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ORIGINAL ARTICLE

HISTOLOGICAL CHANGES OF PLACENTA IN WOMEN WITH COVID-19

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Summary

Background: During pregnancy, COVID-19 viral infection may cause abnormal placental findings. The studies that have focused on the placental structure among infected women with such virus were few.
Aim: This study aims to compare the placental histology of women affected by COVID-19 to that of non-infected women.
Methods: A prospective case-control study that enrolled placentae of 20 pregnant women who delivered at Al-Khansaa Maternity Teaching Hospital in Ninevah Province /North of Iraq was accomplished. Ten women were positive for CoVID-19 in the antenatal period. Placental biopsies were obtained from the placental maternal side and placental fetal side and were prepared for histopathological examination after staining with (H&E) using a light microscope.
Results: This study revealed that the microscopic assessment of placentas women who were diagnosed with COVID-19 exhibited several features in comparison with those of the control group. Among these findings were those of maternal vascular mal perfusion which are represented represented by accelerated villous maturation, thickening of the blood vessel wall, syncytial knots, incomplete villi growth, perivillous fibrin deposition, and congestion of the blood vessels. On the other hand, fetal vascular mal perfusion is represented by delayed villous maturation, increase numbers of large bullous villi with evidence of syncytial injury, reduced vasculosyncytial membrane formation, villous oedema, increase in the nucleated red blood cells' number, cholangitis with intervillous haemorrhage. Placental sections in COVID-19-infected women revealed inflammatory changes that were picked out in both maternal and fetal sides represented by chronic villitis, edematous villi with infiltration with inflammatory cells, and decidual oedema with infiltration with inflam-matory cells. Features of syncytial injury, decidual fibrinoid necrosis, surge in the nucleated red blood cells' counting, infarction, haemorrhage, and calcification were noticed in some sections.
Conclusion: This study observed considerable histopathological lesions in the placentae of mothers infected by the COVID-19 virus against the non-infected group.

Key words: COVID-19 virus; placenta; histological changes

Introduction

Coronaviruses are encapsulated ribonucleic acid (RNA) viruses with a single strand (1). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes Coronavirus disease 2019 (COVID-19) which was considered as an universal pandemic since March 2020 (2).

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There is a growing concern regarding the effect of this virus on pregnants' and infant's health by the clinicians as they are vulnerable to infection with COVID-19 due to the physiological alterations in the cardiorespiratory and immune systems throughout gestation so the retaliation to SARS-CoV-2 infection is changed (3). In addition, severe conditions were reported in cases with low immunity (4, 5).

Several reports on the interconnection between extreme acute respiratory syndrome coronavirus 2 (SARS-CoV-2) throughout gestation and high menace of abortion, preeclampsia, preterm birth, stillbirth, and even maternal mortality were recognized (6, 7). Some physical parameters were shown among cases of COVID-19 in Chinese gravid females (8, 9).

The microscopic examination of the placenta remains the gold standard method to obtain a piece of marked information concerning both maternal and fetal health. The spectrum of viral infection (such as cytomegalovirus, Dengue virus, and Zika virus) throughout gestation may be correlated with placental observations (10-13).

A recent ultra-structural study (via electron microscope) recognized SARS-CoV-2 viruses within placental villi (14), while the more recent one reported the transmission of this virus through the placenta to the fetus as the viral placental loads are more than two folds higher in comparison with that of the nasopharynx in the blood of mother (15). So, there is a potential eliciting of the inflammatory response in the placenta by the virus and resulting in placental injury.

This analysis selected the topic of "placental microscopic repercussion of corona virus" in moms which were positive with this virus as the placental observations that may be correlated with coronaviruses are not known yet highlighted beside the fact that the research that discussed such a topic is still in the infantile period, especially in our locality. So, the present study aims to determine whether the infection of gravid women, in Nineveh Province, with COVID-19 during late gestation is associated with histological changes in the placenta or not set side by side with those of control (non-infected women) and to recognize the frequency of these changes- if present.

Materials and Methods

A prospective case-control study that enrolled analysis of data of 30 women -after obtaining the ethical approval of the Ethical Committee of Medical Researches, Medicine College, Mosul's University (UOM/COM/MREC/21-22) (67) - was performed using the information of written consent form from these moms before starting enrolling their acceptance regarding the utilizing of their data in this analysis.

Ten placentae were obtained from documented positive cases of COVID-19 during the antenatal period (using nasopha-ryngeal Polymerase chain reaction -PCR test) who delivered at term at Al-Khansaa Maternity Teaching Hospital in Nineveh Province, while other ten placentae were obtained from women with no COVID-19 infection to serve as a control group.

Detection of the infection with COVID-19 was performed using the PCR checking for SARS-CoV-2 RT-PCR in the nasopharyngeal swab of the patient via RT-PCR (Analytik Jena, Germany) with institutional authorization and according to the instructions mentioned universally (16) at Central Laboratory of General health, Ninevah Province. The enrolled cases are newly infected with mild uncomplicated status and received only antibiotics and antipyretic protocols. The cases of other medical problems such as hypertension and diabetes mellitus were not included. Premature birth and fetal death are also not enrolled. Females with gestational diabetes mellitus, pre-eclampsia, and smoking are excluded. Cases of anticoagulant therapy are also not considered.

Placental biopsies were obtained from the placental maternal side (decidua) and placental fetal side (chorionic plate). These biopsies were prepared for histopathological examination after staining with hematoxylin/eosin (H&E) using light microscopic technique (17-19). The microphotographs were taken by microscope(Leica) with a camera (Optika) attached.

Using the roles of the criteria of Amsterdam Placental Workshop Group (20), placental histological lesions are classified as characters of vascular mal-perfusion (maternal), characters of vascular mal-perfusion (fetal),

inflammatory category, and others (as increased nucleated red blood cells-RBCs, syncytial injury, and calcification). Microscopic examination was performed for all placentas from control and COVID-19 cases with awareness of the COVID-19 status (16).

Results

Grossly, no obvious macroscopical observations are recorded in this work. The microscopic assessment of placentas women who were diagnosed with COVID-19 in the antenatal period in this work exhibited several features in comparison with those of the control group. Among these findings were those of maternal vascular mal perfusion that were represented by accelerated villous maturation in 8 (80%) of sections. Thickening of the blood vessel wall, syncytial knots, and incomplete villi growth was noticed in some cases. Villi lodged in fibrin (Perivillous fibrin deposition) were shown in 9 (90%) of sections with congestion of the blood vessels (Figures 1 and 2, Table 1).

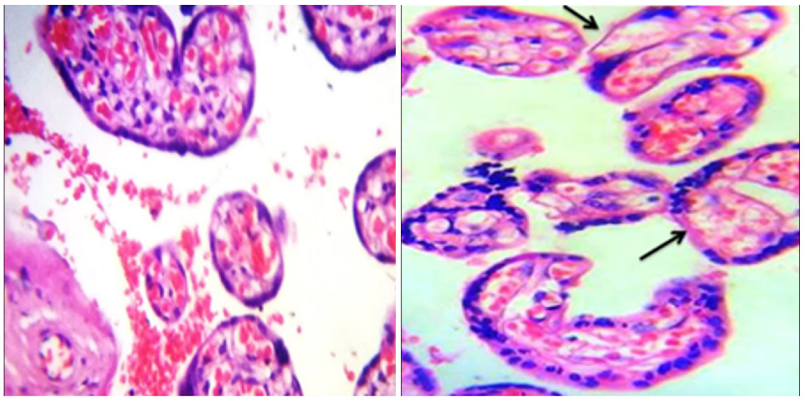

Figure 1. A placental section in a woman of the control group with normal villi floating in the inter-villous space and normal vasculosyncytial membrane is normally found between the capillary and syncytium (arrow) [X20]. H&E stain.

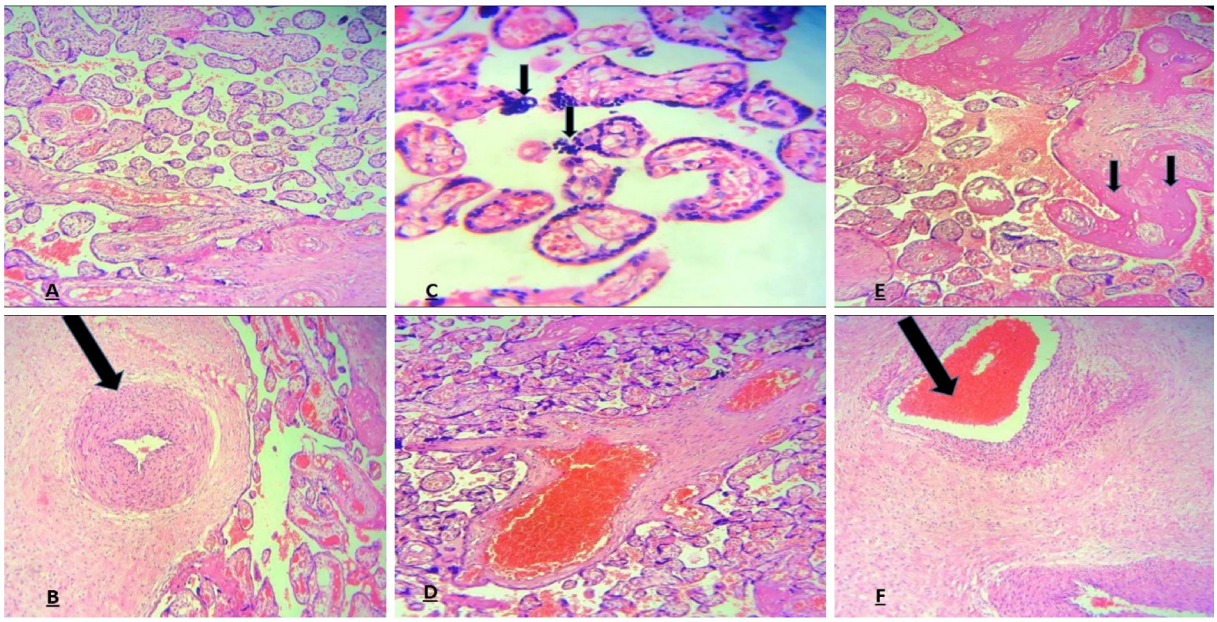

Figure 2. Light microphotographs of placental sections in COVID -19 infected women. Features of vascular mal perfusion (maternal) are noticed and represented by A-accelerated villous maturation of villous hypervascularity [X10], B- thickening of the blood vessel wall [X10], C-syncytial knots [40x] D-incomplete villi growing (large diameter of the villi) [X10], E- perivillous fibrin deposition [X10], F-congestion of the blood vessels [X10] .H&E stain.

Table 1. The frequency of various histological changes in the placentae of both study groups.

		Control group (Non-infected women) n = 10 (%)	Infected group (Women with COVID-19) n = 10 (%)
Histological Lesions	**Maternal vascular mal perfusion**		
	Accelerated villous maturation	2 (20%)	8 (80%)
	Peripheral villous agglutination	1 (10%)	9 (90%)
	Villous fibrinoid necrosis	1 (10%)	6 (60%)
	Fetal vascular malperfusion		
	Delayed villous maturation	2 (20%)	8 (80%)
	Choriongiosis	3 (33%)	7 (70%)
	Odema	3 (33%)	5 (50%)
	Inflammatory lesions		
	Chronic villitis	2 (20%)	8 (80%)
	Deciduitis	2 (20%)	9 (90%)
	Other lesions		
	Decidualfibrinoid necrosis	0 (0%)	1 (10%)
	Increase circulating nucleated RBCs	2 (20%)	6 (60%)
	Calcification	0 (0%)	1 (10%)
	Syncytial injury	0 (0%)	1 (10%)
	Infarction	0 (0%)	1 (10%)
	Haemorrhage	0 (0%)	1 (10%)

On the other hand, fetal vascular malperfusion is represented by delayed villous maturation was seen in 8 (80%) of the sections. An increase in the number of large bullous villi with evidence of syncytial injury with reduced or rarity of vasculosyncytial membrane formation was noticed. Villous oedema was seen in 5 (50%) while increasing numbers of red blood cells -RBCs (of nucleated type) were picked out in 6 (60%) with evidence of intravillous fibrin deposition shown in some sections. Chorangiosis was identified in 7 (70%) with intervillous haemorrhage in some sections (Figure 3).

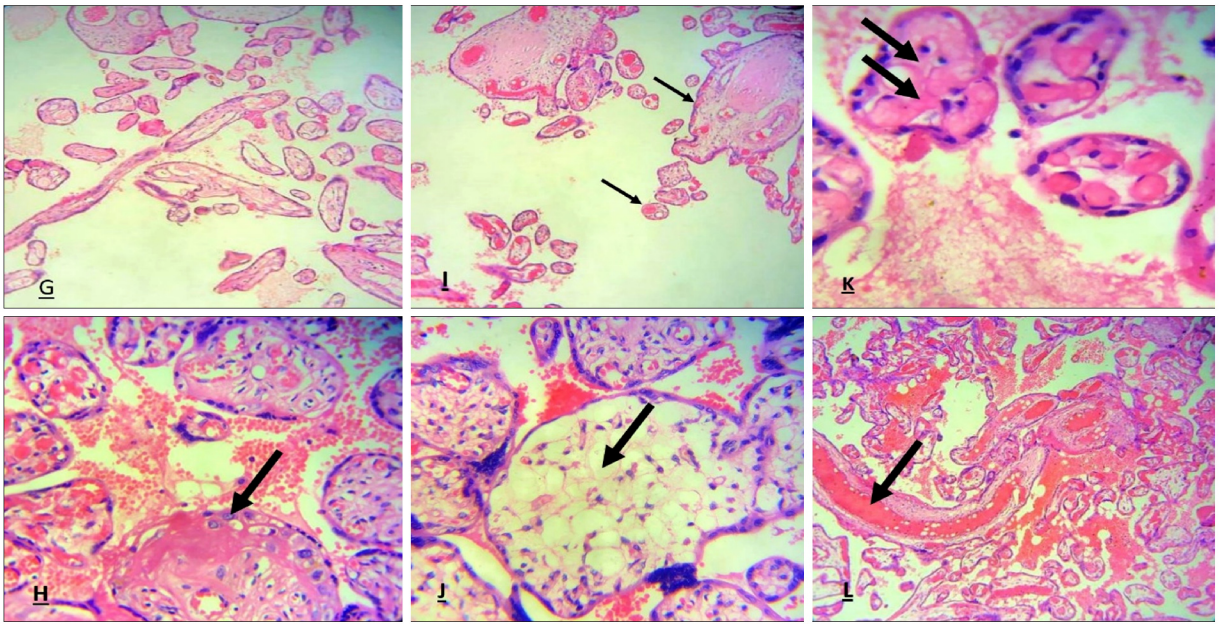

Figure 3. Light microphotographs of placental sections in COVID -19 infected women. The fetal vascular mal perfusion is represented by: G-delayed villous maturation (decrease in the number of 3ry villi) [X10], H- increase in the number of large bullous villi [X40], - reduced vasculosyncytial membrane formation that is normally found between the capillary and syncytium [X10], J-villous oedema [X40], K- evidence of intravillous fibrin deposition [X40], L- chorangiosis and intervillous haemorrhage [X10]. H&E stain.

This work revealed that via light microscopic analysis of placental sections in COVID-19-infected women an evidence of inflammatory changes was seen in both maternal and fetal sides represented by chronic villitis (infiltration with inflammatory cells in villi) in 8 (80%). Edematous villi with infiltration with inflammatory cells were shown. Decidual oedema with infiltration with inflammatory cells(deciduous) was identified in 9 (90%) of the sections (Figure 4).

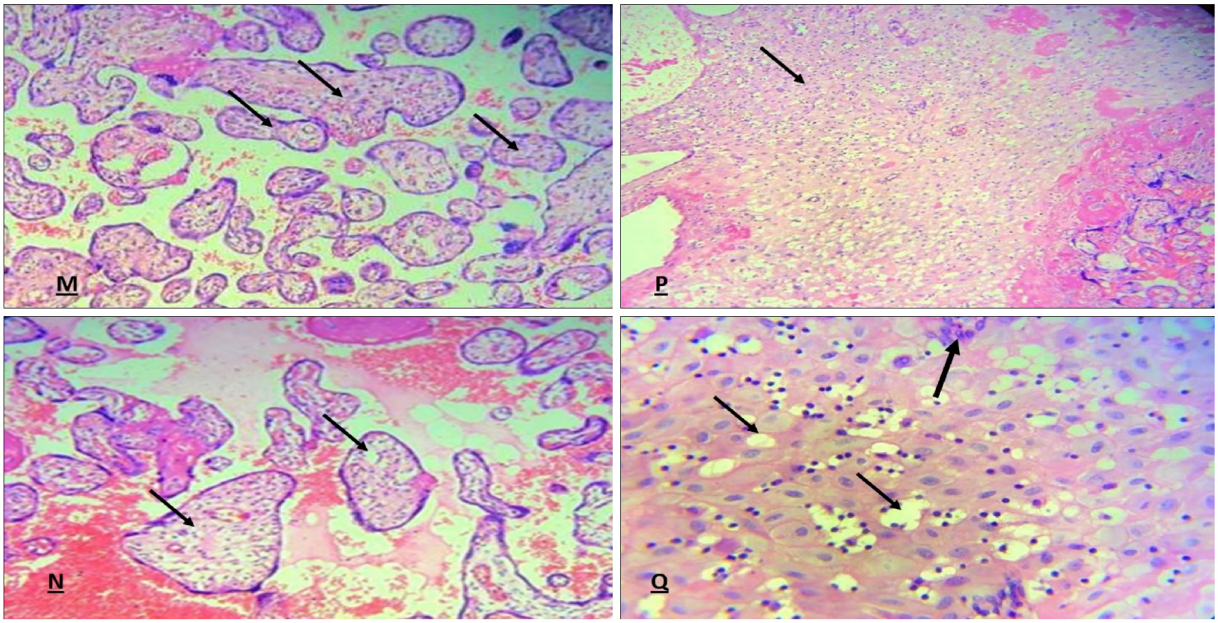

Figure 4. Light microphotographs of placental sections in COVID- 19 infected women with inflammatory changes in both maternal and fetal sides represented by: M- chronic villitis (infiltration of lymphocytes in villi) [X20], N- edematous villi with infiltration of inflammatory cells [X20], P- infiltration of large numbers of inflammatory cells in decidua (deciduitis) [X10], Q-decidual oedema with infiltration with inflammatory cells [X40]. H&E stain.

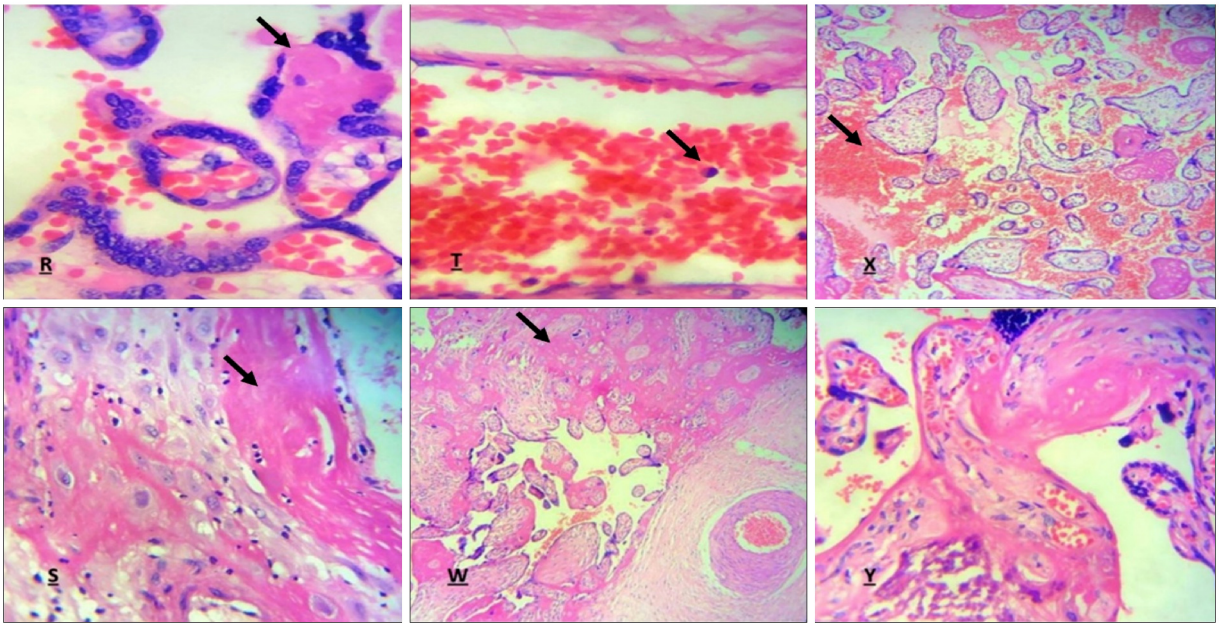

Figure 5. Light microphotographs of placental sections in COVID -19 infected women with R- Features of syncytial injury (loss of syncytium and fibrinoid necrosis of villi) [X40], S- Decidual fibrinoid necrosis with deciduitis [X10], T- congested vessels [40x], W- Infarction [X10], X- Haemorrhage [X10], Y- calcification(arrow) as a plague of basophilic structureless character [X10]. H&E stain.

Light microphotographs of a few placental sections in COVID-19 infected women showed features of other lesions including syncytial injury as increased syncytial knotting. Figure 2, with an area of loss of syncytiotrophoblasts and fibrinoid necrosis. Figure 5, decidual fibrinoid necrosis, infarction, haemorrhage and even calcification (as structures plagues of basophilic character were expressed (Figure 5, Table 1). The frequency of various histological changes in the placentae of both study groups was noticed in (Table 1).

Discussion

In general, venous thromboembolism and micro-angiopathic disease may be identified in nearly all tissues in the human body (i.e. pulmonary, renal, cardiac and brain)via clinical and during the examination of the autopsy. In addition, SARS-CoV- 2 could be related to thrombotic complications (21) which report well-matched histopathological findings of fibrin thrombi and oedema in the pulmonary vessels (22, 23). So, the investigation of whether a similar phenomenon takes place in the fetal-maternal unit is equitable (16).

Selection of the topic of "placental microscopic repercussion of corona virus" in moms which were positive with this virus may be convenient especially in our locality. Contradictory reports on the exact and well-defined placental observations associated with coronaviruses were found (24-26). In addition, the precise mechanism of how SARSCoV-2 may transfer through the placental barrier still entails clarification (27).

To the highest degree of authors' knowledge, there was no preceding work in Nineveh Province and even in Iraq that has discussed the placental alterations in women with COVID-19. In this work, an attempt was made to compare the sections of placentae of non-infected cases with those of who are infected with COVID-19.

Grossly, and as reported previously, the observations are not easy to recognize and they are unexpected to correlate with SARS-CoV-2 exposure as the infection usually was discovered by placental homogenate and swab PCR (that could be associated with contamination by tissue of mother) (28).

The current work revealed that several microscopic placental observations are seen in sections of women with COVID-19. Among these were the features of maternal and fetal malperfusion. These findings were similar to those of (16, 22, 29-31).

In fact, in this work, a trial was planned to discuss the changes in placental structure in women with Covid 19 infection (excluding other disorders including hypertension, diabetes mellitus, premature birth, gestational diabetes mellitus, pre-eclampsia and fetal death) to define the effect of the viral infection per se.

Authors reported that perivillous deposition of fibrin is one of the features in the placenta with COVID-19, which may cause disturbances in the blood flow of the placenta as a result of a decrease in the level of oxygen due to the hypoxic type respiratory disease (24, 32). COVID-19 placentae may show increased intervillous thrombi (33). The increase in accelerated villous maturation in the maternal side of the placentae of COVID patients might be affiliated with distraction in mothers' blood flow (placental) on account of the hypoxic ventilation disorder (16). Another study propounded the irregularity of the coagulation cascade in coronavirus patients accelerating the formation of fibrin clots (21, 22, 34, 35) besides the considerable hemodynamic and prothrombotic alterations in pregnancy which resulted in vascular complications during gestation and during the post- partum phase.

On the other hand, this work revealed a high incidence of delayed villous maturation in the fetal part of placentae of COVID-19 group. These observations were similar to those of another study which considered them as a sign of alteration in metabolism analogues with SARS-CoV-2 infection (36).

There is a delay in the villous maturation (as the presence of chorangiotic vessels, and loss of normal vasculosyncytial membrane), in this research, which is suggested to be the reason for hypoxia and as an accommodation, there is an acceleration in the maternal side- as a response (17, 19).

Marked chorangiosis was shown in the placentae of COVID-19 group. It may be due to low maternal oxygen level (17, 18, 24). In addition, this lesion occurs corresponding to hypoxic status related to respiratory disorder (22).

On the other hand, features of inflammation were seen in sections of COVID-19-infected females. The observation was similar to those of others (26).

Inflammation is one of the lesions observed in viral infections (as in case of SARS-CoV-2) as chronic villitis /deciduitis that may result from the circulating viruses which cause direct infection or loss of tolerance (37).

This work also found an increase in the number of circulating nucleated RBCs in fetal circulation with features of villous oedema as a result of a hypoxic condition. A previous study showed that these lesions were accompanied by other lesions like avascular villi and thrombosis as well as intramural fibrin deposits (35, 38).

Marked inflammatory alterations including chronic villitis, and intervillositis with a connection to SARS-CoV-2 placental infection were noticed in restricted studies (15, 39).

This work showed features of deciduitis. It has been concluded that the appearance of marked chronic histiocytic intervillositis may be detected which is considered as a factor of danger for -COVID-19 -placental infection and mom-to-child transmission (26).

There are conflicting results to answer if the SARS-CoV-2 virus was vertically transmitted (27) beside the fact that the gestational age may affect the mechanisms of this transmission (maternal-fetal) as the gravidity time advances, the peril of vertical transmission was markedly diminished (40) because the placental function as a barrier is more obvious.

In fact, in this work, a trial to do a microscopic analysis of the placenta of infected women with covid 19 in the antenatal period (positive cases by PCR), however, it is difficult to find the exact time of infection.

Key receptors omit t must be available for viral entrance into host cells are co-announced in third-trimester's placentas in scarce manner (27). The restricting defence process against microorganisms to prevent them to reach the fetus are extensively uncertain, however, there is an available suggestion that there is a marked role of syncytiotrophoblasts to resist many pathogens besides the innate defence role of cytotrophoblasts that facing pathogens inside the cells (41). There is good resistance by the syncytiotrophoblast layer against different viruses (herpes simplex and ZIKA in the late stages of pregnancy) (40).

In fact, in the case of syncytial injury, there is a chance for the occurring transmission of infection (especially in the early weeks of gestation) (40, 41).

Interestingly, the evident and distributed increase of syncytial knotting (as a character of maternal vascular mal perfusion) is noticed strikingly in the placentas of infected women. As first described by authors (42), syncytial knots are characterized by aggregated syncytiotrophoblastic nuclei, and their surge may incorporate closely all terminal villi in some disorders as preeclamptic disorder, while they- exclusively- may existed in 10% to 15% of normal terminal villi (41). Further, the placental subjection to hypoxia, hyperoxemia, or oxidative stress could originate a surge in syncytial knotting (43).

Syncytial knots may be seen mainly among placentas with some TORCH infection (44) including rubella, Toxoplasma, cytomegalovirus (CMV), and other infectious agents that were transmitted from mother to fetus (45).

The major lining cells of the placenta -villous syncytiotrophoblast –are the main barrier to infection of the placentas, however, a viral infection of the placenta takes place. Vertical transmission may be frequent in the case of Deoxyribonucleic acid -DNA viruses including Herpes simplex and cytomegalovirus (46) but few suggestions of the vertical transmission of COVID-19 were reported (28).

It is important to do an antenatal test for several viruses including COVID-19, especially in pandemic infection. Sometimes, Ribonucleic acid–RNA- viruses could also reach the placenta but do not leads to marked lesions except hyperplasia of Hofbauer cell, massive perivillous fibrin deposition, and intervillositis by histiocytes (26).

An immune-histochemical study is recommended in future to clarify the role of Hofbauer cells that are harbouring the viruses and even other inflammatory cells (47, 48, 49).

One of the microscopic placental data in cases with COVID-19 of this work is calcification which is attributed to intrusion in moms placental blood flow by virtue of the hypoxemic respiratory disorder (50). There is a need to study the burdon of COVID-19 on the fetus in such cases. To date, no exact significant placental lesions were seen in the amidst of SARS-CoV-2 patients. Regarding the calcification (which exhibited a structureless plague of basophiophilic nature using hematoxylin and eosin protocol) (51). There is a need to perform special staining via Von Kossa stain (for a more accurate diagnosis histologically).

The limitations of the current work enrolled the lacking of follow-up for both mothers and fetuses. In addition, all women included were of mild cases. Limited conclusions were reported by this work and by those of other workers concerning the repercussion of SARS-CoV-2 upon the placenta as the previous reports have variations in the design with few cases (16).

Conclusion

This study observed histopathological lesions that occur in the placentae of mothers infected by the COVID-19 virus in set side by side with those of the non-infected group. There is a need to perform future works on the extensive number of cases with a highlight on the fetal and maternal outcomes in all gestational periods (early and late) besides enrolling the cases of severe infection. An extensive number of placental samples will be useful to recognize the morphological changes including the grossly detected ones.

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Conflict of Interest

None.

Adherence to Ethical Standards

All procedures accomplished in studies enrolling human participants were in conformity with the ethical principles of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later revisions or comparable ethical standards. Informed consent or agreement was attained from all individual pregnants incorporated in this work.

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