The placental pathology in Coronavirus disease 2019 infected mothers and its impact on pregnancy outcome

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A B S T R A C T

Introduction: This study aims at observing placental pathologies in COVID-19 infected women, and analyzing its impact on pregnancy outcome.
Method: This is a descriptive-analytical study done at a tertiary centre of Northern India. All COVID-19 positive pregnant women with gestational age ≥20 weeks, with placental histopathological reporting, were included in this study. A total of 173 COVID-19 pregnant women were included in the study.
Results: Placental abnormalities were noticed in 49·16% of total 179 placentae examined. Maternal vascular malperfusion (27·93%) was the most observed placental pathology followed by villous fibrin deposits (22·90%), fetal vasculopathy (16·75%), and acute inflammation (6·70%). Stillbirths were 22 and NICU admissions were seen in 50 neonates. Abnormal placental abnormalities led to higher stillbirths (p value 0·011) and lower Apgar scores at 1 and 5 min (p-value 0·028; p-value 0·002, respectively). Intervillous fibrin deposits had higher risk associated with lower Apgar score at 1 and 5 min [RR 2·05 (95% CI 1·21–3·48, p-value 0·010) and RR 5·52 (95% CI 2·58–11·81, p-value <0·001), respectively]. RP clot/hemorrhage was also associated with lower Apgar score at 1 and 5 min [RR 2·61 (95% CI 1·52–4·49, p-value 0·002) and RR 3.54 (95% CI 1·66–7·55, p-value 0·001), respectively].
Discussion: Placental abnormalities in COVID-19 infection were associated with significant higher incidence of unexplained stillbirths, and lower Apgar scores. Although, this is the largest descriptive-analytical study done so far, comparative studies are required to draw a clear conclusion regarding the impact of COVID-19 infection on human placenta and its effect on pregnancy outcomes.

1. Introduction

Since the outbreak of the SARS-CoV-2 virus, also known as Coronavirus disease 2019 (COVID-19), the world has seen more than 197 million infections and 4·2 million deaths globally [1]. The immunocompromised state of pregnancy makes it more susceptible to viral respiratory infections [2]. The placenta which forms the maternal-fetal interface, has an attenuated immune response and is known to host several viral infections [3–6]. Adverse maternal environment like hypoxia, inflammatory activation, and increased thrombotic events secondary to COVID-19 infection makes placenta a potential target for the pathological insult which may lead to adverse pregnancy outcomes [7,8]. Although several studies mention various placental features in COVID-19 infection, no consensus regarding characteristic pathological findings has emerged so far [9–11]. Also, the clinical relevance of the placental pathology seen in COVID-19 infection is yet to be established. In this research article, we aim at studying the placental pathologic findings in women with COVID-19 infection and analyzing its impact on

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the pregnancy outcome.

2. Materials and methods

2.1. Study design

This is a descriptive-analytical study conducted from 1st July 2020 to 30th June 2021 at the Postgraduate Institute of Medical Sciences and Research (PGIMER), Chandigarh, India-a tertiary care institute that has a dedicated COVID-19 obstetrics team along with separate portal ultrasound machine with doppler facilities. The data was collected on a prospective basis from 28th August 2020 onwards. There was no funding source for this study.

2.2. Cases selection

All pregnant women with COVID-19 infection confirmed by nasopharyngeal swabs specimens tested with SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) assay or GeneXpert Dx Xpress SARSCoV-2 RT-PCR assay, who delivered at our center were enlisted for the study. The placentae of these women were sent to the department of pathology and virology for histopathological examination and COVID-19 RT-PCR testing, respectively. All those COVID-19 infected women who delivered at or more than 20 weeks of gestation, and in whom the placental examination was reported, were included in the study. The maternal demography characteristics, obstetrical complications, COVID-19 disease severity, mode of delivery, maternal mortality, and neonatal details were recorded for these women. Neonatal growth restriction was considered when the birth weight was below the 10th percentile according to the growth chart.

2.3. Placental morphologic data collection

As per the institute's protocol, all placentae from the COVID-19 mothers were collected soon after the delivery. They were fixed in 10% buffered formaldehyde, labelled, and transported to the department of pathology and virology at PGIMER, Chandigarh. The placental examination was performed and documented as per the Amsterdam guidelines [12]. The placental morphological reports were then uploaded on the institute's software system named HIS- Laboratory Information System (LIS) software module, specially assigned to the department of pathology for data recording.

The reports of the study women were searched from the HIS-LIS software system with the help of their name and hospital registration number. The placental weight to baby weight (PW/BW) ratio was calculated by dividing the placenta weight and the birth weight. In the case of twins, it was calculated by dividing the placenta weight and the total birth weight (the sum of both twin's birth weight). The growth percentiles of placental weight and PW/BW ratio were calculated as per the nomograms [13,14]. The histopathologic parameters were searched and recorded as per the Amsterdam guidelines. Based on the histopathology of placentae, 2 groups were formed. Group 1 included all the COVID-19 women with the normal placental examination, and Group 2 included all the COVID-19 women with the abnormal placental examination. The maternal clinical characteristics and neonatal outcomes in each group were compared and analysed. The placentae that were sent for COVID-19 infection by RT-PCR testing in the department of virology were also followed and recorded.

2.4. Statistical analysis

The data were analysed using Statistical Package for the Social Sciences (SPSS version 20, IBM SPSS Incorporated, Chicago, IL, USA). Numerical data are presented as the mean and standard deviation (SD), or the median, minimum, and maximum (range), when appropriate. Categorical data are presented as relative and absolute frequencies. For quantitative variables, the group 1 and 2 were compared with the Mann-Whitney U test or Student's t-test, depending on the data characteristics. The associations between qualitative categorical variables were investigated using Chi-square or Fisher's exact tests, when appropriate. Risk assessment was performed by calculating the relative risk (RR) with a 95% confidence interval (CI). The statistical numbers were rounded to two decimal places for mean, standard deviation, percentages, relative risk, and 95% confidence interval. The p-values were rounded to three decimal places. A p-value $<0{\cdot}050$ was considered to indicate statistical significance, and a p-value of $<0{\cdot}001$ was considered highly significant.

3. Results

3.1. Clinical characteristics of COVID-19 positive mothers

A total of 332 COVID-19 positive pregnant women with $\geq$20-week gestation reported to our institute from 1st July 2020 to 30th June 2021. Out of these, placental morphologic examination and reporting were done for 173 COVID-19 mothers. The demographic characteristics and obstetric details of these mothers are represented in Table 1. The mean and median age of the COVID-19 positive mothers was 28·87 ± 4·84 and 29 years, respectively. Out of 173 COVID-19 mothers, only 26 were symptomatic for COVID-19 infection, 15 had severe COVID-19 disease, and six maternal mortalities were seen due to the COVID-19 complications. The interval between the diagnosis of COVID-19 infection and the delivery of the women ranged from 0 to 42 days with a median of 1 day (IQR 0–2 days). A total of 160 mothers had singleton gestations and 13 mothers had twin pregnancies. Out of 173 cases, 4 abortions (baby birth weight <500 g and gestation age <24 weeks) were observed. The mean and median gestational age at delivery was 34·95 ± 4·29 and 36 weeks, respectively. A total of 90 preterm deliveries were noted, out of which 55 were early preterm and 35 were late preterm deliveries. The term deliveries were seen in seventy-nine COVID-19 women. Obstetrical complications like gestational diabetes were seen in 22 women, 26 women were diagnosed with premature rupture of membranes (PROM), and 49 women had hypertensive disorders of pregnancy (34 had preeclampsia, 12 had gestational hypertension, and 3 had chronic hypertension). The fetal growth restriction (FGR) was seen in 19 women, antepartum hemorrhage (APH) in 24, and intrahepatic cholestasis of pregnancy (ICP) was reported in 7 women. Vaginal delivery was seen in 57 women and 112 women underwent caesarean section. A total of 186 babies were born to 173 COVID-19 mothers. Ninety-two were male and 94 were female babies. Congenital malformations were reported in 14 babies and 22 babies were stillborn (including abortion cases). Mean and median baby weight at birth was 2156·15 ± 820·88 and 2202 g. Mean and median placental weight was 465·71 ± 171·35 and 461 g. A total of forty-five babies were born with an Apgar score of <7 and 141 babies had an Apgar score of ≥7 at 1 min of life. The Apgar score at 5 min was <7 in 27 babies, and ≥7 in 159 babies. Sixty-three babies were small for gestational age (SGA), 109 were appropriate for gestational age (AGA), and 14 were large for gestational age (LGA) babies. Neonatal intensive care unit (NICU) admissions were seen for 50 neonates out of 164 live babies.

3.2. Placental morphologic features

A total of 179 placentae of COVID-19 mothers were examined and reported. Out of 13 twin placentae, 8 were dichorionic diamniotic (DCDA), 4 were monochorionic diamniotic (MCDA), and one placenta was fused to a single mass when received by the department of pathology, thereby, chorionicity was not established. Out of 8 dichorionic diamniotic (DCDA) placentae, placental examination and reporting were done separately for each twin in 6 cases, however in 2 cases, the twin placentae were fused in the center, and combined examination and reporting was done. Normal histopathological examination was seen in 91 placentae and abnormal histopathological features were observed in

Table 1

Demographic and clinical characteristics of COVID-19 infected mothers included in the study (n = 173).

	N (%)	Median (IQR)
Maternal age (years)	28·87 ± 4·84	29 (25–32)
Symptomatic patients	26 (15)	
Severity of COVID 19	15	
COVID-19 diagnosis to delivery interval (days)	0–24	1 (0–2)
Maternal mortality	6 (3.5)	
Singleton pregnancy	160 (92.5)	
Twin pregnancy	13 (7.5)	
Mean Gestational age (weeks)	34·95 ± 4·29	36 (32.5–38.2)
Gestational age (weeks)		
<24	4 (2.3)	
24-27 + 6	8 (4.6)	
28-31 + 6	25 (14.5)	
32-36 + 6	57 (32.9)	
37-39 + 6	72 (41.6)	
40–42	7 (4.0)	
Abortions	4 (2.3)	
Preterm delivery-	**90 (52)**	
Early	55	
Late	35	
Term delivery	**79 (45.7)**	
Obstetric complications		
Gestational diabetes mellitus including type 2 DM[c]	22	
PROM	26	
Hypertensive disorder of pregnancy-	49	
Gestational HTN	12	
Pre-eclampsia	34	
Chronic HTN	3	
FGR	19	
ICP	7	
APH	24	
Others (e.g. Heart Disease)	2	
Stillbirths	22 (13.4)	
CMF babies	14	
Mode of delivery [a]		
Vaginal delivery	57 (32.9)	
Caesarean section	112 (64.7)	
Total babies born	186	
Mean baby weight (grams)	2156·15 ± 820·88	
Mean placenta weight (grams)	465·71 ± 171·35	
Growth percentile of PW/BW ratio[b]		
<3	23	
3–10	30	
10–25	38	
25–50	41	
50–75	13	
75–90	18	
90–97	4	
>97	5	
Growth percentile of Placental weight[b]		
<3	37	
3–10	21	
10–25	77	
25–50	2	
50–75	28	
75–90	0	
90–97	2	
>97	5	
Apgar score at 1 min		8 (7–8)
<7	45	
≥7	141	
Apgar score at 5 min		9 (8–9)
<7	27	
≥7	159	
NICU admission	50 (26.9)	
Male baby	92 (49.5)	
Female baby	94 (50.5)	
SGA	63 (33.9)	
LGA	14 (7.5)	
AGA	109 (58.6)	

Numerical data is presented as mean ± standard deviation. Categorical data is presented as frequency and percent proportion with one decimal places (%).

Abbreviations: DM- Diabetes mellitus, PROM-preterm rupture of membranes, HTN- hypertension, FGR-fetal growth restriction, ICP-intrahepatic cholestasis of pregnancy, APH- Ante-partum hemorrhage, CMF- congenital malformation, NICU- neonatal intensive care unit, SGA-small for gestational age, LGA-large for gestational age, AGA, appropriate for gestational age.

[a] Four abortion cases with baby birth weight <500 g were excluded.

[b] Out of total 179 placentae examined, four cases were <24 weeks for which the growth percentile was not available, and three were twins, in which combined placental weight was calculated for both the twin placentas. (n = 172).

[c] One women out of 22 had Type II diabetes mellitus.

88 placentae. In many of the placentae, more than one abnormal morphologic feature was noticed. Detailed abnormal morphologic features according to the Amsterdam guidelines are enlisted in Table 2. Representative images are shown in Fig. 1. The most observed placental morphologic abnormality was maternal vascular malperfusion (MVM), which was seen in 50 cases. We found 33 placentae with villous infarction, 20 had retroplacental (RP) clot/hemorrhage, and 14 placentae with increased syncytial knotting. Other features of MVM were not seen in our study. Fetal vasculopathy was seen in 30 placentae. We found only one placenta with a typical feature (villous stromal-vascular karyorrhexis) of fetal vasculopathy (FV). In the rest of the 29 placentae, concentric medial hypertrophy of stem vessels causing partial occlusion of stem vessels was noticed. In none of the placentae, complete stem vessel obliteration was observed. We did not find any other

Table 2

Details of Abnormal placental histopathological finding (N = 88[b]).

	N	Percentage[a] (%)
Delayed villous maturation	2	1·12
Maternal vascular malperfusion (MVM)	50	27·93
Villous infarction-	33	18.43
Central	13	
Peripheral	19	
Maternal floor infarction	1	
Increase in Syncytial knots	14	7·82
RP clot/hemorrhage	20	11·17
Fetal vasculopathy (FV)	30	16·75
Villous Stromal-Vascular Karyorrhexis	1	0·56
Stem Vessel Obliteration	29	16·20
Intervillous thrombi	1	0·56
Villous fibrin deposits-	41	22·90
Villous fibrin (extensive—>70%)	7	
Villous fibrin (multifocal- 30–70%)	11	
Villous fibrin (focal—<30%)	23	
Acute infection	12	6·70
Chorionitis	3	
Chorioaminitis	7	
Subchorioaminitis	2	
Chronic inflammation	9	5·03
Villous fibrosis	9	5·03
Hydropic changes	6	3·35
Villous edema	2	1·12
Chorioangiosis	6	3·35
Pseudoknot	1	0·56
Meconium staining	5	2·79
Abnormal cord	5	2·79
Single umbilical artery	4	
Supernumerary vessels	1	

Abbreviations: RP- retroplacental

[a] Relative frequencies out of total 179 placentae examined.

[b] A total of 173 patients were finally recruited in the study. Out of which, 13 had twin placentae. Out of 13 twin placentae, 8 were dichorionic diamniotic (DCDA), 4 were monochorionic diamniotic (MCDA), and one placenta was fused to a single mass when received by the department of pathology, thereby, chorionicity could not be established. Out of 8 DCDA placenta, 5 were received in pathological department as separate placenta, therefore gross examination was done separately for each placenta. In other twin placentae, reporting was done together. Thus, **160 singleton + (13 + 5) twin placenta = 179 placentae were studied**. A total of 91 placentae were studied normal from 89 mothers and 88 placentae from 84 mothers, had one or more abnormal histopathological findings.
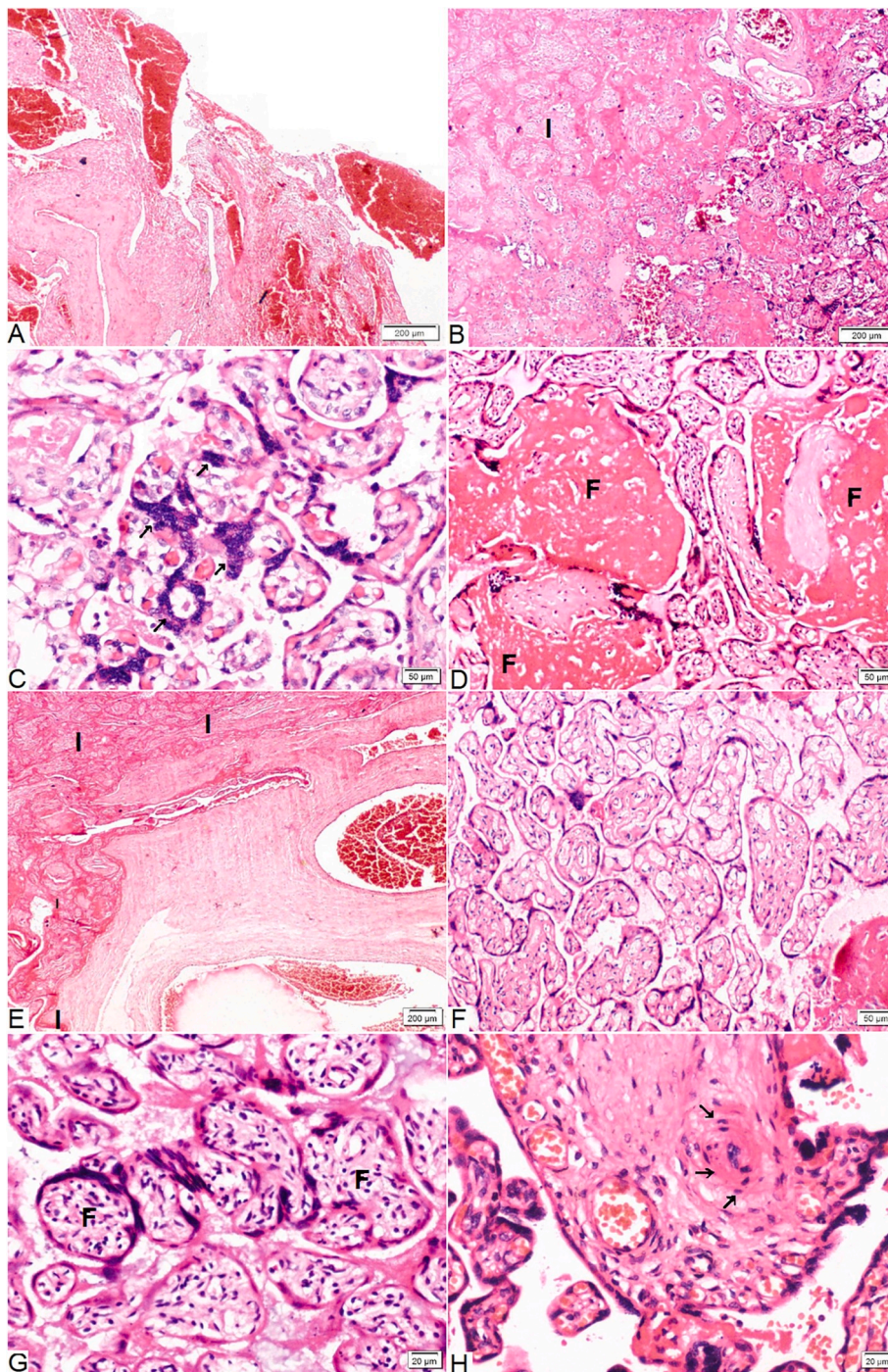
Fig. 1. Placental abnormalities seen in COVID-19 positive women. A, Retroplacental clot; B, Infarction (area marked by letter I); C, increased syncytial knots (arrows); D, increased perivillous fibrin deposition (area marked by letter F); E, Maternal floor infarction (area marked by letter I); F, chorangiosis; G, Villous fibrosis; H, Vascular occlusion seen in stem villous (arrows). (Haematoxylin-Eosin stain, o.m. A, B, E x100; C, D, F x200; G, H x400).

features of fetal vascular changes. Chronic inflammation was seen in nine placentae. Villous fibrin deposition was seen in 41 placentae. Six placentae showed features of chorioangiosis. A total of five abnormal umbilical cords were observed in our study, four had two-vessel umbilical cords, and one had four-vessel umbilical cord (duplication of umbilical vein). Few other morphologic abnormalities that were observed in our study are villous edema (two placentae), delayed villous maturation (two placentae), villous fibrosis (nine placentae), pseudoknot (one placenta), and hydropic changes (six placentae). Meconium staining was seen in five placentae. Umbilical vasculitis was not noticed in our study.

3.3. Placental virology testing for COVID-19 virus

Out of 179 placentae, 15 placentae were tested for the presence of SARS-CoV-2 virus by RT-PCR testing. Only two placentae were tested positive for the SARS-CoV-2 virus. Interesting, the morphologic examination of one of these placentae (fused DADC placenta) was normal: the twin neonates were tested negative for SARS-CoV-2 and discharged healthily. The other singleton placenta showed multifocal villous fibrin deposition and partial occlusion of stem villi. The neonate born with this placenta was also tested positive for the SARS-CoV-2 virus.

3.4. Abnormal placental morphology and clinical outcome

Table 3 demonstrates the comparison of clinical characteristics and neonatal outcomes of the COVID-19 women with normal placental histopathology (group 1, n = 89) and with abnormal placental findings (group 2, n = 81). The mean age and mean gestational age of the two groups were comparable. There was no difference in COVID-19 diagnosis to delivery interval, number of symptomatic COVID-19 mothers, and COVID-19 disease severity in the two groups. Six twin deliveries were observed in group 1 and eight twins were seen in group 2. Preterm deliveries were seen in 42 women in group 1 as compared to 48 in group

Table 3

Comparison of clinical characteristics and pregnancy outcome of COVID-19 positive mothers with normal (N=89$^{\delta,a}$) and COVID-19 positive mothers with abnormal (N=81$^{\delta}$) placental morphological features.

	Group 1 n = 89$^{\delta,a}$	Group 2 n = 81$^{\delta}$	P-value	Statistical Test applied
Maternal age (years)	29·29 ± 4·96	28·51 ± 4·74	0·293	Independent t-test (two-tailed)
COVID-19 diagnosis to delivery interval (median, IQR)	1, 0–1 days	1, 0–2 days	0·258	Mann Whitney test
Symptomatic patients	14	12	0·868	Chi square test
Severity of COVID 19	8	7	0·936	Chi square test
Twin gestation	6	8	0·458	Chi square test
Mean gestational age (weeks)	35·45 ± 3·95	34·44 ± 4·56	0·122	Independent t-test (two-tailed)
Mean placental weight (grams)	471·72 ± 145·01	470·27 ± 197·08	0·956	Independent t-test (two-tailed)
Mean placental weight/baby weight (PW/BW) ratio	0·21 ± 0·07	0·24 ± 0·18	0·066	Independent t-test (two-tailed)
Preterm delivery	42	48	0·167	Chi square test
Gestational diabetes mellitus including type 2 DM	12	10	0·825	Chi square test
Preeclampsia	16	18	0·489	Chi square test
FGR	9	10	0·644	Chi square test
ICP	3	4	0·710	Fisher's Exact test
Abruption Placenta	7	4	0·540	Fisher's Exact test
Stillbirths	4	14	0·011*	Fisher's Exact test
CMF	6	8	0·458	Chi square test
Mean Baby weight (grams)	2333·36 ± 718·44	2182·36 ± 802·59	0·198	Independent t-test (two-tailed)$^{\varphi}$
Apgar score <7 at 1 min	15/94	26/88	0·028*	Chi square test
Apgar score <7 at 5 min	5/94	18/88	0·002*	Chi square test
NICU admission	23/90 = 25·5%	27/74 = 36·5%	0·130	Chi square test
Male baby	47/94	42/88	0·759	Chi square test
SGA	29/94	34/88	0·269	Chi square test

Numerical data is presented as mean ± standard deviation or median and range. Categorical data is presented as frequency or proportion.

Abbreviations: FGR-fetal growth restriction, ICP-intrahepatic cholestasis of pregnancy, CMF- congenital malformation, NICU- neonatal intensive care unit, SGA-small for gestational age.

$^{\delta}$Data of four mothers and their fetus born with fetal weight <500 g were excluded from the statistical analysis [one from group 1 (89–1 = 88 mothers) and three from group 2 (84–3 = 81 mothers)]. Thus, total viable neonates born were 182.

*Statistically significant value.

^{a} In one case of twin gestation, placental examination of one twin placenta was normal and other placenta was abnormal (duplication of umbilical vein, i.e., four vessel cord). Therefore, for the purpose of comparison, the maternal characteristics of the twin babies were duplicated (88 + 1 = 89) and entered in each group.

2. There was no significant difference in preeclampsia or gestational diabetes cases. Also, there was no difference in the number of cases of intrahepatic cholestasis of pregnancy (ICP), abruptio placentae, fetal congenital malformations, and fetal growth-restriction. The total number of male babies were also similar in both groups. The mean baby weight was also comparable in both groups. A significantly higher incidence of stillbirths was observed in group 2 in comparison to group 1 (14 vs 4, p-value 0.011). The number of neonates born with Apgar score <7 at 1 min and 5 min were also significantly higher in group 2 as compared to group 1 (Table 3). However, the total number of NICU admissions was comparable in both the groups. The number of small for gestational age babies was also similar in both the groups. The mean placental weight and PW/BW ratio was also comparable in both the groups.

3.5. Impact of abnormal placental findings on apgar score at 1 min and 5 min

The detailed statistical analysis of the relationship of abnormal placental findings and Apgar score <7 at 1 min and 5 min is shown in Table 4. The presence of villous infarction in placentae resulted in significantly lower the Apgar score at 5 min. The Apgar score at 1 min was not significantly affected by the presence or absence of villous infarction in the placenta. The relative risk of getting significantly lower Apgar score at 1 min and 5 min in the presence of RP clot/hemorrhage was 2·61 and 3.54, respectively. The relative risk for lower Apgar score at 1 min and 5 min in the presence of intervillous fibrin deposits was 2·05 and 5·52, respectively. The other placental morphological findings like chronic inflammation, syncytial knots, acute infection, or stem vessel obliteration did not impact the Apgar score at 1 and 5 min (Table 4).

4. Discussion

Various studies describe the association of maternal covid-19 infection with placental morphology [9,15–19]. However, only a few studies mention the impact of placental morphological changes in COVID-19 infection on pregnancy outcomes [16,20]. Our study, by so far, is the first study that describes the placental morphological features in a large subgroup of COVID-19 infected mothers and correlates these findings with the pregnancy outcome of these mothers.

We studied 179 placentae delivered from 173 COVID-19 infected women with ≥20 weeks' gestation. The incidence of placenta showing at least one abnormal finding on histopathological examination (HPE) in COVID-19 infected mothers was 49·16%. The most common abnormal finding was maternal vascular malformation (27·93%), followed by villous fibrin deposition (22·90%), fetal vasculopathy (16·75%), and acute inflammation (6·70%). The placental abnormalities were not related to the symptoms or disease severity of COVID-19 infection. Sharps et al. analysed 20 placentae and found that MVP is seen in 46% of cases, fetal vasculopathy is seen 35·3%, villitis in 8·7% cases, intervillositis in 5·3% of cases, and chorioamnionitis 6% of cases [10]. Shane et al. found that third trimester placentas were significantly more likely to show at least one feature of MVM, with prominent features of decidual arteriopathy including atherosis and fibrinoid necrosis and mural hypertrophy of membrane arterioles [17]. Zhang et al. in 74 placental examinations found no specific histopathological feature in the placenta for COVID-19 infection. However, they did find that mural hypertrophy had higher odds with COVID-19 infection [19]. Gulersen et al. also found no statistical difference in the histopathological changes in placentae delivered from COVID-19 infected women (n = 50) and matched non-COVID-19 infected women (n = 50) [9]. Hypertensive disorders of pregnancy are major risk factors for MVM [21,22]. The maternal vascular malperfusion can lead to FGR, preterm births, and stillbirths [12,23–25]. We did not find an increased incidence of preeclampsia or clinically detected abruptio placentae in mothers with

Table 4
Relationship of abnormal placental findings with neonatal Apgar score at 1 min and 5 min (n = 182).

Placental morphologic findings[c]	Apgar score <7 at 1 min (n = 41)	Apgar score ≥7 at 1 min (n = 141)	P-value	Relative Risk (95% CI)	Apgar score <7 at 5 min (n = 23)	Apgar score ≥7 at 5 min (n = 159)	P-value	Relative Risk (95% CI)
Villous Infarction	11	22	0·101	1·66 (0·93–2·95)	8	25	0·026[a]	2·41 (1·11–5·21)
Chronic Inflammation	4	5	0·117[δ]	2·08 (0·95–4·55)	3	6	0·089[δ]	2·88 (1·05–7·93)
Syncytial knots	3	10	1[δ]	1·03 (0·37–2·88)	3	10	0·216[δ]	1·95 (0·66–5·71)
Retro-placental clot/ hemorrhage	10	10	0·002[a]	2·61 (1·52–4·49)	7	13	0·001[a]	3·54 (1·66–7·55)
Acute infection	4	8	0·472[δ]	1·53 (0·66–3·58)	3	9	0·180[δ]	2·13 (0·73–6·15)
Intervillous fibrin deposition	15	25	0·010[a]	2·05 (1·21–3·48)	14	26	<0·001[b]	5·52 (2·58–11·81)
Stem vessel obliteration	7	21	0·733	1·13 (0·56–2·29)	4	24	0·759[δ]	1·16 (0·43–3·15)

Note: Categorial data is presented as frequency. Statistical analysis is performed by Pearson Chi square test.
[δ]Statistical analysis performed with Fisher's exact test.
[a] Statistically significant value.
[b] Statistically highly significant value.
[c] The placental morphologic data was duplicated for seven twins (with fused placentae), for the purpose of statistical analyses.

abnormal placental pathologies (Table 3). However, we did find increased incidences of RP clots/hemorrhages on placental morphologic examination (n = 20). It can be a possibility that COVID-19 infection led to silent antepartum hemorrhages.

We also studied the outcome of neonates born to COVID-19 mothers with abnormal placental morphology and compared them with the outcomes of neonates born to COVID-19 mothers with normal placental morphology. We observed that abnormal placentae found in COVID-19 mothers led to a higher incidence of stillbirths (p-value 0·011). These stillbirths were clinically unexplainable as, they were not associated with higher incidence of pre-eclampsia, FGR, ICP, or abruptions. Also, the neonates born to COVID-19 mothers with abnormal placental morphologic features had significantly lower Apgar scores at 1 min and 5 min (p-value 0·028 and 0·002, respectively). However, NICU admissions were not affected by the presence of abnormal placental features. Jaiswal et al. in a small comparative case-control study also studied the impact of placental injury in COVID-19 mothers (n = 27) on the pregnancy outcome and found no significant impact on neonatal outcomes [20]. Rebutini et al. also didn't find any significant impact of placental changes seen in COVID-19 mothers (n = 19) on their pregnancy outcome [16]. We, on the other hand, found a significant association of RP clot/hemorrhage and intervillous fibrin deposition with lower Apgar scores at 1 min and 5 min (Table 4). The increased systemic thrombotic events and microvascular injury syndrome seen in COVID-19 infection can affect the placenta leading to turbulent and slow blood flow, progressive rise in fibrin degradation products, decreased fibrinolysis and increased hypoxic-ischemic injury. Intriguingly, these placental changes can be so unpredictable and quiet, that early detection and intervention can be very difficult at times.

The major limitation of our study is the lack of comparison with non-COVID-19 controls. Thus, we cannot concretely say that the changes seen in our study are directly related to COVID-19 infection. The incidence of placental injury in COVID-19 infection in our study is nearly 50%. We agree that these changes are also seen in other pathologies and in normal cases as well and we found no effect of symptomatic/severe COVID-19 infection on the placental pathologies. Thus, it is difficult to comment regarding the exact pathophysiological changes of COVID-19 infection in our cohort. Further studies are needed to find out the effect of COVID-19 viral load on the severity of the placental injury. However, it can be postulated that it can affect the pregnancy outcomes leading to the higher incidence of silent abruptions, unexplained stillbirths, and lower Apgar scores. Therefore, vigilant antenatal and intrapartum monitoring is a must in all cases of COVID-19 infected women.

To conclude, our study is the largest descriptive-analytical research

that studies the placental abnormalities in COVID-19 infection. The COVID-19 infection is associated with abnormal placental morphologic features in nearly 50% of the cases. The abnormal placental morphologies seen in COVID-19 mothers are associated with poor pregnancy outcomes. The incidence of unexplained stillbirth is significantly higher in these women. Babies born to COVID-19 mothers with abnormal placental histopathology have significantly poor neonatal Apgar scores at 1 and 5 min. Intervillous fibrin deposition and RP clots/hemorrhage are significant risk factors for lower neonatal Apgar scores at 1 min and 5 min. Villous infractions have a significant impact on the neonatal Apgar score at 5 min. Further comparative studies are required to draw a clear conclusion regarding the impact of COVID-19 infection on placenta and its effect on pregnancy outcome.

Ethical clearance

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Contributors

BJ and AC equally contributed to the study. BJ and AC designed and conceptualized the study. BJ helped in data collection and verified the clinical obstetric data. AC did literature search, collected the data, drafted the manuscript, performed statistical analyses. BJ, RS, and SSS helped in data collection and verified the data. BJ, RS, GRVP, VS, RB, SSS, GDP, AB, VS, RB coordinated the sample collection and recording, helped in data interpretation, and edited the manuscript. BJ, AC, and RS take responsibility for the integrity of the data and the accuracy of the data analysis, critically revised the manuscript for important intellectual content, and agreed to submit the final version for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data sharing

Restrictions apply to the availability of these data and so they are not publicly available. The data that support the findings of this study are

available from the corresponding author upon reasonable request and with the permission of the institute.

Declaration of competing interest

We declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2022.07.009.

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