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# Does COVID-19 infection acquired in different pregnancy trimester influence placental pathology?

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**Abstract**

**Objectives:** To determine the morphological characteristics of the placentas from COVID-19 positive mothers in regard to the trimester of COVID-19 infection onset and low weight molecular heparin (LMWH) treatment.

**Methods:** Placentas were collected in the period April 1st till September 1st 2021 after delivery at Department of Obstetrics and Gynecology University Hospital Split, Croatia, and sent for pathological examination. Medical history and pathology reports were used to collect the data. Pregnant women were divided based on the onset of COVID-19 infection and stratified into low molecular weight heparin (LMWH)+ or LMWH–. Depending on the data distribution, the following test were used: chi-squared test. Student's t-test, Mann-Whitney U test, ANOVA and Kruskal–Wallis test.

**Results:** In 38% of patients the onset of COVID-19 infection was the 1st trimester of pregnancy, in 27% in the 2nd and 35% of women were infected in the 3rd trimester The fetal vascular malperfusion (FVM) occurrence was statistically significantly higher in the LMWH– group and if the onset of infection was in the 2nd trimester, while the perivillous fibrin deposition was most likely to happen if the COVID-19 infection that occured in the 1st trimester of pregnancy.

**Conclusions:** The onset of COVID-19 infection has the influence on trophoblast damage and subsequent morphological appearance of the placenta. LMWH use in COVID positive pregnant women decreases the rate of the FVM in examined placentas.

**Keywords:** COVID-19; low molecular weight heparin (LMWH); placenta.

## Introduction

COVID-19 (coronavirus disease 2019) is an infectious disease, caused by the novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), a single-stranded RNA virus [1]. The key feature of COVID-19 infection seems to be endothelial dysfunction caused by the binding of the virus to the ACE2 receptor on endothelial cells, leading to a complement-induced coagulopathy state and susceptibility to formation of micro thrombi [2]. In the general population, COVID-19 is associated with high rates of thromboembolic complication, while in pregnancy it increases the risk of preeclampsia, preterm birth and other adverse pregnancy outcomes [3, 4]. Pregnancy is, by itself, a hypercoagulable state with increased thrombin production and an increase in intravascular inflammation; therefore it's not surprising that COVID-19 infection may have additive or synergistic risk factors for thrombosis during pregnancy and in the post-partum period [5, 6]. All this indicate that COVID-19 could be related to hypercoagulability conditions resulting in uteroplacental malperfusion [7]. To avoid thromboembolic events and associated mortality The Royal College of Obstetricians and Gynecologists (RCOG) recommends that all pregnant women admitted with confirmed or suspected COVID-19 should receive prophylactic low molecular weight heparin (LMWH), unless birth is expected within next 12 h [8]. LMWH has many beneficial effects on pregnancy other than preventing thromboembolic events, such as modulation of physiological processes required for blastocyst adherence, implantation and trophoblast invasion as well as anti-inflammatory properties [9, 10].

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Placenta is a unique organ with great capability of defending itself from the various intruders. Kreis et al. summarized that most of the placental defense mechanisms rest on the unique structure of syncytiotrophoblast (STB) [11]. STB is periodically renewed outer layer of the placental villi that is densely packed leaving almost no cellular gaps for the possible microorganisms to enter the villi. Likewise, the expression of toll-like receptors (TLCs) on STB is scares, thus enabling the entrance of the pathogens. Data on vertical transmission of SARS-CoV 2 are rare but many studies suggested its possibility [12–16]. Several studies have described the morphological characteristics of placentas from COVID-19 positive pregnant women. A higher frequency of maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM) and an increase in perivillous fibrin deposition have been described [16–22].

Our aim was to investigate morphology of placentas in regard to trimester of COVID-19 infection onset and to determine the morphological characteristics of the placentas from COVID-19 positive mothers in regard to LMWH treatment.

## Materials and methods

We included 104 pregnancies with positive PCR for SARS-CoV-2 in period 1st of April until 1st of September 2021 at the University Hospital Centre Split, Croatia. Since 1st of April 2021 the positive PCR test during pregnancy for SARS-CoV-2 has been regarded as an independent criterion for submission of placentas to pathohistological examination. Severity of COVID-19 infection was characterized as asymptomatic, mild, and moderate and severe. Asymptomatic disease was described as absence of any clinical symptoms. Mild disease presentation included presence of: one or more symptoms such as fever, cough, pharyngeal pain, headache, myalgia, nausea, emesis, diarrhea, anosmia, but no dyspnea. Criteria for moderate disease presentation were: evidence of lower respiratory disease by clinical assessment or imaging and oxygen saturation ($SaO_2$)≥95% on room air. Severe clinical presentation was characterized as one or more symptoms among $SaO_2$≤95% in ambient air, $PaO_2/FiO_2$<300 mmHg (i.e. arterial oxygen partial pressure/fraction of inspired oxygen), respiratory rate >30/min or pneumonia involving more than 50% of the lungs' volume at X-ray scan. All of the pregnant women enrolled in the study had asymptomatic to moderate clinical presentation of the disease. There were no pregnant women with severe form of the disease. Our research was limited to the period of the alpha variant predominance and severe cases with delta variant that appeared later were not included in the study.

Placentas from singleton pregnancies were collected shortly upon delivery and fixed in 4% buffered formaldehyde. Two independent perinatal pathologists preformed the gross examination of the placentas and histological analysis.

Following data were collected: gravidity, parity, gestational age at the onset of proven infection and at delivery, mode of delivery, the presence or absence of any pregnancy-related pathologies, neonatal birth weight and length, as well as maternal age and comorbidities. Placental weight, feto-placental weight ratio, MVM, FVM, inflammatory lesions of the villous tree, increase in perivillous fibrin deposition and syncitial knotting, as well as umbilical cord abnormalities were included in the report.

The pregnancies were further divided into two groups based on the LMWH use. All women were advised to use LMWH treatment which was introduced in Croatia as thromboprophylaxis for COVID-19 infected pregnant women in March 2021 and therefore only 30 (28,84%) pregnant women were treated with LMWH. The protocol at The University Hospital Centre Split for COVID-19 pregnant women was adapted from RCOG guidelines [8]. LMWH was administered to COVID-19 positive pregnant women in gestational age ≤32 weeks during 2 weeks (in case of comorbidity for 6 weeks), and those with 32 gestational weeks and above continue the treatment until giving birth. Women with vaginal birth continued LMWH treatment for two weeks, and those delivered by cesarean section had LMWH treatment for six weeks after delivery. No pregnant women in our cohort received the Covid-19 vaccine.

Data were analyzed with IBM SPSS Statistics 20.0. Depending on the data distribution following test were used: chi-squared test. Student's t-test, Mann-Whitney U test, ANOVA and Kruskal–Wallis test. The protocol was approved by the local Ethical Commitee (2181-147/01/06/M.S.-21-02).

## Results

From total number of pregnant women 40 (38.5%) of them were infected in the first trimester of pregnancy, 28 (26.9%) in the second trimester and 36 (34.6%) in the third trimester of pregnancy, respectively. Two study groups were defined based on the use of LMWH. Thirty (28.84%) pregnant women received LMWH, 2 (6%) of which were infected in the 1st trimester, 5 (17%) in the 2nd trimester and 23 (77%) in the 3rd trimester of pregnancy.

Descriptive data of the study groups are presented in Table 1. There was no statistically significant difference in mode of delivery depending on LMWH treatment. LMWH– study group had higher range of gestational age at birth (28–42 gestational weeks) and higher birth weight than LMWH+ group, which was statistically significant.

Pregnancies disorders (thrombophilia, gestational diabetes mellitus and intrauterine growth restriction) were recorded in seven cases in LMWH+ group and in 16 cases (gestational diabetes mellitus, preeclampsia and intrauterine growth restriction) in LMWH– group, without statistical significance between groups. Comorbidities (hypothyreosis, irritable bowel syndrome, high grade squamous intraepithelial lesion and hemiparesis) have been found in eight pregnant women total.

Pathohistological findings of studied placentas are presented in Table 2. Placentas from LMWH+ group had statistically significantly lower weight than placentas in LMWH– group, likewise they did not have any cases of

**Table 1:** Descriptive data of studied patients according to low weight molecular heparin (LMWH) treatment.

| | LWMH+ (n=30) | LWMH− (n=74) | p-Value |
|---|---|---|---|
| Maternal age, years | 30 ± 3.7 | 31 ± 4.6 | 0.639[a] |
| Parity | I (40%) | I (33.78%) | 0.787[c] |
| | II (26.66%) | II (33.78%) | |
| | III (33.33%) | III (29.72%) | |
| Gestational age, weeks | 40 (32–41) | 40 (28–42) | 0.005[b] |
| Birth | | | 0.935[c] |
| Vaginal | 23 (78%) | 59 (80%) | |
| C-section | 7 (23%) | 15 (20%) | |
| Gender | | | 0.271[c] |
| Female | 29 (39%) | 16 (53%) | |
| Male | 45 (61%) | 14 (47%) | |
| Birth weight, grams | 3,315 (950–4,190) | 3,510 (620–5,120) | 0.030[b] |
| Birth length, centimeters | 51 (37–53) | 51 (30–56) | 0.171[b] |

LMWH+: group of patients who received LMWH. LMWH−: group of patient without LMWH. [a]Student's t-test; [b]Mann-Whitney U test; [c]chi-squared test.

FVM, which proved also statistically significant. There were no difference in fetal/placental weight ratio, coiling index abnormality, MVM, perivillous fibrin deposition, exaggerated syncytial knotting, fetal or maternal inflammatory response, as well as villitis of unknown etiology.

The results of difference in placental pathohistological findings according to trimester of COVID-19 infection are presented in Table 3. There was no statistically significant difference in the following pathohistological findings according to trimester of COVID-19 infection: MVM, abnormal coiling index, perivillous fibrin deposition, exaggerated syncytial knotting, maternal inflammatory response, fetal inflammatory response and VUE. There was a statistically significant association of FVM with trimester of infection. The rate of FVM in the second trimester is 2.9 times higher than in the 1st trimester and five times higher in the 2nd than 3rd trimester. There is a statistically significant correlation at the significance level of 94% in the association of FVM with trimester of infection especially for placentas of LMWH− group. We did not find the statistically significant difference in the amount of perivillous fibrin deposition according to trimester of infection, so we combined the results of perivillous fibrin deposition in 2nd and 3rd trimester and compared them to the 1st trimester; yielded statistically significant association of perivillous fibrin and trimester of infection at the significance level of 92%. The amount of perivillolus fibrin deposition is 2.1 times higher if the COVID-19 infection occurs in the 1st trimester compared to the 2nd and 3rd trimester combined.

There was no statistical difference in maternal age, parity, gestational age, gender, birth weight and length nor F/P in relation to the trimester of COVID-19 infection as represented in Table 4. The distribution according to the mode of delivery was statistically significantly different in relation to the trimester of infection. The proportion of caesarean deliveries when the infection occurred in the second trimester is 3.6 times higher than when the infection was in the first trimester. The rate of cesarean delivery when infection occurred in the third trimester is 2.2 times higher than with infection in the first trimester. The distribution pregnant women according to the use of LMWH was statistically significantly different in relation to the trimester of infection. The proportion of pregnant women who received heparin in the third trimester was 3.6 times higher than the proportion of those with infection in the second trimester and by 13 times higher than the rate of those who had an infection in the first trimester.

The highest rate of FVM changes was observed in placentas from pregnancies with acquired Covid infection in the second trimester. All cesarean deliveries were performed for fetal indications and there were no asphyxiated newborns in our cohort.

**Table 2:** Pathohistological findings of placentas according to low molecular weight (LMWH) therapy.

| | LMWH+ | LMWH− | p-Value |
|---|---|---|---|
| Placental weight, grams | 458 ± 70 | 504 ± 102 | 0.027[a] |
| Fetal/placental weight ratio | 7 (2.05–9.37) | 7 (3.8–10.18) | 0.6[b] |
| Maternal vascular malperfusion | 3 (10%) | 5 (6.75%) | 0.876[c] |
| Fetal vascular malperfusion | 0 | 15 (20.27%) High grade 9 Low grade 6 | 0.017[c] |
| Abnormal coiling index | 4 (13.33%) | 11 (14.86%) | 0.973[c] |
| Perivillous fibrin deposition | 5 (16.66%) | 18 (24.32%) | 0.554[c] |
| Exaggerated syncytial knotting | 9 (30%) | 25 (33.78%) | 0.887[c] |
| Maternal inflammatory response | 6 (20%) | 7 (9.45%) | 0.067[c] |
| Fetal inflammatory response | 1 (3.33%) | 2 (2.7%) | 0.636[c] |
| Villitis of unknown etiology | 4 (13.33%) High grade 2 Low grade 2 | 11 (14.86%) High grade 6 Low grade 5 | 0.968[c] |

LMWH+: group of patients who received LMW heparin. LMWH−: group of patient without LMW heparin therapy. [a]T-test; [b]Mann-Whitney U test; [c]chi-squared test.

**Table 3:** Placental pathohistological findings regarding to COVID-19 infection onset according to pregnancy trimester.

| | Recorded lesions, n (%) | I. Trimester n=40 | II. Trimester n=28 | III. Trimester n=36 | p-Value |
|---|---|---|---|---|---|
| Maternal vascular malperfusion | 18 (17%) | 7 (17%) | 4 (14%) | 7 (19%) | 0.863 |
| Fetal vascular malperfusion | 14 (14%) | 4 (10%) | 8 (29%) | 2 (6%) | 0.020 |
| Abnormal coiling index | 15 (14%) | 4 (27%) | 7 (46%) | 4 (27%) | 0.205 |
| Perivillous fibrin deposition | 23 (22%) | 13 (33%) | 5 (18%) | 5 (14%) | 0.122 |
| Exaggerated syncytial Knotting | 34 (33%) | 16 (40%) | 10 (36%) | 8 (22%) | 0.237 |
| Maternal inflammatory response | 13 (12%) | 3 (23%) | 3 (23%) | 7 (54%) | 0.493 |
| Fetal inflammatory response | 3 (3%) | 2 (67%) | 0 | 1 (33%) | 0.479 |
| Villitis of unknown etiology | 15 (14%) | High grade 0 Low grade 3 | High grade 5 Low grade 2 | High grade 3 Low grade 2 | 0.109 |

Review of qualitative data and arithmetic means ± SD or median (Q1–Q3; min–max) of quantitative data in total sample. Chi-squared test, ANOVA, Kruskal–Wallis test.

**Table 4:** Descriptive data of studied patients and placental pathohistological findings regarding to COVID-19 infection onset according to pregnancy trimester.

| | I (40) | II (28) | III (36) | p-Value |
|---|---|---|---|---|
| Maternal age, years | 31.5 ± 4 | 30.6 ± 5 | 30 ± 4 | 0.309[b] |
| Parity | | | | 0.586[a] |
| 1 | 12 (30%) | 9 (32%) | 16 (45%) | |
| 2 | 13 (32%) | 9 (32%) | 12 (33%) | |
| >3 | 15 (38%) | 10 (36%) | 8 (22%) | |
| Gestational age, weeks | 40 (35–42) | 40 (28–42) | 40 (32–42) | 0.893[c] |
| Birth | | | | 0.037[a] |
| Vaginal | 36 (90%) | 18 (64%) | 28 (78%) | |
| C-section | 4 (10%) | 10 (36%) | 8 (22%) | |
| Gender | | | | 0.346[a] |
| F | 18 (45%) | 9 (32%) | 18 (50%) | |
| M | 22 (55%) | 19 (68%) | 18 (50%) | |
| Birth weight, grams | 3,480 (2340–5,120) | 3,495 (620–4,730) | 3,415 (950–4,550) | 0.780[c] |
| Birth length, centimeters | 50.5 (45–56) | 51 (30–56) | 51 (37–54) | 0.874[c] |
| F/P | 7.3 ± 1.3 | 7.1 ± 1.2 | 6.9 ± 1.2 | 0.454[b] |
| FVM | | | | 0.020[a] |
| Yes | 4 (10%) | 8 (29%) | 2 (6%) | |
| No | 36 (90%) | 20 (71%) | 34 (94%) | |
| LMWH | | | | <0.001[a] |
| No | 38 (95%) | 23 (82%) | 13 (36%) | |
| Yes | 2 (5%) | 5 (18%) | 23 (64%) | |

[a]$\chi^2$ test; [b]ANOVA; [c]Kruskal–Wallis test.

# Discussion

The novel observation of our study was the highest prevalence of FVM in the second trimester compared to other pregnancy trimesters. The rate of FVM in the 2nd trimester was 2.9 times higher than in the 1st trimester and five times higher than in the 3rd trimester. FVM were also more frequently reported in previous publications, but without taking into account the trimester of infection [23–25]. Furthermore, we noted FVM only in the placentas from LMWH– group, and none of the FVM cases were found in LMWH+ group regardless of the trimester of infection, duration of LMWH treatment or interval from onset of the infection to delivery. FVM, previously referred to as fetal vascular thrombopathy, encompasses several lesions including thrombotic occlusion of chorionic or stem villous vessels and stem vessel obliteration as well as areas of avascular villi [26]. The etiology of FVM is still under investigation, but the evidence point to several causes, including obstruction of fetal blood flow for any reason (e.g. abnormal coiling index), hypercoagulability and hypoxia. It is difficult to provide reasonable explanation for the influence of LMWH on the FVM occurrence, especially considering the fact that LMWH does not cross the placental barrier [27]. One of the possible explanations would be well known LMWH properties such as anti-thrombotic and anti-inflammatory properties on maternal blood vessels resulting in circulatory improvements reflecting on placental function and structure. This hypothesis is supported by presented data of higher rates of MVM in placentas from LMWH– group compared to LMWH+, although the finding was not statistically significant.

The previous studies reported the increased perivillous fibrin deposition in placentas from COVID-19 pregnancies [28, 29]. Our findings suggest that the occurrence of perivillolus fibrin deposition is 2,1 times higher if the COVID-19 infection occurred in the 1st trimester compared to the 2nd and 3rd trimester combined. Perivillous fibrin is a sign of trophoblast damage of any cause. Excessive perivillous fibrin deposition is believed to be a pathologic immune reaction and has been described in regards to various

pathologies, such as preeclampsia, HELLP syndrome, and rarely viral infections in pregnancy [30–32]. Our results on perivillous fibrin deposition point to the importance of the time of COVID-19 infection. It appears that the earlier time of infection yields the higher risk for trophoblast damage and excess in perivillous fibrin deposition. Although the difference between LMWH+ and LMWH– group regarding perivillous fibrin deposition was not significant, it's important to stress out that 24% of placentas in LMWH– group compared to 16% of placentas from LMWH+ group had increase in perivillous fibrin deposition. Similar to findings on perivillous fibrin, exaggerated syncitial knotting was also more common in placentas from LMWH– group compared to placentas from LMWH+ group and if the onset of infection happened in the 1st trimester of pregnancy. Although the latter also was not statistically significant, we still may speculate that trophoblast is more severe if the infection happens in early in pregnancy, since the exaggerated syncitial knotting is common finding whenever there's damage to trophoblast or trophoblast life cycle, e.g. preeclampsia and HELLP syndrome [33, 34].

Regardless of the trimester of COVID-19 infection all placentas had very similar fetal-placental weight ratio and there was no statistical difference in birth weight. Similar results are described previously in literature [17, 31, 35, 36]. Additional results of the presented study were statistically significant lower birth weight accompanied by lower placental weight, as well as the smaller gestational age range in the LMWH+ group compared to LMWH– group, however there was no difference in the fetal-placental weight ratio adjusted for the gestational age, therefore we believe these findings to be random. Tasca et al. reported that six out of 64 COVID-19 infected pregnant women treated with LMWH had heavier placentas but not more efficient than the non-treated, since the fetal/placental weight ratio did not differ [18]. We had sample of 30 women treated with LMWH. We did not find a statistically significant difference in gestational age at birth in relation to the trimester of infection.

The distribution of mode of delivery was statistically significantly different in relation to the trimester of infection. The proportion of caesarean deliveries with the COVID-19 infection appearing in the second trimester was 3.6 times higher compared to the COVID-19 infection in the first trimester. The rate of cesarean deliveries with infection occurring in the third trimester is 2.2 times higher than with infection in the first trimester. Out of 104 pregnant women none had respiratory insufficiency and none was hospitalized because of COVID-19 infection only. All women included in this study were asymptomatic or with mild symptoms of the first alpha variant of the COVID-19. This relatively higher rate of cesarean deliveries would reflect as the role of fear of vertical transmission especially because the examined pregnant women were infected and gave birth in the first wave of COVID-19 infection, when relatively little was known about the disease itself and the impact on the fetus and mother. We found no statistical difference in the mode of delivery in relation to LMWH treatment.

The distribution of pregnant women according to the use of LMWH was statistically significantly different in relation to the trimester of infection. The vast majority of pregnant women who received LMWH had COVID-19 infection in the third trimester after that in second trimester and at least in first trimester of infection. We can explain this with the fact that LMWH was introduced in our country as prophylaxis for COVID-19 infected pregnant women in March 2021 and the data was collected in the period from April till September 2021, so LMWH was not administered to all women who gave birth in the first months of our study and had COVID-19 in the first trimester. This is why most women received LMWH with infection in the third trimester. This also explains why "only" 30 out of 104 women in the study received LMWH.

Our findings suggest that time of the COVID-19 infection may have the influence on trophoblast damage and thus morphological appearance of the placenta. While LMWH, although entirely beneficial for the mother, does not affect placental changes other than FVM, it may have indirect beneficial effect on the placental morphology. To the best of our knowledge presented study is the first one to describe placental morphological changes depending on the trimester of COVID-19 infection, and the only one that described LMWH treatment regarding the trimester of COVID-19 infection onset. A larger sample size could have provided better insight into studied topic. There was no control group because our research was about the impact of COVID-19 on the placenta depending on the trimester of infection and in relation to LMWH therapy on that same placentas. Further studies are necessary in order to collected more evidence and get insight on the pathophysiological mechanisms behind SARS-CoV 2 and its effect on placenta and pregnancy in general.

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**Competing interests:** Authors state no conflict of interest.

**Informed consent:** Informed consent was obtained from all individuals included in this study.

**Ethical approval:** Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the authors' Institutional Review Board (2181-147/01/06/M.S.-21-02).

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