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Effects of SARS-Cov-2 mRNA vaccine on placental histopathology: Comparison of a population of uncomplicated COVID-19 positive pregnant women

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ABSTRACT

1. Introduction: This study investigates the impact of SARS-CoV-2 infection on placental histopathology in pregnant women, comparing outcomes between vaccinated and non-vaccinated individuals. Despite known adverse pregnancy outcomes linked to SARS-CoV-2 infection, the specific effects on the placenta remain unclear. Although vaccination has demonstrated a substantial reduction in infection severity, its impact on placental health requires more insight.

2. Methods: Between March 2021 and July 2022, 387 COVID-19-positive women were admitted for delivery. Of these, 98 with non-severe symptoms were analyzed: 35 vaccinated during pregnancy, and 63 non-vaccinated. Two independent pathologists evaluated all placental specimens.

3. Results: The only differing obstetrical characteristic between groups was the mode of delivery (p 0.047), lacking clinical implications. Over 85% of placentas exhibited microscopic abnormalities, predominantly maternal vascular supply disorders (vaccinated 89.1%; unvaccinated 85.5%).

Comparing vaccinated and unvaccinated groups revealed statistically significant differences, notably in increased focal perivillous fibrin deposits (IFPFD) [17.1% vs. 33.3% (p 0.04)] and avascular fibrotic villi (AFV) [0% vs. 11.1% (p 0.04)]. Binomial logistic regression confirmed the vaccine's protective role against IFPFD (aOR 0.36; 95%CI 013–0.99) and AVF (aOR 0.06, 95% CI 0.003–0.98). A sub-analysis in vaccinated women showed a positive correlation between the timing of the first dose and IFPFD presence (p 0.018).

4. Discussion: The lower incidence of maternal and fetal vascular malperfusion placental features in vaccinated women, coupled with the timing correlation, supports the vaccine's protective effect on placental tissue in COVID-19-infected pregnant patients. Notably, no side effects were reported post-vaccination, emphasizing the vaccine's safety and advocating for its secure administration in pregnant populations.

1. Introduction

Over the years of the Coronavirus pandemic (SARS-CoV-2) the universal knowledge about the effect of the virus infection on pregnant women, fetuses, and newborns has been continuously enriched [1–3]. It has been clarified that SARS-CoV-2 infection is significantly related to adverse pregnancy outcomes, increasing the odds of premature delivery, pre-eclampsia, stillbirth, maternal and neonatal mortality [4]. Because of its potential clinical consequences, placental involvement in SARS-CoV-2 infection has been the point of interest of many studies [5,6]. It is well known that the placenta expresses receptors for SARS-CoV-2, angiotensin-converting-enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) and, therefore, direct infection of the placenta is possible. However, viremia in pregnant COVID-19-positive patients is uncommon and there is little placental

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Abbreviations

(ACE2) Angiotensin-converting-enzyme 2
(TMPRSS2) transmembrane serine protease 2
(FVM) fetal vascular malperfusion
(MVM) maternal vascular malperfusion
(RT-PCR) quantitative reverse transcription-PCR
(IFPFD) increased focal perivillous fibrin deposits
(AFV) avascular fibrotic villi
(FFPE) formalin-fixed, paraffin-embedded

co-expression of ACE2 and TMPRSS2, which is required for the virus to infect cells [7]. Moreover, the placental expression of ACE2 is higher during early pregnancy while it declines at full term and the placenta direct infection seems to be rare [8]. Several studies focused on the placenta histopathological findings in SARS-CoV-2 infection and identified some common histopathological patterns [9]. More specifically, Sharps et al. in a structured review including 50 studies about placental histopathology in SARS-CoV-2 infected pregnant women, showed how signs of fetal vascular malperfusion (FVM), maternal vascular malperfusion (MVM) and signs of inflammation can be detected even in the absence of a confirmed positivity for SARS-CoV-2 in the newborn or in the placental tissue [10]. When placental infection occurs, a severe inflammatory syndrome named SARS-CoV-2 placentitis is observed. The histopathology of this condition has been described by a series of 68 cases of stillbirth SARS-CoV-2 placentitis associated, where the causes of fetal demise were likely due to hypoxic-ischemic injury resulting from severe placental damage rather than direct placental fetal infection [11]. In this case series, the most frequent microscopic findings were histiocytic intervillositis, perivillous fibrin deposition and trophoblast necrosis, a triad that was identified in 65 of 69 placentas (97%). Frequently, COVID-19 related placental injuries could be detected without any correlation with fetal and/or neonatal outcomes, especially in cases with short latency between SARS-CoV-2 infection and delivery [12].

Considering the above, there has been heightened interest and excitement in vaccination against SARS-CoV-2 in pregnancy. This notwithstanding, there has been a certain hesitation to receive vaccines among pregnant population, due to the concern about the consequences of vaccines for them and their infants. The reassuring evidence from preliminary data on safety and immunization properties of SARS-CoV-2 vaccines [13,14] has led many Governments and Scientific Society, as the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and the Centers for Disease Control and Prevention to state that all pregnant women should be vaccinated to reduce maternal and fetal-neonatal morbidity and mortality [15,16].

Since then, many authors have evaluated the effects of available vaccines on preventing adverse outcomes in case of SARS-CoV-2 infection. A large meta-analysis reported a significative reduction of stillbirth [17], confirming the anticipated positive effect of vaccination. Meanwhile, pathologists worldwide analyzed placental specimens to enlighten the pathways of the immunological protective role. Smithgall et al. compared two cohorts of tested negative for SARS-CoV-2 pregnant women, 164 fully vaccinated and 267 who did not receive the vaccine, reporting no significant difference in placental findings [18]. Same results were for a similar but smaller study by Shanes et al. [19].

Despite this, the research studies available on placental histology in COVID-19 infection and the effects of vaccines have still limitations, due to the small population or confounding factors for each study. Moreover, most of the studies are focused on severe cases with relevant fetal and maternal adverse outcomes [20] or are aimed to evaluate the safety of the available vaccines [21]. Consequently, many concerns remain about placental involvement, the risk of vertical transmission and the effect of the vaccine on the placenta. In this study, we aim to evaluate the potentially protective role of vaccines against placental damage and their detectability through histopathological examination. Therefore, we compare two cohorts of SARS-CoV-2 non-severely affected women, vaccinated and non-vaccinated, to establish whether these two groups show some difference in the histological findings of placentas and in perinatal outcomes. Then we analyze the timing of vaccine administration to evaluate the possible correlation with microscopic placental findings.

2. Materials and methods

This is a retrospective single-center study including SARS-CoV-2 positive pregnant women who delivered between March 2021 and July 2022 at Fondazione Policlinico Universitario "Agostino Gemelli" of Rome. Since the beginning of the pandemic, all pregnant women admitted to the hospital for delivery were tested for SARS-CoV-2, according to the screening policy of the hospital. The diagnosis was performed using a quantitative reverse transcription-PCR (RT-PCR) SARS-CoV-2 test on a nasopharyngeal swab at admission. According to Italian National Health System (*Istituto Superiore di Sanità* - ISS) since September 2021, COVID-19 vaccination was extended to pregnant women in the second and third trimesters of pregnancy using mRNA recombinant vaccines (Pfizer-BioNtech®). The administration of at least two doses of vaccine during pregnancy was considered to define a woman as fully vaccinated.

The infection for SARS-CoV-2 (Delta or Omicron variants) was confirmed in 387 women at admission, whose data were gathered into a computer database. We decided to include singleton, full-term (beyond 37 weeks of gestation), and non-complicated pregnancies in the analysis. Pregnant women with chronic pathologies or pregnancy-related conditions that could potentially have an impact on the histopathology of the placenta (chronic hypertension, pre-eclampsia, gestational or pre-gestational diabetes, intrahepatic cholestasis of pregnancy) were excluded, as were smokers. A total number of 98 patients were eligible for the analysis, n = 35 vaccinated and n = 63 not vaccinated. We evaluated maternal features (age, ethnicity, parity, body mass index BMI, gestational age at infection, clinical symptoms, of SARS-CoV-2 infection) and data about the delivery (gestational age, mode of delivery, neonatal birthweight, cord blood gas analysis). After birth, all the placentas of the patients included were collected, sealed, and sent to our Pathology Department for macroscopic and microscopic histopathologic examination.

The primary outcome of our study was to assess the differences in terms of placental histological findings between vaccinated and non-vaccinated SARS-CoV-2 positive women, to find out the effect of vaccine administration. Then we performed a sub-analysis of the vaccinated group to analyze the possible correlation between doses of vaccine and timing of administration on placental inflammatory microscopic features.

All the participants gave written consent at the hospitalization after a positive SARS-CoV-2 screening test. This study received acceptance by the Departmental Ethics Committee of the Catholic University of Sacred Heart, Rome (DIPUSVSP-17-05-2133). This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

2.1. Placental examination

The placentas collected after delivery were fixed in 10% neutral buffered formalin and examined in the Pathology laboratory. The macroscopical examination was carried out according to an international protocol in adherence to the Amsterdam placental workshop group consensus statement [22]. The sections were cut in 1-cm thickness slices, formalin fixed, paraffin embedded (FFPE), and subsequently stained with Hematoxylin and Eosin (H&E). Slides were reviewed independently by two placental pathologists (VA and EN) blinded to the

vaccination status of the participants and blinded to each other. Pathologists evaluated at least two sections of the umbilical cord and of the membranes and up to six full-thickness sections of each placenta. When diagnostic discordance was present, slides were reviewed at a multi-headed microscope and discussed until a diagnostic agreement was reached. According to Amsterdam Placental Workshop Group placental pathological findings were classified in: maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), delayed villous maturation, acute chorionamnionitis and villitis of unknown etiology [23].

2.2. Statistical analysis

Statistical analysis was performed using SPSS Version 20 (Statistical Package for Social Science, Chicago, Illinois - USA). The normality of data distribution was assessed using the Kolomogorov-Smirnov test. Categorical variables were expressed as frequencies, while continuous variables normally distributed were disclosed as mean ± standard deviation (SD). The means were compared using Student's T-test, whereas the chi-square and Fisher's exact tests were employed to compare the frequencies between the two groups. Chi-square was also used to calculate odds ratio (OR) using 2 × 2 contingency tables for binary variables. The 95% confidence interval (95%CI) was calculated to provide a range within which we can reasonably infer that the true OR lies.

Bivariate logistic regression analysis was employed to assess the relationship between the presence of placental abnormalities in SARS-CoV-2 pregnant patients and the adjusted OR (aOR), including different predictor variables that showed significant differences in the comparison of the two populations. A $p < 0,05$ was considered statistically significant.

3. Results

The baseline characteristics of the study population are shown in Table 1. No statistically significant differences arose from the comparison of the two groups in terms of maternal or neonatal features, including maternal age, BMI, neonatal birth weight, and the presence of mild symptoms of COVID-19 infection. A moderately significant difference between the vaccinated and non-vaccinated pregnant women resulted in the mode of birth (p 0,047). Analyzing histopathological placental findings distribution (Fig. 1), it is evident how the most represented alterations are by far those of the maternal compartment (MVM), similarly distributed between the two groups. More than 85% of analyzed placentas showed microscopical abnormalities. Among the MVM lesions, only increased focal perivillous fibrin deposits (IFPFD) (that accounts for 27,6% of total MVM) showed a statistically significative difference between vaccinated women and those not-vaccinated (respectively 17,1% vs 33,3%, p 0,04) with an OR of 0,36 (95%CI 0,15–1,15). Other features of MVM as increased syncytial knots (p 0,93), villous agglutination (p 0,19) and distal villous hypoplasia (p 0,44) did not show any relevant differences between the two groups (Table 2). No features of villitis, insufficient vascular remodelling, fibrinoid necrosis, microscopic accretism and intramural fibrin deposits were present in all the placenta specimens in both groups. The most relevant difference in terms of FVM has been found in avascular fibrotic villi (AFV) distribution, present only in the unvaccinated women group (7 cases, 11,1%; p 0.04).

Then we performed a sub-analysis in vaccinated participants to evaluate the relationship between time since vaccination and the risk of developing IFPFD (the only features presenting statistically significant differences in our study group) (Table 3). Interestingly, comparing the mean interval between the first dose and the delivery using Student's T-test, the placentas of women receiving earlier the vaccine showed a statistically significant difference in the incidence of IFPFD (p 0,018) (Fig. 2). So, the longer the first dose-to-delivery interval, the lower the incidence of IFPFD. On the other hand, no differences came out considering the last dose and the delivery (p 0,141). The same analysis was not performed for AFV since this FVM was not retrieved in placentas from vaccinated patients.

Table 1
Maternal and neonatal characteristics of the 98 COVID-19 positive pregnant women.

Maternal and neonatal Characteristics	All COVID-19 cases (n 98)	Vaccinated women (n 35)	Not vaccinated women (n 63)	p-value
Age	33,0 (±6,0)	32,6 (±5,23)	33,06 (±6,35)	0,71
Ethnicity				
- White (86)	86 (87,7%)	32 (91,4%)	54 (85,7%)	0,41
- Black (3)	3 (3,1%)	0 (0%)	3 (4,76%)	0,19
- Others (9)	9 (9,2%)	3 (8,5%)	6 (9,5%)	0,87
Pre-pregnancy BMI	24,37 (±4,04)	24,11 (±4,17)	24,52 (±4,00)	0,63
Parity				
−0	67 (68,4%)	22 (62,8%)	45 (71,4%)	0,38
−1	26 (26,5%)	12 (34,3%)	14 (22,2%)	0,19
−2	3 (3,1%)	1 (2,8%)	2 (3,1%)	0,93
- >2	2 (2,0%)	0 (0%)	2 (3,1%)	0,28
Gestational age at screening positive	38,5 (±1,46)	38,4 (±1,35)	38,5 (±1,53)	0,92
Major respiratory symptoms (pneumonia, respiratory distress)	0	0	0	–
Presence of minor symptoms	34 (34,7%)	13 (37,1%)	21 (33,3%)	0,70
Gestational age at delivery	39,2 (±1,23)	38,9 (±2,61)	39,2 (±1,1)	0,56
Mode of delivery				
- Vaginal	63 (64,3%)	27 (77,1%)	36 (57,1%)	0,047
- Cesarean	35 (35,7%)	8 (22,9%)	27 (42,9%)	0,047
Birthweight	3214,84 (±399,3)	3239,14 (±367,8)	3201 (±417,9)	0,64
NICU admission	0	0	0	–
Arterial pH	7,25 (±0,06)	7,26 (±0,06)	7,25 (±0,06)	0,85
Venous pH	7,31 (±0,05)	7,30 (±0,05)	7,31 (±0,05)	0,86

Results are shown as frequency (%) or mean ± standard deviation. T-Student test or Chi-Square has been used to test the statistical differences and obtain OR in discrete variables. Statistically significant differences are considered for $p < 0,05$ (BMI, body mass index; NICU, neonatal intensive care unit)-.

Various bivariate logistic regression analyses have been performed to test the grade of correlation of placental abnormal findings and potentially confounder variables, considering the ones that showed statistically significant differences between the two groups. Mode of delivery that resulted differently between the two groups (p 0,05) is not a predictor of the most significant histopathological features analyzed (for IFPFD p 0,45 aOR 1,4–95%CI 0,578–3447; for AFV p 0,23 aOR 2,58–95%CI 0,543–12,2). The same analysis has been performed to test the weight of vaccination status in predicting IFPFD and AFV. SARS-CoV-2 vaccination appears to be protective for IFPFD (aOR 0,36; 95% CI 0,13–0,99) with a significant p-value less than 0,05 (p 0,049) while considering AFV, logistic regression showed no significant results (p 0,99).

4. Discussion

Many studies aimed to evaluate histopathological findings between placentas derived from vaccinated and non-vaccinated pregnant women found no statistically significant results. In the reports about placental histopathology in the case of SARS-CoV-2 infection, the presence of intervillous fibrin deposits, associated with (focal or diffuse) trophoblast necrosis with the collapse of intervillous space and variable presence of inflammatory infiltrate, are considered the "hallmark" of the severe infection associated to increased risk of fetal demise [24].

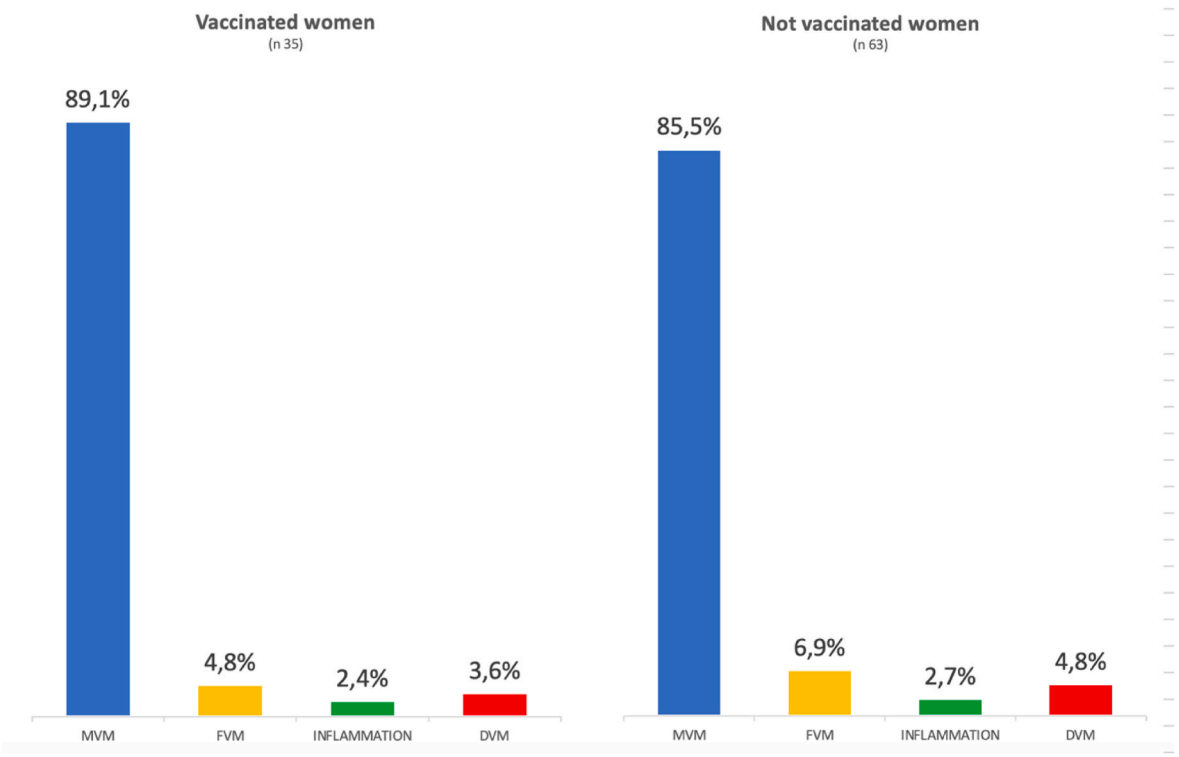

Fig. 1. Distribution of placental histopathological lesions among the two groups, classified as maternal or fetal vascular malperfusion, inflammatory features or delayed villar maturation.

Table 2
Comparison of histopathological placental findings between previously vaccinated Covid-19 positive women and positive patients not vaccinated.

Placental features	All COVID-19 cases (n 98)	Vaccinated women (n 35)	Not vaccinated women (n 63)	p-value	OR
Placental weight	500,8 (±109,0)	488,8 (±108,0)	507,5 (±109,7)	0,42	–
Centile GA	16,9	15,5 (±18,8)	17,7 (±19,1)	0,59	–
Centile BW	17,0	13,1 (±14,6)	19,2 (±19,9)	0,11	–
Microscopic lesions					
- **Present**	85 (86,7%)	30 (85,7%)	55 (87,3%)	0,82	0,87
- **Absent**	13 (13,3%)	5 (14,3%)	8 (12,7%)	0,82	1,15
Infarct lesions	8 (8,16%)	2 (5,7%)	6 (9,5%)	0,51	0,58 (0,11–3,02)
Accelerated maturation	1 (0,98%)	0 (0%)	1 (1,59%)	0,45	0,63 (0,55–0,74)
Villous agglutination	82 (83,7%)	27 (77,1%)	55 (87,3%)	0,19	0,49 (0,17–1,45)
Distal villous hypoplasia	18 (18,4%)	5 (14,3%)	13 (20,6%)	0,44	0,64 (0,21–1,98)
increased Syncytial knots	95 (96,9%)	34 (97,1%)	61 (96,8%)	0,93	1,1 (0,97–12,7)
Inflammatory lesions	8 (8,1%)	3 (8,57%)	5 (7,9%)	0,91	1,1
- **Stage 1**	5 (5,1%)	2 (5,7%)	3 (4,7%)	0,83	1,2
- **Stage 2**	3 (3,1%)	1 (2,85%)	2 (3,1%)	0,28	0,9
Chorangiosis	34 (34,7%)	9 (25,7%)	25 (39,7%)	0,16	0,53 (0,21–1,31)
Delayed villous maturation	12 (12,2%)	3 (8,6%)	9 (14,3%)	0,41	0,56 (0,14–2,23)
Avascular fibrotic villi	7 (7,1%)	0 (0%)	7 (11,1%)	0,04	0,06 (0,003–0,98)
Neointimal hyperplasia	17 (17,3%)	4 (11,4%)	13 (20,6%)	0,25	0,50 (0,15–1,65)
Increased focal perivillous fibrin deposition	29 (27,6%)	6 (17,1%)	23 (33,3%)	0,04	0,36 (0,13–0,99)
Intervillous thrombosis	9 (9,2%)	2 (5,7%)	7 (11,1%)	0,37	0,48 (0,01–2,47)

Results are shown as frequency (%) or mean ± standard deviation. T-Student test or Chi-Square has been used to test the statistical differences and obtain OR in discrete variables. Statistically significant differences are considered for $p < 0,05$ (GA gestational age; BW birthweight).

Although massive fibrin deposition is known to be related to very poor obstetrical outcomes and a high risk of recurrence [25], foci of fibrin deposition can be found in a very high number of placentas at term of pregnancy. Particularly, IFPFD is described as a physiological adaptation to trophoblast vascular injuries [26]. In a recent study, Heeralall and colleagues reviewed the literature reporting the most frequent morphological placental features related to COVID-19 [27]. IFPFD has been retrieved in more than 150 cases of placental specimens deriving from COVID-19-positive pregnant women [28–34].

AFV are histologically defined as terminal villi showing a total loss of villous capillaries and hyaline fibrosis of the villous stroma. Small foci are the finding of 3 or more foci of 2–4 avascular villi, intermediate foci are 5–10 villi, and large foci are more than 10 villi [35]. Multiple foci of avascular villi are a defining feature of FVM [22]. They are considered as an insufficiency of downstream fetal blood flow in a specific villous area [23]. Patberg et al. [36] and Al-Rawaf et al. [37] reported that the placentas of women delivering at term with COVID-19 were more likely to have evidence of FVM presenting as avascular villi and mural fibrin deposition.

Our study confirms previous results even in the case of subclinical presentation of the infection, with no relevant signs at the expense of the mother or of the fetus. In agreement with Brien and colleagues [38],

Table 3
Sub-analysis of the vaccinated population in terms of the presence of increased focal perivillous fibrin deposition (IFPFD).

Variables of vaccine administration	Vaccinated women (n = 35)	IFPFD absent (n = 29)	IFPFD present (n = 6)	p-value
First dose-to-delivery interval (days)	153,20 (±69,74)	160,76 (±73,76)	116,67 (±26,06)	0,018
Last dose-to-delivery interval (days)	84,60 (±41,29)	79,89 (±43,09)	107,33 (±21,08)	0,141
Distribution of number of doses of vaccine				
−1	5 (14,28%)	2 (6,89%)	3 (50%)	
−2	25 (71,42%)	22 (75,86%)	3 (50%)	
−3	5 (14,28%)	5 (17,24%)	0 (0%)	

Results are shown as frequency (%) or mean ± standard deviation. T-Student test or Chi-Square have been used to test the statistical differences. Statistically significant differences are considered for $p < 0,05$.
IFPFD, increased focal perivillous fibrin deposition.

only a minor percentage of the placentas shows no microscopical abnormalities in our population (13,3%), with no differences even after stratification for SARS-CoV-2 vaccination status. One of the peculiar points of interest of the present study lies in the characteristics of the selected population: pregnant women with uncomplicated pregnancies at term, with no pre-existing risk factors for placental impairment, but resulted infected by SARS-CoV-2 with mild-to-no symptoms. The homogeneity of the two groups of patients allowed us to focus our attention on the most frequent COVID-19 clinical presentation in pregnancy unbiased by comorbidities or severe complications. The only statistically significant difference in the comparison of obstetrical outcomes between vaccinated and unvaccinated women is related to the mode of delivery. Unvaccinated participants seem to have a higher likelihood of undergoing C-Section rather than vaginal delivery. Considering possible adverse maternal or neonatal outcomes, this trend is not related to a higher incidence of delivery complications or a lower APGAR score at birth. Furthermore, binomial logistic regression showed that the mode of delivery is not a predictor of placental histopathological lesions. Considering placental histopathology, a statistically significant difference was found in the incidence of IFPDF (an MVM feature) and AVF (an FVM-related lesion) between the vaccinated and non-vaccinated women (Fig. 3). The lower incidence of nonspecific placental features related to both maternal and fetal vascular injuries in patients subjected to vaccination in pregnancy suggests a protective effect. This, along with the evidence of a positive correlation between the timing of vaccination and the relative risk to present IFPDF, led us to affirm that vaccination for COVID-19 during pregnancy should be encouraged and proposed to every woman during pregnancy. According to the other reports published since the first vaccination, no side effects have been reported in our study following any of the doses during pregnancy, not for the mother, not for the fetus. All scientific societies and Health departments all over the world agree to recommend vaccination for pregnant women, considered a fragile population. Further evidence supporting the use of vaccination for the pregnant population derives from the fact that placentitis, the most relevant risk factor for poor perinatal outcomes in case of infection, does not seem to occur in vaccinated women [39]. A recent systematic review indicates a decrease in stillbirths ranging from 1% to 27% among vaccinated individuals compared to those who are unvaccinated, with an OR of 0.85 (95%CI 0.73–0.99). The findings consistently reveal, when vaccination status is disclosed, a noticeable absence of fetal deaths attributed directly to SARS-CoV-2 placentitis in the vaccinated population [40]. All the evidence converges to recommend the SARS-CoV-2 vaccination during pregnancy or in women who plan to have a pregnancy to reduce the risk of dramatic adverse outcome [41]. Moreover, we can't predict the future trend of SARS-CoV-2 infection, but the recent pandemic has taught us that prevention could be the best approach to deal with health emergencies on a large scale as the one we've just faced.

Although the results of the present study provide interesting information about the possible functioning of viral mRNA-based vaccines against SARS-CoV-2, a deeper immunological evaluation of the long-term behavioral pattern of the vaccination is needed. Furthermore, no exhaustive data are present about the booster doses, the possible effects of the infection in early pregnancy, and a complete cycle of vaccination.

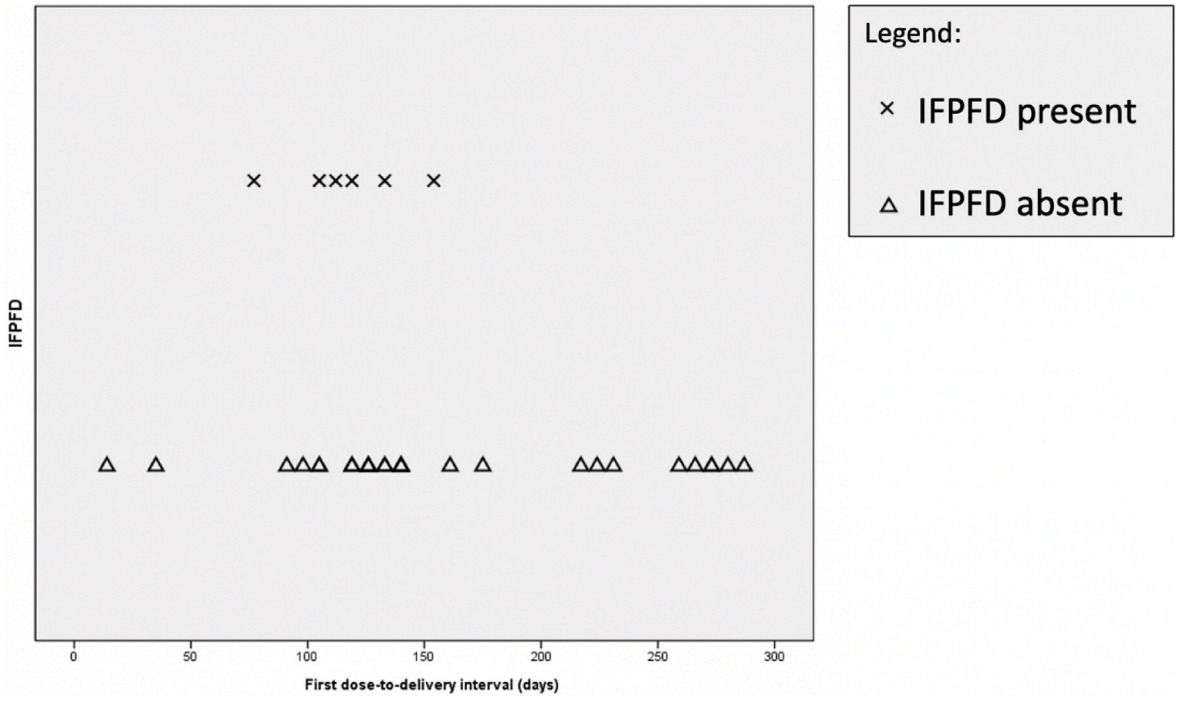

Fig. 2. Scatter-plot graph illustrating the association between the first dose-to-delivery interval and the risk of increased focal perivillous fibrin deposits in vaccinated patients.

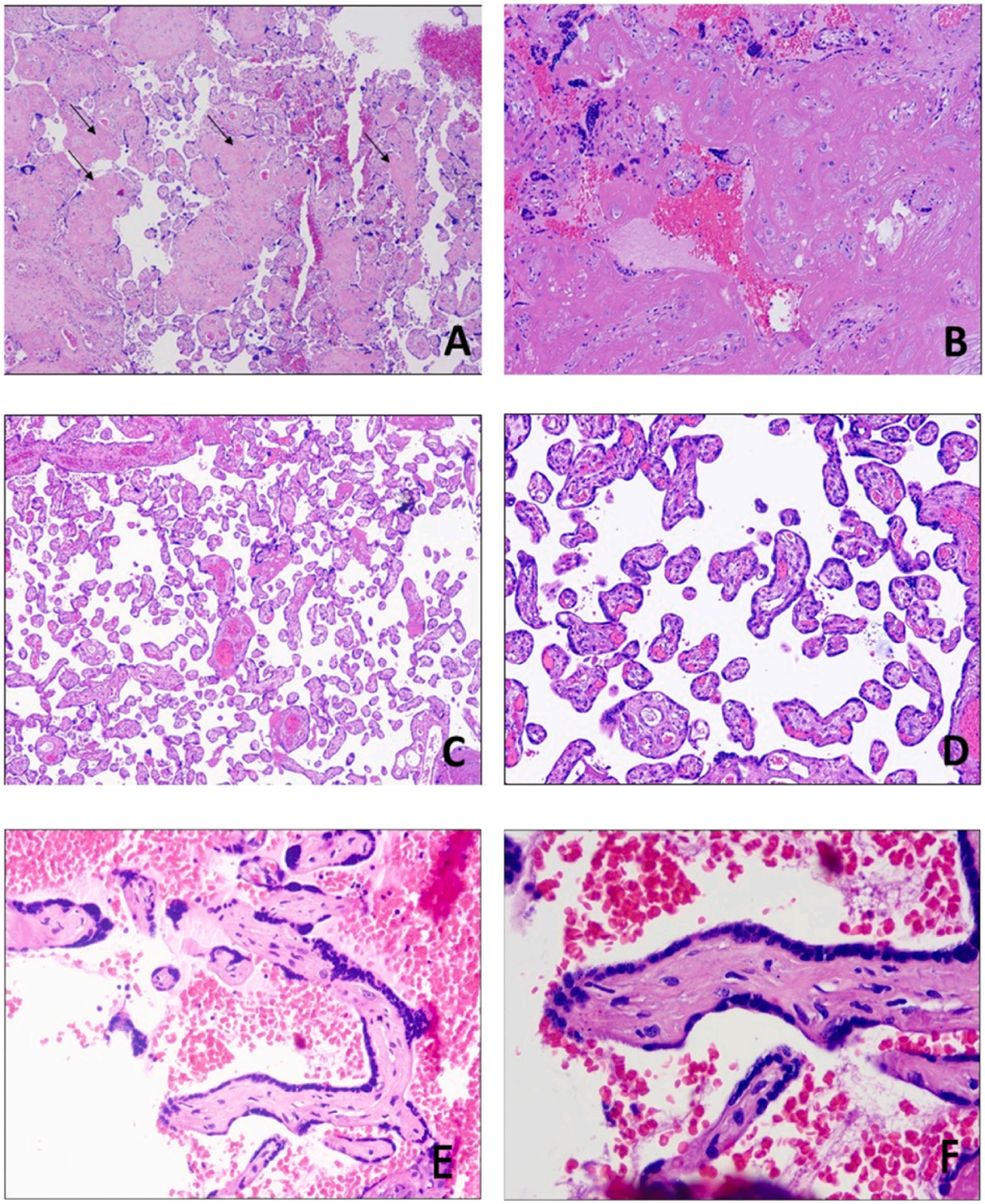

Fig. 3. Hematoxylin-eosin stained microscopical pictures of placental tissue from different COVID-19 positive patients at term of gestation.

Knowing exactly how the vaccine works in a particular condition as pregnancy, with two patients at the same time, will give more awareness of future development in pharmaceutical research, extendible to other infectious diseases. The specific mechanisms that led to the development of SARS-CoV-2 placental alterations are still not completely known. Once again, in this scenario, the placenta has a crucial role in being the dynamic and essential interface between mother and fetus. Deepening inside the universe of placental response to the new class of genetic recombinant vaccinations available will tell us how to protect safely the fetal-maternal dyad. The SARS-CoV-2 vaccine is the first recombinant vaccine recommended during pregnancy and could be the first of many others in the future.

Moreover, the results of the analysis of the timing of the vaccine in pregnancy and its effect on the incidence of nonspecific histopathological signs of placental adaptation to vascular injuries give us important information about the possible immunological behavior of mRNA recombinant vaccines in pregnancy. This opens a new scenario for the adaptive placental mechanisms in response to a potential vascular injury due to viral infection during the third trimester of pregnancy. Despite the high number of COVID-19 cases in pregnancy at our hospital during the pandemic, the number of patients considered for the study is low. The numerosity of the vaccinated group, along with the retrospective

nature of the study, represent the limitations for confirming our data on a large scale. Similar studies from other international research groups could lead to confirming our results and fully understanding the behavior of SARS-CoV-2 infection in pregnancy, in the era of efficient and safe vaccination.

In conclusion, the present study contributes to the growing literature on COVID-19 infection's effects on pregnancy, specifically on the placenta, which has a pivotal role in being the interface between the mother and the fetus. The reported data showed a promising protective positive effect of the SARS-CoV-2 mRNA vaccine on the risk of developing nonspecific histopathological placental features related to maternal vasculopathy. Also, the elapsed time between the first dose of vaccine and delivery shows a negative correlation with IFPDF: the earlier the vaccine, the lower the incidence of this particular placental lesion. A deeper insight into the molecular immunological behavior of the recombinant vaccine in pregnancy will give us useful indications for the future.

CRediT authorship contribution statement

Silvio Tartaglia: Writing – original draft, Data curation. **Chiara Di Ilio:** Data curation, Conceptualization. **Federica Romanzi:** Methodology, Data curation. **Sascia Moresi:** Resources, Investigation. **Eleonora Nardi:** Investigation, Formal analysis. **Elisa Bevilacqua:** Supervision, Project administration. **Vincenzo Arena:** Writing – review & editing, Data curation. **Antonio Lanzone:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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