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**Authors**: Pınar Kumru, Seyhan Hidiroglu, Ebru Cogendez, Habibe Ayvaci, Betül Yilmazer, Hümeyra Erol, Oya Demirci, Pınar AY

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**ORIGINAL PAPER/OBSTETRICS**

# Does asymptomatic/uncomplicated SARS-CoV-2 infection during pregnancy increase the risk of spontaneous preterm birth?

Pınar Kumru[1], Seyhan Hidiroglu[2], Ebru Cogendez[1], Habibe Ayvaci[1], Betül Yilmazer[1], Hümeyra Erol[3], Oya Demirci[1], Pınar Ay[2]

*[1]Department of Obstetrics and Gynecology, University of Health Sciences, Zeynep Kamil Women and Children's Disease Training and Research Hospital, Zeynep Kamil, Dr. Burhanettin Üstünel Sokağı, Üsküdar/İstanbul, Turkey*
*[2]Department of Public Health, Marmara University Faculty of Medicine, Istanbul, Turkey*
*[3]Division on Nursing, University of Health Sciences, Zeynep Kamil Women and Childrens Diesease Training and Research Hospital, Department of Obstetrics and Gynecology, İstanbul, Turkey*

**Short title: SARS-CoV-2 infection and preterm birth**

**Corresponding author:**
Pınar Kumru
Department of Obstetrics and Gynecology, University of Health Sciences, Zeynep Kamil Women and Children's Disease Training and Research Hospital, Zeynep Kamil, Dr. Burhanettin Üstünel Sokağı No:10, 34668 Üsküdar/İstanbul, Turkey
e-mail: pkumru@gmail.com

## ABSTRACT

**Objectives:** The aim of this study was to analyze the perinatal outcomes of asymptomatic/uncomplicated SARS-CoV-2 infection during pregnancy and the relationship between gestational age at the time of infection and spontaneous preterm birth (PTB).
**Material and methods**: This was a retrospective cohort study. The study population included pregnant women who were 19–45 years old and who had been admitted to a Research and Training Hospital for singleton birth delivery. Women who had contracted SARS-CoV-2 during their pregnancy (n = 102) were compared to those who were not infected (n = 378) for

the development of spontaneous PTB and other perinatal outcomes. The factors associated with spontaneous PTB were analyzed through univariate and multivariate methods.
**Results:** Spontaneous PTB developed in 22.5% of the pregnant women with a history of SARS-CoV-2 infection and in 5.3% without a history of the infection ($p < 0.001$). The multivariate model determined that compared to the non-infected women, the OR of spontaneous PTB among those who had contracted the virus in the first, second, and the third trimesters were 9.13 ($p < 0.001$), 1.85 ($p = 0.292$) and 7.09 ($p < 0.001$), respectively. Pregnancy cholestasis (3.9% vs 0.5%; $p = 0.020$) and placental abruption (3.9% vs 0.5%; $p = 0.040$) were significantly higher in cases with a history of SARS-CoV-2 infection compared to the non-infected women.
**Conclusions:** Asymptomatic or uncomplicated SARS-CoV-2 infection during pregnancy increases the risk of spontaneous PTB. This risk is higher particularly among pregnant women who develop the infection in the first and the third trimesters.

**Key words:** SARS-CoV-2; COVID-19 pandemic; pregnancy; preterm birth; perinatal outcome

## INTRODUCTION

The 2019 Coronavirus Disease (COVID-19) pandemic is an ongoing major global health crisis in our time. To date, close to 233 million cases infected with SARS-CoV-2 have been confirmed, and 4.8 million deaths have been reported [1]. A multicenter prospective study from Spain, one of the countries most affected by the pandemic, reported that SARS-CoV-2 screening of 16,308 pregnant women who were admitted for delivery and had no suspected infection or symptoms showed a 2.07% positivity rate [2]. Indeed, the current literature highlights the prevalence of asymptomatic infections and recommends that all pregnant women be routinely screened for SARS-CoV-2 infection during their hospital stay [3].

According to the data of centers in London and New York that routinely order SARS-CoV-2 testing for patients admitted to the labor floor, 88% of infected women remain asymptomatic [4]. It has been determined that SARS-CoV-2 infection causes changes in systemic immune response and an increase in the pro-immune inflammatory response in pregnancy, as well as in non-pregnant women. In addition, histopathological examinations have shown that the virus causes pathologic changes of the placenta [5]. The World Association of Perinatal Medicine (WAPM) has reported that COVID-19 infection may

increase the risk of hypoxemia in pregnant women, thereby increasing maternal morbidity and mortality compared to the general population [6]. Recent studies have shown that pregnant women infected with SARS-CoV-2 are more at risk of adverse perinatal outcomes such as maternal death, need for maternal intensive care, preterm birth (PTB), premature rupture of membranes (PROM), venous thrombosis, and neonatal intensive care need compared to the general population [7, 8].

However, most of the studies conducted so far have reported maternal and neonatal outcomes of pregnant women who had complicated SARS-CoV-2 infection during pregnancy or were infected with SARS-CoV-2 peripartum. The effect of COVID-19 on pregnancy outcomes in women who had asymptomatic or uncomplicated SARS-CoV-2 infection during pregnancy has not been adequately demonstrated. In addition, the relationship between gestational age at SARS-CoV-2 infection and pregnancy outcomes remains unclear.

### Objectives

The aim of this study is to analyze the perinatal outcomes of asymptomatic/uncomplicated SARS-CoV-2 infection during pregnancy and the relationship between gestational age at the time of infection and spontaneous PTB.

## MATERIAL AND METHODS

### Setting and study participants

Designed as a retrospective cohort study, this study was carried out between March 2021 and June 2021 in Zeynep Kamil Women and Children's Diseases Training and Research Hospital. The study population is women admitted for delivery and followed up during the postpartum period in clinic.

Pregnant women aged between 19–45 years, between 22 and 42 weeks of gestation, and who had a negative SARS-CoV-2 polymerase chain reaction (PCR) test at admission to the delivery room were included in the study. SARS-CoV-2 PCR test includes real-time PCR (qPCR)(RT-qPCR) that targets the RdRp gene fragment. All pregnant women who presented to our hospital for delivery, regardless of the presence of symptoms, underwent screening for SARS-CoV-2. The laboratory has been authorized by the Republic of Turkey Ministry of Health, General Directorate of Public Health, Microbiology Reference Laboratory. For PCR analysis, swab samples from the oropharynx and nasopharynx were used. Women who gave birth at ≤ 22 weeks of gestation, stillbirths and termination of pregnancy cases, multiple

pregnancies, and positive SARS-CoV-2 PCR test at the time of admission were excluded from the study.

**Sample size calculation**

The sample size was calculated using OpenEpi (Version 3). The primary outcome was PTB rate, which was reported to be approximately 23% in women with COVID-19 in a systematic review by Capobianco et al. [9]. In Turkey, among the general population without a history of COVID-19, the PTB rate is approximately 10%. Considering the relatively limited number of people with COVID-19, we thought that it was appropriate to include a positive history of COVID-19 and non-exposed group in a 1:3 ratio; therefore, we planned to include at least 79 postpartum women in the positive history of SARS-CoV-2 group and at least 235 postpartum women in the negative history of SARS-CoV-2 group for a 5% alpha error and 80% power.

**Definition of the variables**

Outcome variable: In the study, the primary outcome was spontaneous PTB, which was defined as spontaneous (spontaneous rupture of membranes or spontaneous onset of contractions and onset of labor) or iatrogenic [planned cesarean section or induction of labor due to maternal (severe preeclampsia, abruptio placentae) or fetal (FGR and fetal distress) reasons] delivery before 37 weeks of gestation. Exposure variable: The exposure group consisted of women who were diagnosed with COVID-19 by PCR test at any time during pregnancy. Some of the women were tested due to symptoms, while others were tested because they had been in contact with a COVID-19 patient. PCR results were obtained from electronic patient records, and the time of infection was recorded to determine the trimester of the exposure. Clinical symptoms of the disease (fever, shortness of breath, air hunger, weakness, cough, headache, inability to taste and smell), the need for hospitalization due to COVID-19, and the need for medication or intensive care were questioned.

The COVID-19 clinical disease spectrum of the participants was determined according to the criteria of the NIH and the Turkish Ministry of Health. According to this spectrum, all cases were asymptomatic or met the criteria for mild disease [10]. Two out of 104 women with a positive history of COVID-19 infection were excluded because they did not meet the inclusion criteria, and 102 women were included in the study. The non-exposure group consisted of pregnant women who were not diagnosed with COVID-19 by PCR test during their pregnancy. Considering that there may be those without a positive PCR test even though

they had COVID-19, symptoms of upper and lower respiratory tract diseases during pregnancy were questioned, and those with possible suspected COVID-19 were excluded from the study.

Cases without exposure were determined by the systematic sampling method. The 3rd, 6th, 9th, and 12th women, starting from the 3rd woman in the registry on the day of admission to the postpartum service of the participant included in the exposure group, constituted the non-exposure group. Three hundred seventy-eight pregnant women were included in the group without exposure. The participants' sociodemographic characteristics, medical history, obstetric history [spontaneous PTB, preeclampsia, gestational diabetes mellitus (GDM), intrahepatic cholestasis of pregnancy], and current obstetric characteristics (antenatal period, birth, and neonatal period information) were evaluated. The definitions of perinatal outcomes (GDM, preeclampsia, small for gestational age (SGA), low birth weight (LBW), and intrahepatic cholestasis of pregnancy) were determined according to international criteria [11–15].

**Data collection tools**

Gestational age was calculated by using the first day of the last menstrual period and was confirmed by first trimester crown-rump length (CRL). Socio-demographic, personal health, antenatal period, birth, and postnatal characteristics of the participants and clinical characteristics of COVID-19 were obtained from the electronic database of our institution. Missing data were obtained by phone interviews with patients.

**Ethical approval**

The study was approved by the local ethics committee (decision number 65, dated 03/2021). All procedures in our study were carried out per the 1964 Declaration of Helsinki and subsequent amendments.

**Data analysis**

The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov). Descriptive statistics are presented as median [interquartile ranges (IQR)] for the numerical variables and as ratios for the categorical variables. The median differences between groups were compared using the Mann-Whitney U test. The Kruskal-Wallis test was used to compare the quantitative data of three groups that did not show normal distribution. In the comparison

of qualitative data, Chi-Square test or Fisher's Exact Chi-Square test was used when test conditions could not be met. For multivariate analyses, logistic regression backward stepwise method was used. Variables with $p < 0.1$ and those found to be associated in the literature were included in the multivariate model. The strength of the relationship was defined by the OR (95% confidence interval). $p < 0.05$ was evaluated as statistically significant.

**RESULTS**

Between March and June 2021, a total of 1387 pregnant women gave birth at Zeynep Kamil Women and Children's Diseases Training and Research Hospital. All patients were screened for SARS-CoV-2 infection at the time of admission to the maternity ward, and 15 (1.08%) women were excluded due to SARS-CoV-2 PCR positivity. The study population is shown in the flowchart (Fig. 1).

The demographic characteristics of the participants are presented in Table 1. Univariate analysis evaluating the relationship between perinatal and neonatal outcomes of the participants with SARS-CoV-2 infection history are presented in Table 2. Spontaneous PTB was detected in 22.5% of cases with a history of SARS-CoV-2 infection and 5.3% of cases without a history of infection; the difference was statistically significant ($p < 0.001$). In our study, iatrogenic preterm birth rates were found to be statistically similar in the group with and without a history of COVID-19 ($p = 0.058$). In the group with a history of COVID-19, pregnant women had iatrogenic preterm deliveries due to severe preeclampsia (n = 4, 3.9%) and abruptio placentae (n = 4, 3.9%). Among the pregnant women without a history of COVID-19, pregnant women had iatrogenic preterm deliveries due severe preeclampsia (n = 34, 9%), abruptio placentae (n = 3, 0.8%), and FGR and fetal distress (n = 20, 5.3%).

The relationship between the gestational week of COVID-19 exposure and fetal anomaly was examined and no statistically significant difference was found ($p = 0.9$). However, fetal CNS anomalies were detected in three (10.3%) out of 29 women with a history of COVID-19 in the first trimester, and all these patients were symptomatic (all of them had fever, respiratory distress, headache, and malaise) (Tab. 3). The median (IQR) gestational week at which the participants were infected with SARS-CoV-2 was 22.0 weeks (13.0–29.0); 29 (28.4%) were infected in the first trimester, 41 (40.2%) were infected in the second trimester, and 32 (31.4%) were infected in the third trimester. When the groups were compared according to the trimester of infection, no significant differences were found in terms of maternal age, BMI, and mode of delivery ($p > 0.05$). However, the gestational age at birth of the pregnant women who were infected in the first trimester was lower than in

pregnant women who were infected in the second and third trimesters (p = 0.005). Birth weight was also found to be lower if the infection was contracted in the first trimester compared to the second trimester (p = 0.018). The rates of spontaneous PTB were found to be higher in pregnant women who were infected in the first (34.5%) and third (28.1%) trimesters than in pregnant women who were infected in the second trimester (9.8%) (p = 0.034).

All cases diagnosed with intrahepatic cholestasis of pregnancy were women who had the infection in the third trimester. Although not statistically significant, placental abruption was detected in 10.3% of the cases infected with SARS-CoV-2 in the first trimester (p = 0.086). Birth weight of < 2500 g was more common among those who had the infection during the first and third trimesters, but this result was not statistically significant (p = 0.060). Neonatal complications did not differ between groups (p > 0.05) (Tab. 3).

Models were created using multivariate logistic regression (Backward LR) analysis to evaluate the independent effects of variables associated with spontaneous PTB. The model included maternal age groups, BMI, smoking, mode of conception (spontaneous/in vitro fertilization), fetal sex, and history of COVID-19 during pregnancy.

In multivariate logistic regression analysis, when the status of not having COVID-19 infection during pregnancy is taken as a reference, we calculated that the risk of spontaneous PTB was 9.13 times higher (95% CI 3.68–22.66; p < 0.001) in those who were infected in the first trimester, and 7.09 times higher (95% CI 2.85–17.62; p < 0.001) in those infected in the third trimester. If the infection occurred in the second trimester, the risk of spontaneous PTB birth was 1.85 times higher (95% CI 0.59–5.79; p = 0.292); this result was not statistically significant (Tab. 4).

## DISCUSSION

It is known that various viral infections increase the risk of fetal anomalies, fetal growth restriction (FGR), and PTB by negatively affecting fetal health [16]. When the first data on COVID-19 and pregnancy began to emerge, it was reported that almost all PTB were iatrogenic, due to deteriorating maternal status of COVID-19 or because of obstetric complications not related to COVID-19 [17]. Recent studies have reported that SARS-CoV-2 infection leads to an increased risk of PTB and LBW [9, 18–21].

Two systematic reviews from studies conducted in the early period of the pandemic reported an increased incidence of PTB, LBW, cesarean section, and NICU (Neonatal İntensive Care Unit) admissions in pregnant women infected with SARS-CoV-2 [18, 22]. Most of these studies were laboratory-confirmed, admitted to the intensive care unit, and

nearly all had positive findings on thoracic computed tomography (CT) scans. Therefore, these studies have undeniable limitations such as that most of the cases were in critical condition, sample sizes were small, and there was a lack of information about pre-pregnancy medical conditions. SARS-CoV-2–positive pregnant women with comorbidities are more likely to develop complications [23]. From this point of view, we analyzed the perinatal outcomes of asymptomatic and uncomplicated women and, by this, to reveal what kind of damage COVID-19 actually causes in pregnancy. The reason why we have chosen asymptomatic/uncomplicated pregnant women as the study population is that the most common form of COVID-19 is mild and moderate disease, and the literature data on this subject is limited.

The WAPM COVID-19 Working Group retrospectively analyzed the data of 266 women who had a singleton pregnancy, had laboratory-confirmed SARS-CoV-2 infection, and gave birth between February and April 2020. It was reported that 94.4% of women had a live birth, 26.3% had PTB before 37 weeks of gestation, 27.5% of newborns were admitted to the NICU, and 2.0% neonatal deaths were reported. What draws our attention is that approximately 70% of the pregnant women included in the study were in the third trimester [6]. In the meta-analysis by Capobianco et al., consisting of 13 publications and 114 cases, the authors reported a high rate of maternal and neonatal complications in infected individuals [9]. Elshafeey et al. analyzed the results of 385 SARS-CoV-2–positive pregnant women [24]. In that study, 95.6% of the cases were mild infections, similar to the case group we selected in our study. However, in the study of Elshafeey et al., SARS-CoV-2–positive pregnant women were not compared to uninfected pregnant women. The authors reported PTB (< 37 weeks of gestation) in 39 pregnant women, LBW (< 2500 g) in 20 newborns, fetal distress in 20, and need for NICU admission in 8 newborns. In our study, 23 cases had spontaneous PTB (< 37 weeks of gestation), 15 cases had LBW (< 2500 g), and 31 newborns required NICU admission in the asymptomatic or uncomplicated SARS-CoV-2 infection group. The rate of spontaneous PTB in pregnant women with a history of COVID-19 was significantly higher than in pregnant women without exposure to COVID-19.

Maternal SARS CoV-2 infection causes maternal immune activation resulting in pro-inflammatory cytokine release. This leads to the disturbance of placental perfusion and ultimately to placental dysfunction. Vascular malperfusion, fetal vascular thrombosis, infection with widespread inflammation, fibrin deposition, and intervillous thrombosis have been demonstrated in placenta samples of pregnant women infected with SARS-CoV-2 [5]. Smithgall et al. [25] collected placenta samples from 51 women with SARS-CoV-2 positive at

delivery, and pathological examination was performed. Interestingly, it was reported that the frequency of placental histopathological findings was independent of the clinical status, and there was no difference between symptomatic and asymptomatic cases in terms of histopathological findings. This information suggests that asymptomatic or uncomplicated COVID-19 may also increase the risk of obstetric complications such as PTB, FGR, and LBW.

Another important issue that remains unknown is whether perinatal outcomes change according to the timing of infection (in which trimester). Although the WAPM COVID-19 Working Group reports that the incidence of combined adverse fetal outcomes increases significantly if infection occurs in the first trimester, we observed that spontaneous PTB occurred 9.13 and 7.09 times more often in women who were infected during the first and third trimesters, respectively, independent of other risk factors. Although we found that second trimester infection did not independently affect the risk of spontaneous PTB, we think that a possible type 2 error should not be ignored, and this issue should be re-examined with prospective studies in larger samples.

PTB is an important public health problem that may adversely affect the health of the newborn and has short- and long-term effects [26]. The global prevalence of PTB has been reported as 10.6% [27]. As information from studies cumulates, countries may need to reconsider their healthcare policies regarding COVID-19. Determining vaccination strategies in pregnant women will be important in preventing COVID-19 and associated obstetric complications, especially PTB.

In our study, with its retrospective cohort design, SARS-CoV-2 infection during pregnancy was confirmed by PCR test positivity, and the gestational age at the time of the infection was correctly determined; these are the strengths of our research. Until now, most studies have evaluated PTB cases without distinguishing them as spontaneous and iatrogenic. However, in our study, we evaluated iatrogenic PTB cases of obstetric or maternal origin separately from spontaneous PTB cases. Therefore, our findings will help to explain the relationship between spontaneous PTB and COVID-19, for which there is not yet enough information in the literature.

Our study has some limitations. A significant number of COVID-19 infected individuals survive the disease without any symptoms or are not diagnosed by PCR. The diagnostic value of the PCR test is limited to 50-60%, and it may result in missed diagnosis. This may cause misclassification bias between the groups that had and did not have the

infection. Since our research was conducted in a single center, the generalizability of the results to the general population is limited.

## CONCLUSIONS

In conclusion, asymptomatic or uncomplicated pregnant women infected with SARS CoV-2 during the first and third trimesters should be followed up carefully and closely for spontaneous PTB, at least as much as pregnant women with complicated disease. In addition, one should keep in mind placental abruption and intrahepatic cholestasis of pregnancy during the course of follow-up. The fact that SARS CoV-2 infection has been associated with the risk of PTB in all spectrums, regardless of the severity of the disease, may reveal the importance of the COVID-19 vaccine in pregnancy, although data on its safety are limited. In this context, it seems reasonable to offer the vaccine option to pregnant women after proper counseling.

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***Author contribution***

P Kumru: Project development, data collection, data analysis
S Hıdıroğlu: Project development, methodology, editing, supervision
E Cogendez: Manuscript writing / editing
H Ayvacı: Data collection
B Yılmazer: Data collection
H Erol: Data collection
O Demirci: Supervison
P Ay: Project development, methodology, supervision

***Conflict of interest***

All authors declare no conflict of interest.

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**Table 1.** Socio-demographic and health characteristics of participants (n: 480)

| | | **Exposure group[a] n: 102** | **Nonexposure group[b] n: 378** | **p value** |
|---|---|---|---|---|
| ***Maternal Characteristics and Maternal Comorbidities*** | | | | |
| **BMI [kg/m$^2$], median (IQR)** | | 31.2 (27.3–34.1) | 30.4 (27.3–33.3) | 0.352 |
| | | **n (%)** | **n (%)** | |
| **Age Range [years]** | 19–24 | 14 (13.7) | 67 (17.7) | 0.462 |
| | 25–34 | 66 (64.7) | 220 (58.2) | |
| | 35–45 | 22 (21.6) | 91 (24.1) | |
| **Educational status** | Primary school | 26 (25.2) | 80 (21.2) | 0.215 |
| | Secondary school | 19 (18.6) | 101 (26.7) | |
| | High school | 30 (29.4) | 121 (32.0) | |
| | University | 27 (26.5) | 76 (20.1) | |
| **Family income** | Low | 17 (16.7) | 56 (14.8) | 0.896 |
| | Medium | 76 (74.5) | 287 (75.9) | |
| | High | 9 (8.8) | 35 (9.3) | |
| **Employed** | | 27 (26.5) | 76 (20.1) | 0.165 |
| **Social security** | | 86 (84.3) | 317 (83.9) | 0.912 |
| **Nulliparous** | | 31 (30.4) | 110 (29.1) | 0.799 |
| **In vitro fertilization** | | **5 (4.9)** | 3 (0.8) | **0.013*** |
| **History of smoking[c]** | | 22 (21.6) | 73 (19.3) | 0.612 |
| **Husband's history of smoking** | | 54 (52.9) | 225 (59.5) | 0.232 |
| **Chronic diseases** | | 30 (29.4) | 108 (29.1) | 0.953 |

[a]Women with a history of PCR + SARS-CoV-2 Infection; [b]Women with no history of SARS-CoV-2 Infection; [c]current smoker or ex-smoker; IQR — interquartile range; BMI — body mass index; *Statistically significant difference

**Table 2.** Pregnancy, birth, postpartum period, and neonatal outcomes of the participants (n: 480)

| | | **Exposure group[a] n: 102** | **Nonexposure group[b] n: 378** | **p value** |
|---|---|---|---|---|
| **Obstetric Outcomes of the Participants** | | | | |
| **Gestational age at delivery median [weeks] (IQR)** | | 38 (37–39) | 39 (37–39) | 0.271 |
| | | **n (%)** | **n (%)** | |
| **Mode of birth** | C/S | 68 (66.7) | 241 (63.8) | 0.586 |
| | Vaginal delivery | 34 (33.3) | 137 (36.2) | |
| **Spontan. preterm delivery (< 37 weeks)** | | **23 (22.5)** | 20 (5.3) | **< 0.001*** |
| **Iatrogenic preterm labor (< 37 weeks)** | | 8 (7.8) | 57 (15.1) | 0.058 |
| **Spontan. early preterm delivery (< 34 weeks)** | | 6 (5.9) | 16 (4.2) | 0.435 |
| **Spontaneous PPROM** | | 6 (5.9) | 15 (4.0) | 0.415 |
| **Hypertensive disease** | | 12 (11.8) | 43 (11.4) | 0.913 |
| **Type of hypertensive disease** | Chronic HT | – | 1 (0.3) | 0.663 |
| | Gestational HT | 4 (3.9) | 8 (2.1) | |
| | Preeclampsia/Eclampsia | 8 (7.8) | 30 (7.9) | |
| | Superimposed Preeclampsia | - | 4 (1.1) | |
| | No hypertensive disease | 90 (88.2) | 335 (88.6) | |
| **GDM** | | 24 (23.5) | 61 (16.1) | 0.083 |
| **Cholestasis** | | **4 (3.9)** | 2 (0.5) | **0.020*** |
| **Abruptio Placenta** | | **4 (3.9)** | 3 (0.8) | **0.040*** |
| **Neonatal Outcomes** | | | | |
| **Newborn birth weight [grams], median (IQR)** | | 3305.0 (2740–3580.0) | 3230.0 (2880.0–3580.0) | 0.999 |
| | | **n (%)** | **n (%)** | |
| **Fetal gender** | Female | 43 (42.2) | 201 (53.2) | **0.048*** |
| | Male | **59 (57.8)** | 177 (46.8) | |

| | | | |
|---|---|---|---|
| **Admitted in NICU** | 31 (30.4) | 95 (25.1) | 0.284 |
| **Apgar 5 score < 7** | 5 (4.9) | 6 (1.6) | 0.061 |
| **SGA** | 10 (9.8) | 35 (9.3) | 0.867 |
| **LGA** | 19 (18.6) | 81 (21.4) | 0.536 |
| **Birthweight < 2500 gm** | 15 (14.7) | 50 (13.2) | 0.699 |
| **Birthweight > 4000 gm** | 5 (4.9) | 18 (4.8) | 1.0 |
| **Neonatal Death** | 1 (1.0) | 4 (1.1) | 1.0 |
| **Fetal anomaly** | 9 (8.8) | 21 (5.6) | 0.226 |
| **Cardiac anomaly** | 2 (2.0) | 4 (1.1) | 0.612 |
| **CNS anomaly** | 4 (3.9) | 4 (1.1) | 0.067 |

[a]Women with a history of PCR + SARS-CoV-2 Infection; [b]Women with no history of SARS-CoV-2 Infection; IQR — interquartile range; C/S — Cesarean section; PPROM — Preterm premature rupture of membranes; GDM — Gestational diabetes mellitus; HT — Hypertension; NICU — Neonatal İntensive Care Unit; SGA — Small for gestational age (Intergrowth 21); LGA — large-for-gestational-age; CNS — Central nervous system; *Statistically significant difference

**Table 3.** The relationship between trimester during SARS-CoV-2 infection and maternal, current obstetric, postpartum, and neonatal period characteristics (n: 102)

| | | **Infection in 1st trimester n: 29** | **Infection in 2nd trimester n: 41** | **Infection in 3rd trimester n:32** | **p value** |
|---|---|---|---|---|---|
| **Maternal and Current Obstetric Outcomes of the Participants** | | | | | |
| **BMI [kg/m$^2$], median (IQR)** | | 31.2 (27.6–34.0) | 31.6 (29.6–34.9) | 30.2 (26.5–33.6) | 0.408 |
| **Gestational age at delivery [weeks], median (IQR)** | | **37.0 (36.0–39.0)** | 39.0 (38.0–39.0) | 38.0 (37.0–39.5) | **0.005*** |
| **Newborn birth weight [grams], median (IQR)** | | **2940.0 (2490.0–3440.0)** | 3400.0 (3210.0–3600.0) | **3125.0 (2650.0–3595.0)** | **0.018*** |
| | | **N (%)** | **N (%)** | **N (%)** | |
| **Age Range [years]** | 19-24 | 4 (13.8) | 4 (9.8) | 6 (18.8) | 0.752 |
| | 25-34 | 19 (65.8) | 29 (70.7) | 18 (56.2) | |
| | 35-45 | 6 (20.7) | 8 (19.5) | 8 (25.0) | |
| **Symptomatic SARS-CoV-2** | | **22 (75.9)** | 17 (41.5) | **21 (65.6)** | **0.010*** |
| **Mode of birth** | C/S | 20 (69.0) | 29 (70.7) | 19 (59.4) | 0.566 |
| | Vaginal delivery | 9 (31.0) | 12 (29.3) | 13 (40.6) | |
| **Spontan. preterm delivery (< 37 weeks)** | | **10 (34.5)** | 4 (9.8) | **9 (28.1)** | **0.034*** |
| **İatrogenic preterm labor (< 37 weeks)** | | **6 (20.7)** | 1 (2.4) | 1 (3.1) | **0.010*** |
| **Spontaneous PPROM** | | 4 (13.8) | 1 (2.4) | 1 (3.1) | 0.100 |
| **Hypertensive disease** | | 6 (20.7) | 4 (9.8) | 2 (6.2) | 0.190 |

| | | | | | |
|---|---|---|---|---|---|
| **Type of hypertensive disease** | Chronic HT | – | – | – | 0.469 |
| | Gestational HT | 2 (6.9) | 1 (2.4) | 1 (3.1) | |
| | Preeclampsia/Eclampsia | 4 (13.8) | 3 (7.3) | 1 (3.1) | |
| | Superimposed Preeclampsia | – | – | – | |
| | No hypertensive disease | 23(79.3) | 38 (90.5) | 30 (93.8) | |
| **GDM** | | 6 (20.7) | 10 (24.4) | 8 (25.0) | 0.912 |
| **Cholestasis** | | – | – | **4 (12.5)** | **0.011*** |
| **Abruptio placenta** | | 3 (10.3) | – | 1 (3.1) | 0.086 |
| **Neonatal Outcomes** | | | | | |
| **Admitted to NICU** | | 10 (34.5) | 10 (24.4) | 11 (34.4) | 0.558 |
| **Apgar 5 score < 7** | | 1 (3.4) | 2 (4.9) | 2 (6.2) | 0.880 |
| **SGA** | | 4 (13.8) | 4 (9.8) | 2 (6.2) | 0.613 |
| **LGA** | | 4 (13.8) | 9 (22.0) | 6 (18.8) | 0.689 |
| **Birthweight < 2500 gr** | | 7 (24.1) | 2 (4.9) | 6 (18.8) | 0.060 |
| **Birthweight > 4000 gr** | | 1 (3.4) | 1 (2.4) | 3 (9.4) | 0.361 |
| **Fetal anomaly** | | 3 (10.3) | 3 (7.3) | 3 (9.4) | 0.900 |
| **Neonatal death** | | 1 (3.4) | – | – | 0.281 |

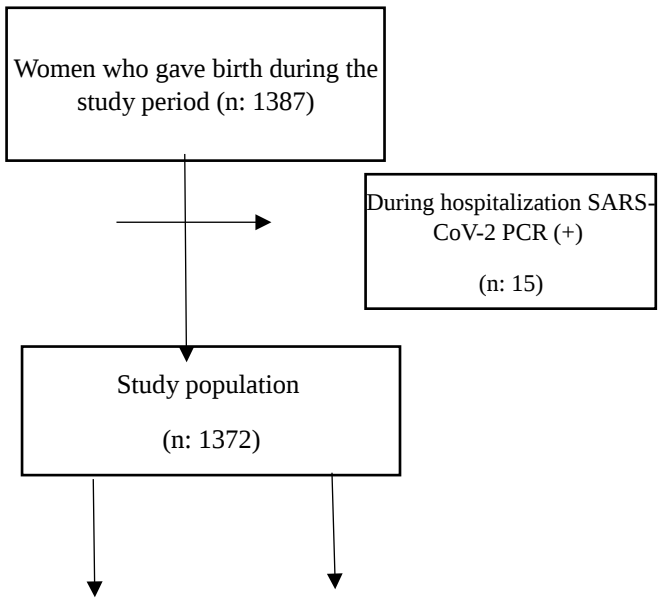
BMI — body Mass Index; IQR — interquartile range; C/S — cesarean section; PPROM — preterm premature rupture of membranes; GDM — gestational diabetes mellitus; HT — hypertension; NICU — neonatal Intensive Care Unit; SGA — small for gestational age (Intergrowth 21); LGA — large-for-gestational-age; CNS — central nervous system; *Statistically significant difference

**Table 4.** Characteristics associated with spontaneous preterm birth, univariate and multivariate analyses

| **Spontaneous Preterm Delivery** | | | | | |
|---|---|---|---|---|---|
| | | **Univariate analysis (OR)** | | **Multivariate analysis (aOR)** | |
| | | **OR (95% CI)** | ***p* value** | **aOR (95% CI)** | ***p* value** |
| **SARS–CoV–2 positive status in pregnancy** | SARS–CoV–2 negative | 1.0 | – | 1.0 | – |
| | 1st Trimester | 9.42 (3.88–22.90) | < **0.001*** | **9.13** (3.68–22.66) | < **0.001*** |
| | 2nd Trimester | 1.94 (0.63–5.96) | 0.250 | 1.85 (0.59–5.79) | 0.292 |
| | 3rd Trimester | 7.00 (2.87–17.10) | < **0.001*** | **7.09** (2.85–17.62) | < **0.001*** |
| **Age [years]** | 19–24 | 1.0 | – | – | – |
| | 25–34 | 1.78 (0.67–4.75) | 0.249 | – | – |
| | 34–45 | 1.16 (0.37–3.68) | 0.803 | – | – |

| | | | | | |
|---|---|---|---|---|---|
| **BMI [kg/m$^2$]** | | 0.95 (0.89–1.01) | 0.117 | 0.94 (0.88–1.01) | 0.096 |
| **Educational status** | Primary school | 0.52 (0.17–1.60) | 0.252 | – | |
| | Secondary school | 1.38 (0.57–3.33) | 0.475 | – | |
| | High school | 1.15 (0.48–2.74) | 0.749 | – | |
| | University | 1.0 | – | – | |
| **Income of family** | Low | 0.56 (0.18–1.72) | 0.312 | – | |
| | Medium | 0.46 (0.19–1.12)) | 0.087 | – | |
| | High | 1.0 | | – | |
| **Working Status** | Yes | 0.90 (0.73–2.98) | 0.168 | – | |
| | No | 1.0 | | – | |
| **Fetal gender** | Female | 1.0 | **0.014*** | 1.0 | **0.023*** |
| | Male | 2.30 (1.18–4.48) | | **2.25** (1.12–4.53) | |
| **IVF pregnancy** | No | 1.0 | **0.013*** | – | – |
| | Yes | 6.48 (1.49–28.11) | | – | |
| **Smoking habit**[a] | No | 1.0 | 0.165 | – | – |
| | Yes | 1.65(0.81–3.35) | | – | |
| **Chronic diseases** | No | 1.0 | 0.587 | – | – |
| | Yes | 0.82 (0.40–1.68) | | – | |
| **Hypertensive diseases during pregnancy** | No | 1.0 | 0.340 | – | – |
| | Yes | 0.56 (0.17–1.86) | | – | |

BMI — Body Mass Index; IVF — In vitro fertilization; [a]current smoker or ex–smoker; OR — Odds ratio; CI — confidence interval; Adjusted odds ratio (aOR) — multiple imputation model adjusted for age groups, BMI, smoking habit, IVF pregnancy and SARS-CoV-2 positive status in pregnancy; 1.0 = as a reference; *Statistically significant difference



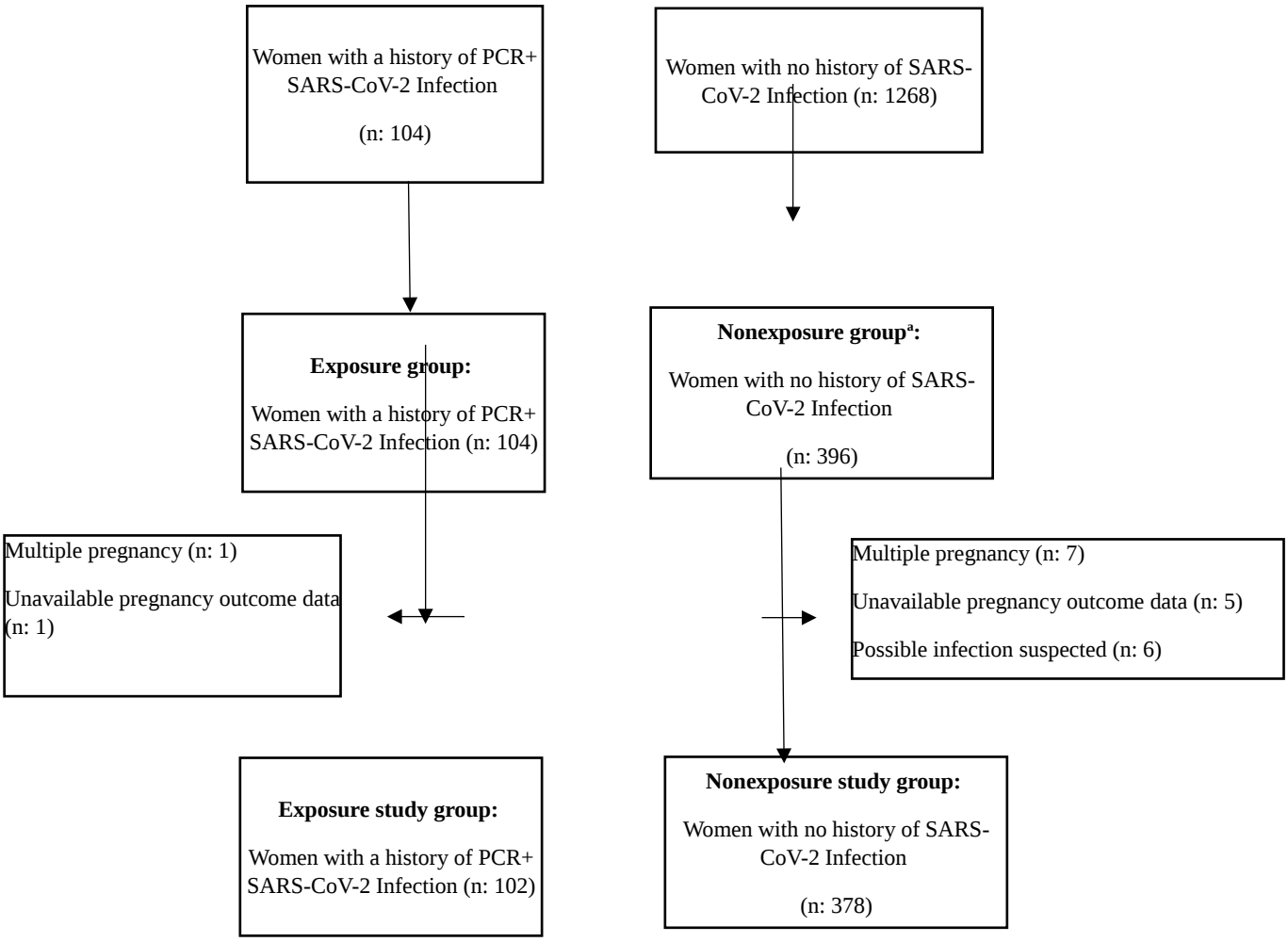



**Figure 1**. Flow chart of the study population; [a]Cases without exposure were determined by the systematic sampling method; PCR — polymerase chain reaction