon. All pregnant women, whether symptomatic or not, were tested for Covid-19 infection via PCR upon presentation for delivery. We randomly collected placentas from Covid-19 uncomplicated gestations and 3rd trimester or intrapartum Covid-19 infected mothers after obtaining an informed consent. Our control population included all previously healthy mothers, singleton, term, and uncomplicated pregnancies regardless of the mode of delivery during the same period of the study. The Covid- 19 infected group had similar medical and obstetrical background only for coronavirus infection during the 3rd trimester or upon admission. Placentas of the two groups were grossly and histologically examined by a single pathologist who was blinded to the placentas of each group. Examination was based on the Amsterdam Consensus Statement guidelines.

Results A total of 22 Covid-19 positive cases and 21 Covid-19 negative cases were included. The results showed no statistical significance for any of the placental pathologies including maternal vascular malperfusion, amniotic fluid infection including maternal response and fetal response, villitis of unknown etiology, intervillositis and chorangiosis and fetal vascular malperfusion, except for the vascular ectasia, were 5 cases were identified in the Covid-19 positive group ($p < 0.05$).

Conclusion Covid-19 infection during the 3rd trimester of pregnancy is not a risk factor for the development of placental histopathologies.

Keywords Pregnancy, Placenta, Covid-19, Placental histopathologies

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been threatening public health worldwide. Coronavirus disease has clinical medical implications on the respiratory, neurology, enterology, dermatology, and cardiac systems along with its systemic manifestations [1].

Since the declaration of the pandemic on March 2020, obstetrical related complications have been widely studied [2]. Covid-19 infection was revealed to be associated with higher risk of maternal and fetal morbidity and mortality. Pregnant women are at increased risk of preeclampsia/eclampsia, severe infections, intensive care unit admission, preterm birth and maternal mortality [3–5]. Newborns have a greater severe neonatal morbidity index and severe perinatal morbidity and mortality index [3, 5].

Pathologic studies of placentas, the largest fetal organ, can highlight the issue of vertical transmission. It is evident that the Covid-19 virus can infect the placenta, and SARS-CoV-2 virions were visualized in syncytiotrophoblasts of the placental villi [6–12]. Vertical transmission is possible as shown in the studies in a minority of cases with 3% proportion during the 3rd trimester [13]. The actual mechanism of virus transfer through the placenta versus protective means against its transmission is still under investigation.

Other respiratory RNA viruses including Parainfluenza, Metapneumovirus Respiratory Syncytial Virus, and Influenza are rarely if ever transmitted to the fetus [14]. There was no case of vertical transmission identified among pregnant women infected with other coronavirus infections (severe acute respiratory syndrome SARS and Middle East respiratory syndrome MERS) during epidemics [2, 15, 16].

There are limited studies tackling the effects of covid-19 infection on placental histopathology.

Specific histopathological findings of placenta were identified to be associated with specific viral infections in pregnancy. Lymphoplasmacytic villitis is associated with cytomegalovirus infection [17], and intervillositis is reported in the setting of Zika virus [18] and Dengue virus [19]. As for coronavirus COVID 19, some studies found no specific significant differences between placentas of covid-19 infected mothers in comparison to normal controls [6, 8, 20]. Fetal vascular malperfusion is the most common significant finding associated with placentas of covid-19 infected gestations [12, 21–23]. Studies show conflicting data about inflammatory changes. Elizabeth T. et al. reported significant increased incidence of villitis of unknown etiology [21]. Chorangiosis and lymphohistiocytic villitis may occur in context of SARS-CoV-2 infection of the placenta [10, 12]. On the other hand, Shanes et al. and Singh et al. showed no significant increase in acute or chronic inflammatory pathology compared to controls [12, 22].

Our study aims to evaluate the histopathological findings of placentas exposed to covid-19 infection in contrast to control placentas of pregnant women who tested negative for Covid 19.

Materials and methods

This is a retrospective cohort study involving COVID-19 positive women who delivered singleton gestation at ≥ 31 weeks at Saint George Hospital University Medical Center, from 28 January 2021 to 31 June 2021. All women within this time period were tested for nasopharyngeal polymerase chain reaction PCR for COVID-19 at admission irrespective of symptomatology. The placentas of these singleton gestations were sent for gross and microscopic pathological examination. A control group of COVID-19 negative pregnant women without medical or obstetrical complications was chosen during the same period with singleton gestation at ≥ 31 weeks. A case of twin pregnancy was excluded from the research. Chart review was performed to obtain relevant demographic and clinical data. This study was approved by the University of Balamand Institutional Review Board (IRB-REC/O/036–21/1621).

Testing for Covid was done with nasopharyngeal swab using ANDiS FAST SARS-CoV-2 RT-qPCR detection kit by 3D Biomedicine Science and Technology Co., Limited, CE (IVD) with an analytical sensitivity or limit of detection of 200 copies/mL. Testing for placental infection by COVID-19 was performed on all COVID positive and COVID negative cases by FFPE RNA extraction followed by COVID qPCR.

The placentas were delivered to the pathology department fixed in 10% neutral buffered formaldehyde and were left for fixation for at least one week to reduce the risk of contamination. The gross examination was done according to the guidelines of the 2016 Amsterdam Placental Workshop Group Consensus Statement. One block containing two sections from the umbilical cord and membrane rolls and a minimum of three sections from the placenta (central, paracentral and peripheral sections) were submitted as well as additional blocks if gross lesions were identified. Tissue blocks were processed and hematoxylin and eosin-stained sections were studied. Microscopic examination was performed mainly by a single pathologist (Z.M) for all the placentas. The pathologist was blinded to the COVID-19 status. Histologic evaluation also followed the 2016 Amsterdam consensus criteria and terminology.

The histopathological findings of the placentas from COVID-19 positive pregnant women in the third trimester ($n = 22$) were compared to a control group of

COVID-19 negative pregnant women ($n = 21$). The placental pathologies were divided as no clinically significant pathology, maternal vascular malperfusion MVM (mainly infarcts and retroplacental hemorrhage), fetal vascular malperfusion FVM (thrombosis, avascular villi, intramural fibrin deposition, villous stromal –vascular karyorrhexis, stem vessel obliteration and vascular ectasia), amniotic fluid infection including maternal response (acute subchorionitis, acute chorioamnionitis and necrotizing chorioamnionitis) and fetal response (chorionic vasculitis or umbilical phlebitis, involvement of the umbilical vein and one or more of the umbilical arteries, and necrotizing funisitis), villitis of unknown etiology VUE, intervillositis and chorangiosis. Cases with intervillous thrombus were also identified as well as increased perivillous fibrin and increased syncytial knots.

For the statistical analysis, we used means, medians, and standard deviations to summarize quantitative variables, and percentages/proportions to summarize qualitative variables. In our bivariate analysis, we used chi-square or Fisher exact test when appropriate for categorical variables. We used Student's t-test or non-parametric tests (Mann-Whitney) for the continuous variables. All statistical analyses were done using SPSS V28©.

Results

A total of 22 third trimester placentas of Covid-19 positive cases and 21 third trimester placentas of Covid-19 negative controls were studied. Twelve cases (28%) were COVID positive on admission and thirty-one (72%) were Covid negative on admission. Transplacental infection was confirmed in all COVID positive cases by qPCR.

There were no statistically significant results concerning the placental weights per percentile between COVID-19 positive and negative cases in the third trimester (NS $p = 0.07$) and no differences between birth weight according to covid status upon admission (NS $p = 0.123$). The prevalence of small for gestational age by placental age of < 10 th percentile in covid positive cases (one case or 5%) was close to that of the covid negative cases (zero). The prevalence of large for gestational age by placental weight of > 90% was quite similar between the covid positive cases (5 cases or 23%) and covid negative cases (6 cases or 29%).

The mean age of the covid positive third trimester pregnant women was 29.8 and that of the covid negative cases 32.9 (Table 1). The median age of covid positive cases was 29 with SD 3.4 and the median age for covid negative cases 33 with SD 4.5. Thus, the covid positive patients were significantly younger by about 3 years compared to covid negative cases (t-test p value = 0.013 also significant with NP test).

Eight covid positive cases (36%) were Gravida G1, eleven (50%) were G2, and three (14%) were G3 or more. Four cases (19%) of covid negative cases were G1, nine (43%) were G2 and eight (38%) were G3 or more. Thus, 86% of covid positive third trimester patients were G1 or G2 compared to 62% of covid negative patients (p 0.066 using Chi square) (Table 2).

Among all the covid positive and negative patients, seventeen women (40%) were Parity 0 P0, twenty-three (54%) were P1, two (5%) were P3 and one (2%) was P5. Zero preterm pregnancies were noted in forty-two patients (98%) and one (2%) had one preterm pregnancy.

Thirty women (70%) had zero miscarriages or abortions, ten (23%) had one miscarriage, one (2%) had two, and two (5%) had four miscarriages/abortions (Table 3).

Table 2 Gravida

	COVID + 3rd	COVID – 3rd	COVID + adm	COVID – adm
Gravida 1	8 (36%)	4 (19%)	2 (17%)	10 (32%)
G2	11 (50%)	9 (43%)	7 (58%)	13 (42%)
G3 and more	3 (14%)	8 (38%)	3 (5%)	8 (26%)

1–12 (28%)

2–20 (47%)

3–5 (12%)

4–3 (7%)

5, 6, 8 – each 1 (2% × 3)

COVID positive patients (3rd trimester): 86% were gravida 1 or 2, compared to 62% of the COVID negative patients (in the 3rd trimester) – p 0.066 (using Chi square)

Table 1 Age in each group: patients with positive COVID were significantly younger by about 3 years

	COVID + 3rd	COVID – 3rd	COVID + adm	COVID – adm
Mean age	29.8	32.9	29.3	32.1
Median age	29	33	29	32
SD	3.4	4.5	3.3	4.3
p-value (*t*-test)	0.013		0.046	
	Also significant with NP test		0.05 with NP test	

Table 3 Miscarriage/abortion

	COVID + 3rd	COVID – 3rd	COVID + adm	COVID – adm
No abortions	18 (82%)	12 (57%)		
At least one abortion	4 (18%	9 (43%)		
p-value (chi sq)	0.078			

0–30 (70%)

1–10 (23%)

2–1 (2%)

4–2 (5%)

Those who had COVID 3rd trimester had less history of abortions (NS)

Table 4 GA – no significant difference between the 2 groups

	COVID + 3rd	COVID – 3rd	COVID + adm	COVID – adm
GA mean	38.2	38.9	37.7	38.8
GA median	38.5	39	38.5	39
	$P = 0.094$		$P = 0.125$	

Mean 38.5

Median 39

SD 1.5

Min 31; Max 40

Table 5 Delivery

	COVID + 3rd	COVID – 3rd	COVID + adm	COVID – adm
Vaginal	12 (55%)	11 (52%)	7 (58%)	16 (52%)
c-section	10 (50%)	10 (50%)	5 (42%)	15 (48%)
	$P = 0.887$		$P = 0.692$	

Vaginal 23 (53.5%)

C-Sect. 20 (46.5%)

Indication c-section: mostly repeat (10 = 50% of those who had c-section)

No statistical differences

Seventeen (40%) had no living children, twenty-two (51%) had one, one (2%) had two, two (%5) had three, and one (2%) had five living children.

The mean gestational age GA of covid positive third trimester patients was 38.2, the GA median 38.5, and the mean GA of the covid negative cases was 38.9 and the GA median 39 (NS $p = 0.094$) (Table 4).

Twenty-three cases (53.5%) had vaginal delivery and twenty (46.5%) had C-section (NS $p = 0.887$). Ten (50%) C-sections were repeat C-sections (Table 5).

Only thirty-eight cases had data for presentation with thirty-seven cases vertex (97%) and one (3%) transverse.

Bishop score was available on twelve cases (mostly 3) and induction data on twenty-seven cases (Pitocin 18 or 67% and Cytotec/Pitocin 9 or 33%).

There were no pathological placental lesions in six covid positive cases and four covid negative cases; eighteen (or 82%) covid positive placentas showed any placental lesion and seventeen (or 81%) covid negative cases revealed any placental lesion, a difference which was not statistically significant. The prevalence of Maternal Vascular Malperfusion MVM was nearly identical for both covid positive cases (fourteen cases or 64%) and covid negative cases (fifteen cases or 71%), with statistically no significant difference.

Fetal Vascular Malperfusion FVM was studied (avascular villi, vascular stromal karyorrhexis, intramural fibrin deposition or stem vessel obliteration) in both groups with only vascular ectasia detected in five covid positive cases, with statistically significant difference ($p = 0.048$).

There were two covid positive cases with amniotic fluid infection, maternal response (two cases of acute subchorionitis and zero cases of acute chorioamnionitis, but no case of necrotizing chorioamnionitis). There were two cases of acute subchorionitis in covid negative patients, and the difference was not statistically significant. There was one case of amniotic fluid infection, fetal response in the form of umbilical phlebitis in the covid positive group (but no case of umbilical cord vein or artery involvement and no necrotizing funisitis). This patient was the same covid positive patient who had also acute subchorionitis. Two cases of amniotic fluid infection fetal response in the form of chorionic vasculitis were observed in the covid negative patients. The difference was not statistically significant.

There was one case of villitis of unknown etiology, one case of chronic intervillositis in the covid positive group, and no case in the covid negative group, but the difference did not reach statistical significance, similar to the findings of Patberg et al. [21]. One case of chorangiosis was identified in the covid positive group and no case in the covid negative group, but still the difference was not statistically significant. There were intervillous thrombi in two cases of covid positive patients

and nine cases of covid negative patients, a statistically significant difference ($p = 0.011$). Increased perivillous fibrin with increased syncytial knots were seen in four covid positive cases and five covid negative cases, again a statistically not significant difference.

Nasopharyngeal swab PCR tests were performed only on thirteen live born neonates from Covid positive mothers and were negative (59%) and the other nine babies from covid positive mothers were not tested for PCR Covid. Schwartz et al. described cases of vertical transmission of SARS-CoV-2 correlated to chronic intervillositis. We could not study this feature because in our two cases of VUE and chronic intervillositis, the babies were not PCR tested. All the babies of the control group also were not tested for Covid, thereby precluding a solid discussion about vertical transmission (Table 6).

Two babies from covid positive mothers and one from the covid negative group needed NICU; therefore, most of the newborns did not need NICU (40/43 = 93%) and there was no statistical significance between the two groups.

There were no significant differences between the cases which were covid positive in the third trimester and the Covid positive cases upon admission (Table 7).

Table 6 histopathological findings and placental weights

Placental weight	COVID19 positive (*n* = 22)	COVID19 negative (*n* = 21)
< 10 th percentile	1	0
10-25 th percentile	3	7
25-50 th percentile	4	3
50-75 th percentile	10	1
75-90 th percentile	1	4
> 90 th percentile	3	6

Age

Mean 31.
Median 31.
SD 4.2.
Min 24 – Max 41.

Parity

0 – 17 (40%).
1 – 23 (54%).
3 – 2 (5%).
5 – 1 (2%).

Preterm

0 – 42 (98%).

Table 7 Statistical analysis

code		COVID19 positive (22)	COVID19 negative (21)
0	No clinically significant placental lesion	6	4
1	MVM -retroplacental/marginal hemorrhage/hematoma And/or -infarcts	14	15
2	FVM: -avascular villi -Vascular stromal karyorrhexis -Intramural fibrin deposition -stem vessel obliteration -Only vascular ectasia (alone nonspecific)	0 0 0 5	0 0 0 0
3	Amniotic fluid infection, maternal response -acute subchorionitis -Acute chorioamnionitis -necrotizing chorioamnionitis	2 **2** 0 0	2 1 1 0
4	Amniotic fluid infection, fetal response -chorionic vasculitis or umbilical phlebitis -Umbilical cord vein or artery involvement -necrotizing funisitis	1 0 **1** (same patient as subchorionitis) 0 0	2 2 0 0 0
5	VUE/Chronic intervillositis	1/1	0
6	chorangiosis	1	0
7	Intervillous thrombus	2	9
8	Increased perivillous fibrin	4	6

1 – 1 (2%).

Living

0 – 17 (40%).
1 – 22 (51%)
2 – 1 (2%).
3 – 2 (5%).
5 – 1 (2%).

Presentation (analysis of 38 cases with data)

Vertex 37 (97%).
Transverse 1 (3%).
Bishop score on 12 cases: mostly 3.
Induction data on 27 cases: Pitocin 18 (67%); Cytotec/Pitocin 9 (33%).

COVID positive during the 3rd trimester

Yes 22 (51%).
No 21 (49%).

COVID positive on admission

Yes 12 (28%).
No 31 (72%).

Discussion

All pathologic findings were near equally present among the SARSCoV-2–positive and SARS-CoV-2–negative groups. Minor differences between the two groups were noted; however, these differences in prevalence did not reach statistical significance, as supported by authors like Levitan et al. [24].

The only statistically significant finding of vascular ectasia in covid −19positive cases compared to the controls (5/22 or 23% versus 2/21 or 0%, $p = 0.048$) is disputable as many references do not consider vascular ectasia alone as specific for FVM. It may be related to umbilical cord compromise in combination with FVM [25, 26]. There were no significant differences when comparing the COVID status upon admission groups. FVM was significantly more frequent in covid positive cases with Patberg et al. [21] but the significant pathologies were avascular villi and mural fibrin deposition, not vascular ectasia alone as in our study. Glynn et al. [23] also found significantly higher incidence of FVM in acute covid infection cases.

We did not encounter increased incidence of MVM in the covid positive group comparative to other studies [6, 21], but a few other authors found significant increase in the cases of MVM in covid positive placentas [10, 12].

As Covid-19 is a virus, it can cause acute or chronic inflammatory pathologies, but we had three cases of amniotic fluid infection in the covid group and two cases in the control. We had one case of chronic intervillositis and VUE, which were not statistically significant compared to the control group, a finding similar to Hecht et al.'s and Shanes et al.'s study [6, 12]. There was one case of villitis of unknown etiology, one case of chronic intervillositis in the covid positive group, and no case in the covid negative group, but the difference did not reach statistical significance, similar to the findings of Patberg et al. [21]. Our findings concerned focal inflammatory processes. Other authors also tackled in detail the issue of inflammatory response like focal or diffuse chronic histiocytic intervillositis and massive perivillous fibrin deposition [27, 28], but we could not find any similar case of diffuse placentitis or massive perivillous fibrin deposition. Our few cases of perivillous deposition were rather focal.

Absence of significant placental pathological findings in placentas from covid positive mothers correlated with the findings of many authors [4, 6, 29].

Intervillous thrombi were significantly more frequently encountered in the control than the covid group (9/21 or 43% versus 2/22 or 9% $p = 0.0011$). Other authors discovered the reverse, with a significant increase of the incidence of intervillous thrombi in the covid group [12]. Although intervillous thrombi are considered incidental findings, some references consider it associated with hypertension or coincident infarction. In our study, it is probably an incidental finding to have significantly more cases of intervillous thrombus in the control group.

Perivillous fibrin deposition was not significant unlike other studies [30].

This study is subject to a few limitations.

The small number of the sample studied is probably behind the absence of significant findings, limiting the power to detect significant differences. None of our cases were tested for COVID RNA or protein, and we could not perform electron microscopic studies, unlike many other studies [6, 10, 12, 30]. The lack of immunohistochemical stains searching for viral spike protein in syncytiotrophoblastic cells or expression of ACE2 protein prevents us from assuming or refuting the possibility of vertical transmission or direct placental infection [31].

Another limitation was the fact that gross and microscopic examinations of the placentas from covid positive cases and the controls were examined by a single pathologist (Z.M) who was blinded to the covid status of the placentas. Having one pathologist on the study can have the advantage of reducing the impact of interobserver variability.

Another drawback is the lack of information concerning symptomatic versus asymptomatic patients.

Weakness also includes the lack of data concerning the newborns, be it PCR results or follow-up.

Significant histopathological findings were lacking, but we do not know if such changes occur during the first or second trimesters as our study concerns only third trimester placentas.

Conclusion

There are, to the best of our knowledge, no published case series in the Lebanese literature of placental pathology in women diagnosed with COVID-19 during pregnancy.

There was no statistically significant difference in the prevalence of any specific placental pathological findings between the SARS-CoV-2–positive and SARS-CoV-2–negative control groups.

Our study results suggest that there is no characteristic histopathology in most placentas from women with SARS-CoV-2 infection, in concordance with the results of other similar works [6, 24, 29].

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Authors' contributions
ZM, JI, EC, SA and EA were responsible of the write up and the review of the manuscript. MB, SE, JK, JG, JN, JF, ND, ES and EA were responsible of the recruitment of patients. ZM was responsible of the histopathological reading, and JI of the statistical analysis.

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Data availability
All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
This study was approved by the University of Balamand Institutional Review Board (IRB-REC/O/036-21/1621). Subjects included in the study signed individual informed consents. This study adhered to the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing of interests
The authors declare no competing interests.

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