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# Article Review on Histopathologic Features of Placenta and Adverse Outcome in Pregnant Women with COVID-19 Positive

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**Abstract:** *Introduction:* The placenta is the highly specialized organ of pregnancy that supports the normal growth and development of the fetus. During intrauterine fetal life placenta is the main metabolic, respiratory, excretory, and endocrine organ. Histologic features of normal placenta are differing according to the trimester of pregnancy. COVID-19 infection affects placenta and fetal membrane. Pregnant women with COVID-19 positive result in placental hyperfusion defects in maternal vessels and oxygenation in the intervillous space affecting perinatal outcome. *Methods:* Systematic reviews, meta-analysis, cross sectional and cohort studies were obtained through searches on PubMed, Medline, Science Direct, Google Scholar, library genesis, Scopus and Web of Science. Key words used for searching are “placenta”, “COVID-19”, “placenta development”, and “placenta histopathology”. *Result:* Total of 16 articles were included in this review. Many articles are reviewed whether the COVID-19 affects placenta histology and pregnancy adverse outcome in intrauterine life. Finally article which fulfills inclusion criteria are identified and reviewed. Review indicated that histopathologic features of placenta and adverse pregnancy outcome in COVID-19 confirmed pregnant women briefly. *Conclusion:* COVID-19 affects the placenta during pregnancy. Histopathologic findings of placenta in pregnant women with confirmed COVID-19 positive are fibrin deposition, micro classification, thrombus, avascular villi, infraction, and villous edema. Most common pregnancy adverse outcome are preterm birth, miscarriage and still birth.

**Keywords:** Used for Searching Are “Placenta”, “COVID-19”, “Placenta Development”, “COVID-19 on Pregnancy”, “Placenta Histopathology”

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## 1. Introduction

Human development is a continuous process that begins when an oocyte from a female is fertilized by a sperm from a male. At intrauterine life, the embryo are attached and surrounded by placenta and fetal membranes to mother's body to obtain oxygen and nutrients [1].

Human placenta develops from the outer layer of pre-implantation embryo, which forms at approximately five days after fertilization [2]. Placenta is highly specialized organ of pregnancy that supports the normal growth and development of fetus [3] Human placenta is discoid shape [4].

During intrauterine fetal life placenta is the main metabolic, respiratory, excretory, and endocrine organ [5]. It develops from two components which is maternal (basal plate) and fetal (chorionic plate). Maternal part develop from

endometrium while fetal part formed from blastocyst [6]. The chorionic plate is covered by the amnion. The amnion is made up of a single layer of epithelium and amniotic mesenchyme, an avascular connective tissue. The placenta increases 14g for every 100g that the product increases. The weight of placenta is hypo trophic if less than 300g and hypertrophic if more than 700g [7, 8].

Basal plate is maternal surface of the placenta. It is an artificial surface that emerges from placental separation from the uterine wall during childbirth. The basal plate is a mixture of extra-villous fetal trophoblasts and all types of maternal cells of the decidualized uterus, including decidual stromal cells, macrophages, and other immune cells. The basal plate also includes huge amounts of extracellular matrix, fibrinoid, and blood clots. It is subdivided into 10 to 40 slightly elevated regions, called cotyledons, and dividing the

cotyledons are the septa that trace the lobe borders as irregular pillars. The cotyledons that are visible on the maternal surface of the placenta show a good correspondence to the position of the villous trees derived from the chorionic plate in the intervillous space [7, 8].

Histologic features of normal placenta are differing according to the trimester of pregnancy. At first trimester placenta features are: chorionic plate, intervillous space surrounding the placental villi, cell islands, and the basal plate from which a septum protrudes into the intervillous space [9].

Histological Features of the third trimester placenta are chorionic plate, including the amnion different types of villi, fibrinoid deposits in various locations, anchoring villi with rudimentary cell columns, cell islands, septa, and the basal plate. In contrast to the first trimester, the width of the intervillous space is highly variable with large “subchorionic lakes” below the chorionic plate and narrow intervillous pores between the terminal villi [9].

During pregnancy, changes in the body's immunity make the individual more susceptible to viral infections. In addition, an immature innate and adaptive immune system of the developing fetus makes it very susceptible to infections with potential detrimental effects on the brain of the fetus and newborn development and function [10]. Studies revealed that COVID-19 infection affect placenta and fetal membrane [11].

Placental abnormalities may affect the placental functions, interfering in turn with maternal and fetal wellbeing [12]. There was evidence in pregnant women with COVID-19 positive result in placental hyperfusion defects in maternal vessels and oxygenation in the intervillous space affecting perinatal outcome [13].

The novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) was first reported in December 2019 in the city of Wuhan, Hubei Province, China. Physicians noted cases of pneumonia of unknown origin, which were later recognized as being caused by a novel beta coronavirus [14] Coronavirus is a positive single-stranded enveloped RNA virus belonging to the family Coronaviridae. The term Coronaviridae is derived from the structural characteristic of the crown-like or halo-like appearance of the

glycoprotein [13].

SARS-CoV-2 enters the body through nasal passage and as a first line affects respiratory system by binding to angiotensin-converting enzyme 2 (ACE2). Viral infections gain access to placenta through lower reproductive tract or hematogenous transmission from maternal blood circulation [15]. Due to high abundance of ACE2 on placenta cell surface COVID-19 also affect placenta [16-18].

Orvos JM. 2021 revealed that placental abnormalities were increased in COVID-19 positive mothers. As a result fetal vascular malperfusion are high among patient with COVID-19 positive with AOR of 12.63 [19]. Jonathon L. et al 2020 indicated that SARS-CoV-2 can infect the placenta but vertical transmission are rare in women with COVID-19 positive [20].

The strong link between trophoblastic damage and SARS-CoV-2 infection in the placenta suggests that this lesion is a specific marker of SARS-CoV-2 infection in the placenta. Diffuse trophoblastic damage affecting chorionic villous tissue can result in fetal death associated with COVID-19 disease [21].

Morphological studies of placenta with COVID-19 indicated that decidua vascular mural hypertrophy (p-value<0.09), absence of spiral arteries remodeling (p-value<0.03), and low placental weight [22].

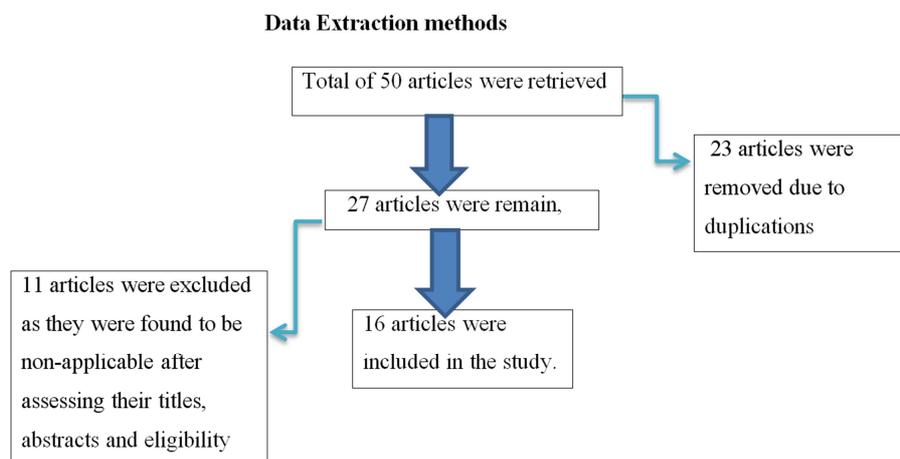
## 2. Objective

- 1) To review the histopathologic features of placenta in women with COVID-19 positive
- 2) To review COVID-19 adverse outcome in pregnancy

## 3. Methods

### 3.1. Literature Search Strategy

Systematic reviews, meta-analysis, cross sectional and cohort studies were obtained through searches on PubMed, Medline, Science Direct, Google Scholar, library genesis, Scopus and Web of Science.



**Figure 1.** Flow of literature selection.

### 3.2. Inclusion and Exclusion Criteria

Studies published in English language were considered. Articles from 2019 to 2021 were included in the study. Complete articles on the topic of interest were included. Incomplete and abstract only articles are omitted from the

review. Some articles with redundant ideas were also omitted by taking the most recent one. Articles published before 2019 were not included. Articles on pregnant women with COVID-19 positive and other risk like pre-eclampsia, gestational diabetes etc. are excluded.

## 4. Results and Discussion

*Table 1. Review of histopathologic features of placenta and adverse outcome in pregnant women with COVID-19 positive.*

Authors, year	Study design	Study area	No of participants	Findings
Hosier et al, 2020	Clinical trial	Switzerland	56 pregnant patients who delivered	diffuse intervillous fibrin was present, inflammatory infiltrate
Tiffany M. et al, 2021	Case report	USA	1 pregnant with COVID-19 positive	subchorial hematoma, complete occlusion of stem villous vessel, partial occlusion of vessel and thrombus, placenta infarct, and avascular villi
Shane's D. 2020	Experimental	China	16 placenta of pregnant mother	intervillous thrombi, villous edema, Atherosclerosis and fibrinoid necrosis
Singh N. et al, 2021	Case series	USA	50 (49 specimens of placenta and 1 conceptus)	increased micro- calcifications, increased fibrin, increased syncytial knotting, small fibrotic villi, and villous agglutination
Smithgall MC, 2020	Experimental (histopathologic examination)	USA	51 COVID-19 positive pregnant women	subchorial thrombus, infarction, segmental avascular villi, thrombotic vasculopathy, villous agglutination
Levitan D. et al, 2021	Experimental (histopathologic examination)	London	64 COVID-19 positive pregnant women and 85 control group without COVID-19 positive pregnant women	hypertrophy of the vessel walls, fibrinoid necrosis with lipid-laden macrophages (acute atherosclerosis), distal villous hypoplasia associated with increased syncytial knots and villous infarction
Schwartz A. et al, 2020	Experimental	USA	29 COVID-19 positive pregnant women and 106 control group without COVID-19 positive pregnant women	chronic histiocytic intervillitis present, Necrosis of the syncytiotrophoblast layer on chorionic villi
Bertero L., 2021	Cohort	Italy	11 COVID-19 positive pregnant women and 58 control group without COVID-19 positive pregnant women	villous agglutination with loss of trophoblasts and micro-calcification, placental inter-villous hematoma, microvascular thrombosis, Significant foci of decidua and villous inflammation, consistent with multifocal and low grade chronic villitis
plegio F. et al, 2021	cohort	Mexico	11 COVID-19 positive women and 4 control group without COVID-19 positive pregnant women	decidua vasculopathy characterized by fibrinoid necrosis, karyorrhexis, avascular villous, chorangiomas, accumulation of fibrin, thrombosis, vessel obliterations and avascular villi
Pulinx B et al, 2020	Case report	Germany	1 COVID-19 positive women	intervillous fibrin depositions, aggregates of histiocytes and cytotoxic T lymphocytes, ischemic necrosis of the surrounding villi
Corona virus 19 adverse outcome in pregnant women				
Hodžić J et al, 2021	Cross-section studies	Bosnia	24 pregnant with COVID-19 positive delivered	preterm birth, admission of newborns to the intensive care unit and intrauterine fetal death
Singh V, 2021	Observational study (cross-sectional)	India	132 COVID -19 positive pregnant women	preterm delivery, caesarian delivery and most of neonates admitted to neonatal intensive care unit
Kazemi SN, 2021	Systematic review	Japan	11 articles reviewed	Miscarriage or abortion, vertical transmission of the virus to fetus, placental insufficiency
Verma S, 2020	Article review	USA		premature rupture of membrane, preterm birth, miscarriage, still birth, non-reassuring fetal distress that result in cesarean section, fetal growth restriction and pre-eclampsia
Patberg ET, 2021	Cohort study	New York	77 COVID-19 positive women and 56 control group without COVID-19 positive pregnant women	preeclampsia, fetal growth restriction, oligohydramnios, and fetal vascular malperfusion abnormalities

### 4.1. Histopathologic Features of Placenta in Patient with COVID-19 Positive

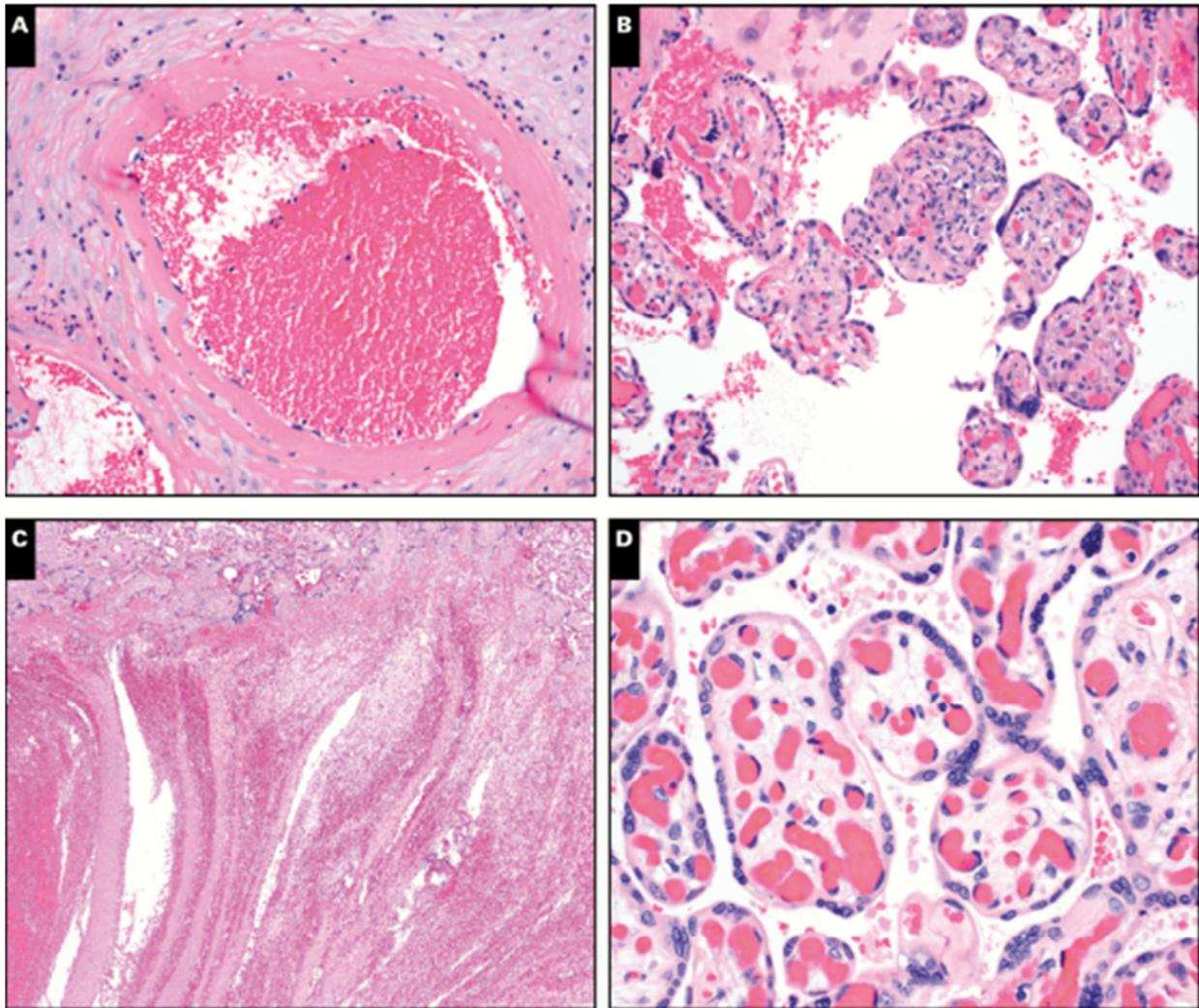
Hosier H. et al 2020 described the histopathology of placenta in pregnant women with COVID-19 positive as

diffuse intervillous fibrin was present, and there was an inflammatory infiltrate composed of T lymphocytes and macrophages [23]. Tiffany M. et al revealed that placenta histopathology in COVID-19 as subchorial hematoma, complete occlusion of stem villous vessel, partial occlusion of

vessel and thrombus, placenta infarct, and avascular villi [24].

Shane's D. 2020 indicated histologic features of women with COVID-19 positive are intervillous thrombi, villous edema, Atherosclerosis and fibrinoid necrosis [13]. Singh N. et al

revealed microscopic findings of viral positive placenta specimens, included increased micro-calcifications, increased fibrin, increased syncytial knotting, small fibrotic villi, and villous agglutination [25].



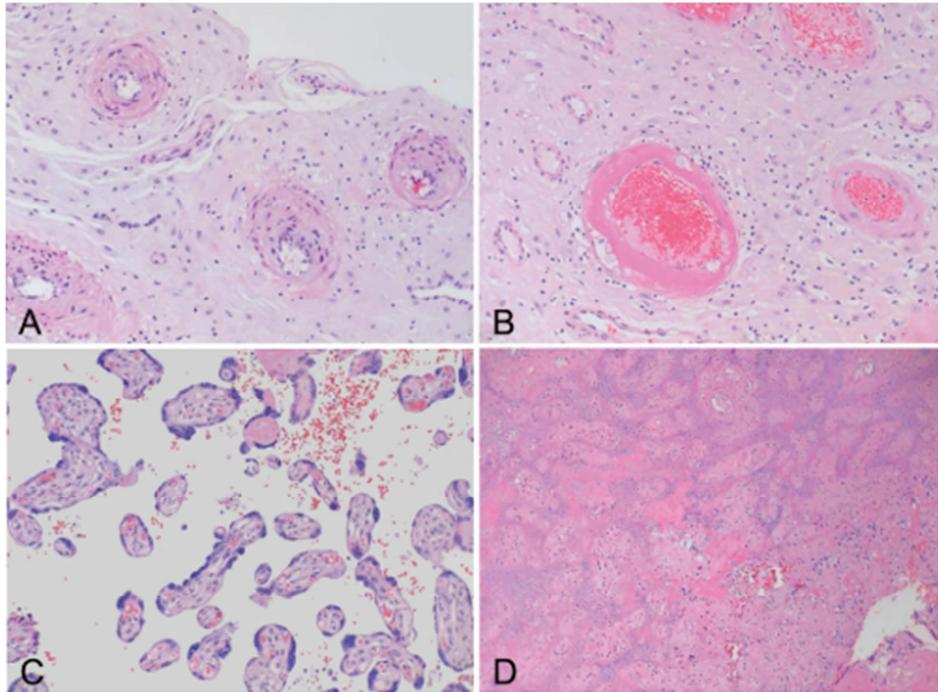
**Figure 2.** Placenta histopathologic findings in COVID-19 women showed A, Maternal arteriole with atherosclerosis and fibrinoid necrosis (H&E  $\times 20$ ). B, Small focus of fetal villi with lymphocytic villitis (H&E  $\times 20$ ). C) Intervillous thrombus showing lines of Zahn (H&E  $\times 5$ ). D, Fetal villi with chorangiosis and edema (H&E  $\times 40$ ) [13].

Studies described that histopathologic findings of placenta with women COVID-19 positive are subchorial thrombus, infarction, segmental avascular villi, thrombotic vasculopathy, villous agglutination [26]. Levitan D. et al revealed microscopic findings of placenta in COVID-19 positive as hypertrophy of the vessel walls, fibrinoid necrosis with lipid-laden macrophages (acute atherosclerosis), distal villous hypoplasia associated with increased syncytial knots and villous infarction [27].

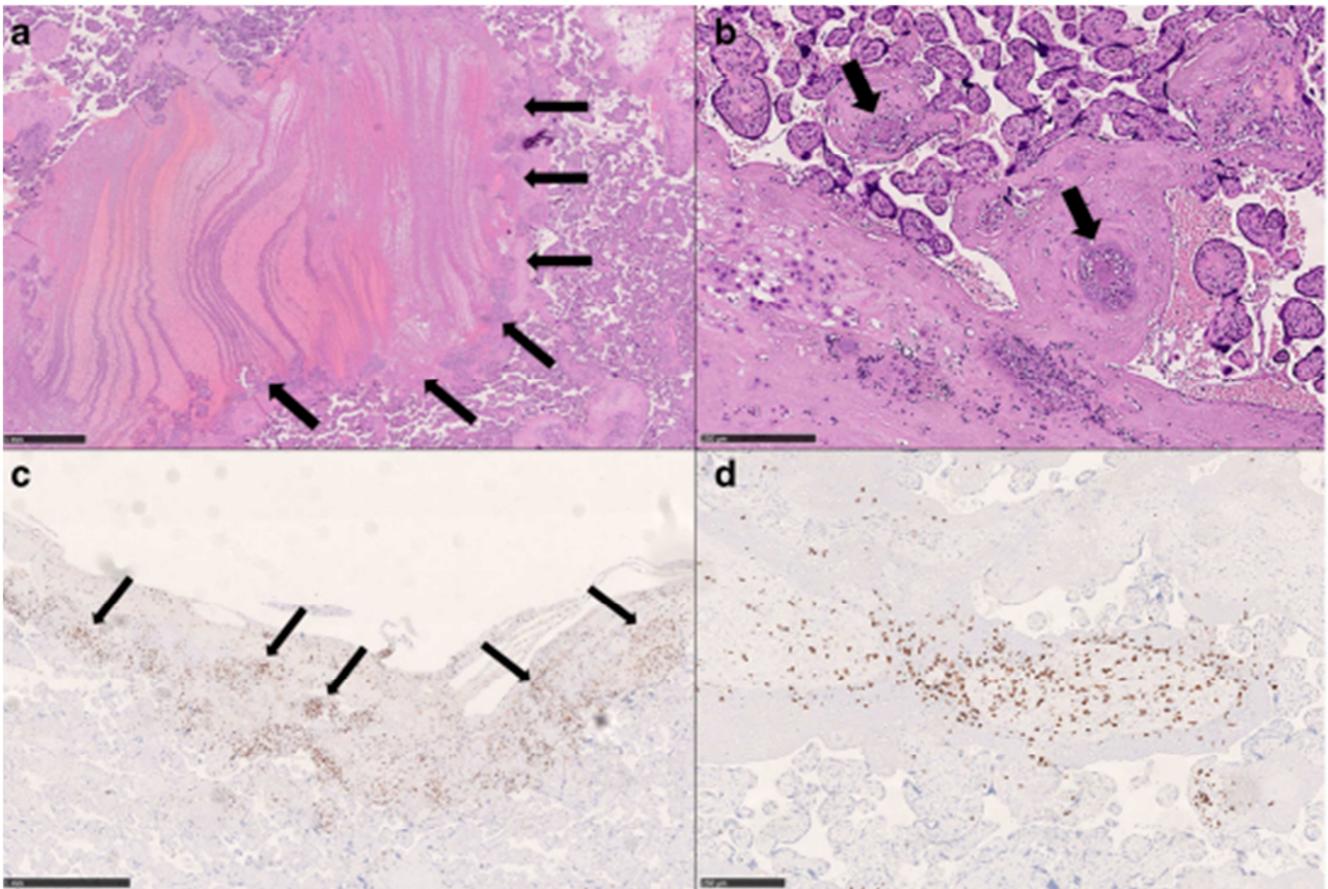
Studies revealed that histological examination, the placenta presence of diffuse perivillous fibrin and an inflammatory infiltrate composed of macrophages and T lymphocytes found [23]. Shanes D. et al described that histologic findings of placenta as mural fibrin deposition in fetal vessels, delayed villus maturation in pregnant women with COVID-19 positive [13].

According to study conducted by Rad H. et al revealed increased fibrin deposition, Infraction, decidua vasculopathy, Hofbauer cell hyperplasia, sub chorionic laminar necrosis, villous edema, avascular villi and delayed villous maturation are most common histopathologic findings in placenta of SARS Co-2 pregnant women [17]. Schwartz A. et al 2020 indicated that prominent chronic histiocytic intervillitis present in which the inflammatory cells in the intervillous space stained positive with the CD68 antibody, Necrosis of the syncytiotrophoblast layer on chorionic villi [28].

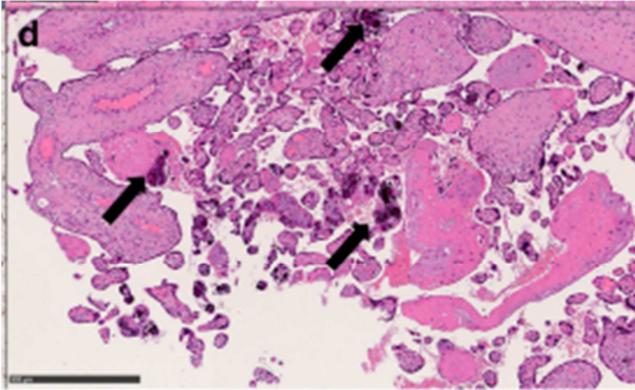
Bertero L. described the histopathologic findings of patient with COVID-19 positive as villous agglutination with loss of trophoblasts and micro-calcification, placental inter-villous hematoma, microvascular thrombosis, Significant foci of decidua and villous inflammation, consistent with multifocal and low grade chronic villitis [29].



**Figure 3.** (A) Hypertrophy of the vessel walls B) fibrinoid necrosis with lipid-laden macrophages (acute atherosclerosis); (C) Distal villous hypoplasia associated with increased syncytial knots and villous infarction (D) (H&E, magnifications 3200 [A and B] and 3100 [C and D]) [27].

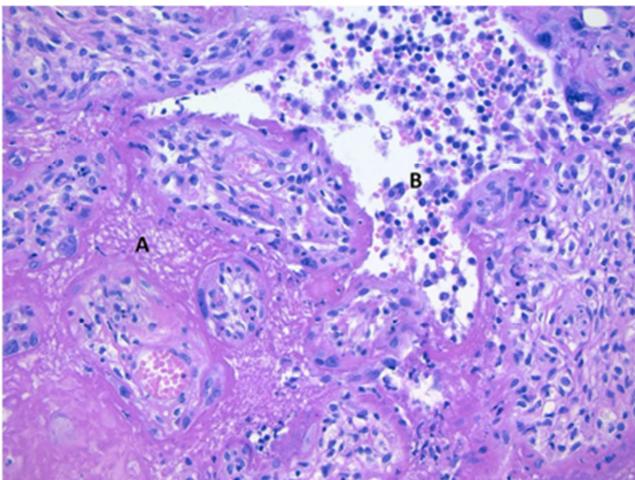


**Figure 4.** Placenta histopathologic findings in COVID-19 women indicate a) intervillous hematomas (A: HE, 20X) b) microvascular thrombosis (B: HE, 100X) c) Significant foci of decidual and villous inflammation (C: anti-CD8 IHC, 30X; D: anti-CD8 IHC, 80X), consistent with multifocal, low grade chronic villitis [29].



**Figure 5.** Placenta histopathologic finding in COVID-19 women indicate Villous agglutination with loss of trophoblasts and micro calcification (HE: 70x) [29].

According to study conducted by Plegio F. et al 2021 indicated decidua vasculopathy characterized by fibrinoid necrosis, karyorrhexis, avascular villous, chorangiosis, accumulation of fibrin, thrombosis, vessel obliterations and avascular villi [30]. Pulinx B et al revealed histopathologic features of placenta in patient with severe acute respiratory system corona virus 2 as intervillous fibrin depositions, aggregates of histiocytes and cytotoxic T lymphocytes, ischemic necrosis of the surrounding villi [15].



**Figure 6.** (H&E stained 20x) of the placenta with intervillous fibrin depositions (A) and aggregates of histiocytes and cytotoxic T lymphocytes (B) [15].

#### 4.2. Adverse Outcome in Pregnant Women with COVID-19 Positive

The COVID-19 pandemic impacts reproductive and perinatal health both directly through infection and indirectly as a consequence of changes in health care, social policy, or social and economic circumstances. Pregnant women who have symptomatic COVID-19 may experience more severe outcomes than people who are not pregnant [31]. According to study conducted Hodzic et al indicated pregnancy during COVID-19 associated with preterm birth, admission of newborns to the intensive care unit and intrauterine fetal

death [32].

Studies revealed that preterm delivery, caesarian delivery and most of neonates admitted to neonatal intensive care unit. The possibilities of vertical transmission are exist with low incidence [33]. Tiffany M. et al indicated that in pregnant women with no significant preexisting conditions or pregnancy complications suggests that fetal death is a potential outcome of COVID-19 during pregnancy [24].

According to study conducted COVID-19 prenatal leads to miscarriage. Those studies indicated that the risk of abortion was found at whole trimester. However, First trimester pregnancy was more risk for abortion due to placental insufficiency. Evidence on cause of miscarriage is limited whether the miscarriage due to maternal or due to vertical transmission of the virus to fetus [34].

Studies described that there was no significant maternal death occurred as a complication of COVID-19 in pregnancy women. However, many adverse outcomes are reported including premature rupture of membrane, preterm birth, miscarriage, still birth, non-reassuring fetal distress that result in cesarean section, fetal growth restriction and pre-eclampsia [10].

Patberg T. et al described adverse prenatal outcome as preeclampsia, fetal growth restriction, oligohydramnios, and fetal vascular malperfusion abnormalities significantly higher in the COVID-19 confirmed pregnant women [35].

## 5. Conclusion and Recommendation

### 5.1. Conclusion

In COVID-19 Positive pregnant women the placenta undergoes alteration in structure and function. This review indicate that histopathologic change of placenta in pregnant women with confirmed COVID-19 positive such as fibrin deposition, micro classification, thrombus, avascular villi, infraction, and villous edema. This alteration related to placenta malperfusion that may leads to oxygen deficiency in the fetus. These abnormalities are risk for pregnancy adverse outcome. Most common pregnancy adverse outcome related COVID-19 are preterm birth, miscarriage and still birth.

### 5.2. Recommendation (Gaps)

- 1) Further study is needed on mechanism of SARS-CoV-2 infection entry in placenta.
- 2) Further study is needed on mechanism of SARS-CoV-2 infection affect prenatal pregnancy.
- 3) Further study is needed on long term complication of COVID-19 on neonates born to prenatal affected mothers.

## Declaration

### Authors' Contributions

Gutu Belay reviewed and prepared the draft of the manuscript.

### Conflict of Interest

The authors declare no conflict of interest in preparing this article.

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