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The Effect Of Past Covid-19 Infection On Early Pregnancy Losses**Geçirilmiş Covid-19 Enfeksiyonunun İlk Trimester Gebelik Kayıpları Üzerine Etkisi**Çağanay SOYSAL¹Elif YILMAZ¹ Orcid ID:0000-0002-4381-6099 Orcid ID:0000-0001-5107-6492¹ Dr. Sami Ulus Women's and Children's Health Teaching and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey**ÖZ**

Amaç: Bu çalışmanın amacı, gebe kalmadan önceki 1 yıllık süreç içerisinde geçirilmiş Covid-19 enfeksiyonunun erken gebelik kayıpları üzerine etkisinin araştırılmasıdır.

Materyal-Metod: Çalışma prospektif tanımlayıcı bir çalışma olup, 01.03.2021-01.09.2021 tarihleri arasında Ankara Dr. Sami Ulus Kadın Doğum, Çocuk Sağlığı ve Hastalıkları E.A.H. Kadın Hastalıkları ve Doğum Bölümü Obstetrik Polikliniği'nde yürütülmüştür. Gebelik takibi nedeniyle ilk kontrolüne gelen 18-35 yaş arasındaki ilk trimesterdeki gebelerden gebe kalmadan önceki 1 yıl içerisinde Covid-19 enfeksiyonu geçirdiğini ifade eden gebeler çalışma grubuna (n=150), çalışma grubuna alınan gebeden sonra ilk trimesterinde başvuran, 18-35 yaş arasında olup gebelik öncesi Covid-19 enfeksiyonu geçirme öyküsü olmayan ilk gebe de kontrol grubuna dahil edilmiştir (n=150). Gebeler 20. gebelik haftasına kadar takip edilmiş ve iki grubun erken gebelik kaybı oranları (<20 hafta herhangi bir müdahale olmaksızın spontan abort yapma ya da intrauterin GS olmasına rağmen fetal kalp atımlarının yokluğu) karşılaştırılmıştır.

Bulgular: Covid-19 enfeksiyonu geçiren gebelerden 8'i (%5,3), geçirmeyen gebelerden 9'u (%6,0) erken gebelik kaybı yaşamış olup, iki grup arasında erken gebelik kayıp oranları açısından istatistiksel olarak anlamlı bir fark saptanmamıştır (p>0,05). Çalışma grubunda gebelik kaybı yaşamayan gebelerin gebelikten ortalama 6,04±2,94 ay, gebelik kaybı yaşayan gebelerin ise ortalama 6,75±3,15 ay önce Covid-19 enfeksiyonu geçirdiği saptanmış olup istatistiksel açıdan anlamlı bir fark izlenmemiştir (p>0,05).

Sonuç: Çalışmada gebelik öncesi geçirilen Covid-19 enfeksiyonu ile erken gebelik kaybı arasında bir ilişki saptanmamış olmasına rağmen, Covid-19 enfeksiyonunun, plasental vaskülopati üzerindeki etkisi göz önünde bulundurulduğunda erken gebelik kaybı ile ilişkisi geniş prospektif çalışmalarla netleştirilmeli ve en azından gebelik öncesi dönemde anne adayları bu konuda doğru yönlendirilerek kaygı yaşamaları engellenmelidir.

Anahtar Kelimeler: Covid-19, gebelik öncesi, erken gebelik kaybı

ABSTRACT

Aim: The aim of this study was to investigate the influence of covid-19 infection on early pregnancy losses within one year before pregnancy.

Materials and Method: The study was a prospective descriptive study conducted between 01/03/2021 and 01/09/2021 in the obstetric outpatient clinic of the Department of Obstetrics and Gynecology of Dr Sami Ulus Obstetrics, Child Health, and Diseases Training and Research Hospital in Ankara. Of the pregnant women between the ages of 18 and 35 years who came to the first control for obstetric follow-up, the pregnant women in the first trimester who reported having had a Covid-19 infection within one year before pregnancy were included in the study group (n=150), and the pregnant women in the first trimester who had no history of Covid-19 infection before pregnancy were also included in the control group (n=150). The pregnant women were followed up until 20 weeks of gestation, and the early pregnancy loss rates of the two groups (spontaneous abortion at < 20 weeks without any intervention or absence of fetal heartbeats despite intrauterine GS) were compared.

Results: Eight (5.3%) pregnant women who had covid-19 infection and 9 (6.0%) women who did not have covid-19 infection experienced early pregnancy loss, and no statistically significant difference was found between the two groups in early pregnancy loss rates (p >0.05). In the study group, the pregnant women who did not experience pregnancy loss averaged 6.04±2.94 months before pregnancy and the pregnant women who experienced pregnancy loss averaged 6.75±3.15 months before covid-19 infection, and no statistically significant difference was found (p>0,05).

Conclusion: Although there was no association between preconceptional covid-19 infection and early pregnancy loss in this study, the association between covid-19 infection and early pregnancy loss should be clarified in larger prospective studies. In this regard, expectant mothers should be counseled and their fears should be alleviated at least in the pre-pregnancy period.

Keywords: Covid-19, preconception, early pregnancy loss.

Sorumlu Yazar/ Corresponding Author:

Elif Yılmaz

Adres: Dr. Sami Ulus Women's and Children's Health Teaching and Research Hospital, Department of Obstetrics and Gynecology, Turkey

E-mail: elifkasyilmaz@gmail.com

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INTRODUCTION

Pregnant women who are more susceptible to viral infections are among the potential risk groups for coronavirus disease (Covid19), which emerged in 2019 with the first case in Wuhan, China, and was declared a pandemic by the World Health Organization in 2020. Due to the physiological changes that occur, particularly in the cardiorespiratory system and immune system, during pregnancy, the risk of severe illness and death from Covid19 infection is much higher in pregnant women compared with nonpregnant women (1). In addition, women exposed to covid-19 infection during pregnancy are also at risk for adverse obstetric and neonatal outcomes (2). Angiotensin-converting enzyme 2 (ACE2) is a receptor for severe acute respiratory syndrome coronavirus (SARS-CoV). Recent studies have shown that SARS-CoV2 can enter the target cell and infect the host cell by binding to ACE2 in the ovary, uterus, vagina, and placenta. It has also been shown to regulate the expression of ACE2 in cells (3,4,5). Because of its presence in the placenta, its effects on pregnancy and childbirth have recently been highlighted, and covid-19 infection has been found to be associated with preeclampsia, preterm birth, stillbirth, and low birth weight in pregnant women. It has also been reported that complications are more common in severe covid-19 cases than in mild covid-19 infections (6,7,8). In addition to complications at advanced weeks of pregnancy, women who have received covid-19 in early pregnancy are seriously concerned about whether the risk of miscarriage has increased, but the results of the limited number of studies on this topic are conflicting. While there are studies that say that the miscarriage rate does not increase in pregnant women who received Covid-19 in the first trimester, there are also studies that say that placental inflammation that occurs during a viral infection increases the possibility of fetal growth retardation and miscarriage (9,10). The aim of this study was to investigate the effects of covid-19 infection on early pregnancy loss within 1 year before conception.

MATERIALS AND METHODS

Approval was obtained from the Ethics Committee of Dr Sami Ulus Obstetrics, Child Health, and Diseases Training and Research Hospital in Ankara under protocol code 2021/10-228. The study was a prospective descriptive study conducted between 01/03/2021 and 01/09/2021 in the Obstetrics Polyclinic of the Department of Obstetrics and Gynecology of Dr. Sami Ulus Obstetrics, Child Health, and Diseases Training and Research

Hospital in Ankara. Pregnant women between the ages of 18 and 35 years who were in their first trimester and came for their first checkup because of pregnancy surveillance were surveyed, and the pregnant women who reported that they had Covid-19 infection within one year before pregnancy were included in the study group (a total of 150 pregnant women in 6 months). After each pregnant woman was enrolled in the study group, the next pregnant woman between the ages of 18 and 35 years who was in the first trimester and who had not been diagnosed with Covid-19 infection before pregnancy was also enrolled in the control group, resulting in 150 individuals enrolled in the control group in this manner (n=150). Pregnant women were followed until 20 weeks of gestation, and those with early pregnancy loss (spontaneous abortion at < 20 weeks without any intervention or absent fetal heartbeats despite intrauterine GS) were identified, and the pregnancy loss rates of the two groups were compared. Multiple pregnancies, pregnant women with additional systemic diseases, pregnant women younger than 18-35 years, and unintended pregnancies were excluded from the study.

Statistical analyzes were performed using the SPSS package program (IBM SPSS Statistics 24). Frequency tables and descriptive statistics were used to interpret the results. Non-parametric methods were used for measurements that did not conform to the normal distribution. In the nonparametric methods, "Mann-Whitney U" test (Z-table value) was used to compare the measured values of two independent groups. "Pearson- χ^2 " cross-tabulations were used to examine the relationships between two qualitative variables.

RESULTS

No statistically significant difference was found between the study and control groups in gravida, parity, number of living children, and paired test scores. The groups were found to be independent and homogeneous with respect to the specified characteristics ($p > 0.05$) (Table 1).

Table 1. Comparison of some parameters according to groups

	Study sample (n=150)		Control group (n=150)		Statistical analysis* Probability
		Median [Min-Max]		Median [Min-Max]	
Gravida	2,22±1,17	2,0 [0,0-6,0]	2,18±1,13	2,0 [0,0-6,0]	p=0,799
Parity	1,02±0,93	1,0 [0,0-4,0]	1,04±0,90	1,0 [0,0-4,0]	p=0,795
Live birth	0,98±0,91	1,0 [0,0-4,0]	1,03±0,90	1,0 [0,0-4,0]	p=0,585
Double Test					p=0,437
• None	46	30,7	47	31,3	
• Normal	97	64,7	100	66,7	
• High risk	7	4,6	3	2,0	

*Mann-Whitney U test

Eight (5.3%) pregnant women who had Covid-19 infection and 9 (6.0%) women who did not have infection experienced early pregnancy loss, and no statistically significant difference was found between the two groups in the rate of early pregnancy

Table 2. Comparison of Pregnancy Loss Rates of Study and Control Groups

	Study (n=150)		Control (n=150)		Statistical analysis* Probability
	n	%	n	%	
Early pregnancy loss					p=0,803
Yes	142	94,7	141	94,0	
None	8	5,3	9	6,0	

*Pearson-χ² crosstabs

The results of the relationship between the time interval of Covid-19 infection before conception and early pregnancy loss are shown in Table 3. It was found that the pregnant women who did not experience pregnancy loss had an average of 6.04±2.94 months before Covid-19 infection, the pregnant women who experienced pregnancy loss had an average of 6.75±3.15 months before Covid-19 infection, and no statistically significant difference was found ($p > 0.05$).

Table 3. The time Between Covid-19 Infection- Pregnancy and Pregnancy Loss Relationship

	None (n=142)		Early Pregnancy Loss (n=8)		Statistical analysis* Probability
		Median [Min-Max]		Median [Min-Max]	
Time Between Covid Infection and Pregnancy	6,04±2,94	6,0 [0,3-11,0]	6,75±3,15	7,5 [1,0-10,0]	p=0,434

*Mann-Whitney U test

When all pregnant women who participated in the study were evaluated for gravida, parity, and live birth, no statistically significant difference was found between subjects with and without pregnancy loss ($p > 0.05$). Logistic regression analysis showed that none of the parameters influenced miscarriage status in the first trimester.

Table 4. Comparison of some parameters according to the early pregnancy loss status in the whole sample

	None (n=283)		Early Pregnancy Loss (n=17)		Statistical analysis* Probability
		Median [Min-Max]		Median [Min-Max]	
Gravida	2,22±1,17	2,0 [0,0-6,0]	1,82±0,73	2,0 [1,0-3,0]	p=0,226
Parity	1,05±0,93	1,0 [0,0-4,0]	0,71±0,59	1,0 [0,0-2,0]	p=0,173
Living	1,02±0,91	1,0 [0,0-4,0]	0,71±0,59	1,0 [0,0-2,0]	p=0,205

*Mann-Whitney U test

DISCUSSION

Early pregnancy loss is one of the most common pregnancy complications. Whether the infection leads to an increased risk of early pregnancy loss may be a serious concern, especially in expectant mothers who plan to become pregnant and have Covid 19 infection, the results of the limited number of studies on this topic are still conflicting. In this study, the effect of Covid-19 infection in the year before conception on early pregnancy loss was investigated, and no significant difference was found between pregnant women who had Covid-19 infection in the year before conception and those who did not have Covid-19 infection. It was also found that the number of months between Covid-19 infection and pregnancy had no significant effect on pregnancy loss in the first trimester.

The literature states that the risk of becoming infected with Covid-19 is not increased in pregnant women compared to non-pregnant women. However, there are many publications that pregnant women with Covid-19 infection have more severe infection than nonpregnant women (11,12,13). In their systematic review and meta-analysis, Allotey et al. (2020) examined 192 publications to determine the clinical characteristics, risk factors, and maternal and perinatal outcomes of pregnant women with coronavirus infection. Although they found that pregnant women with covid 19 infection had fewer symptoms such as fever, shortness of breath, and myalgia, they concluded that

the need for intensive care and mechanical ventilation was higher, and the risk of maternal death was also shown to be increased (11). Similarly, in their 2021 study of data from 35 hospitals in Washington state, Lokken et al. found that pregnant women were both more likely to have severe covid 19 disease and at higher risk of dying from the disease compared with nonpregnant adults (12). In a cohort study involving 33 hospitals in 14 U.S. states, Metz et al. examined the association between severity of covid 19 infection and perinatal outcomes in pregnant women and concluded that more perinatal complications occurred in pregnant women with severe disease compared with pregnant women without symptoms or with mild disease (14). In the literature, covid-19 infection, particularly in the form of pneumonia, is generally thought to increase the risk of preterm delivery during pregnancy (15,16). In addition to preterm birth, other complications associated with covid-19 infection during pregnancy include stillbirth, increased cesarean section rate, preeclampsia, increased risk of postpartum hemorrhage, and low birth weight (6,17). A systematic review and meta-analysis that included 28 studies of 790 954 pregnant women, of whom 15 524 pregnant women had SARS-CoV-2 infection, found that the likelihood of developing preeclampsia was similar in pregnant women who had symptomatic infection (18). Although the association between advanced gestational age and birth complications and covid-19 infection during pregnancy has been more extensively studied in the literature and there is a clearer consensus on adverse outcomes, research on the association between early pregnancy complications and covid-19 infection in early pregnancy is limited. The literature is becoming more extensive, and the general consensus is that pregnancy loss is not increasing. Freiesleben et al (2021) enrolled 1019 pregnant women in their study, in which they examined the association between covid-19 infection and nuchal thickness and pregnancy loss in the first trimester. As a result of the study, they did not detect a relationship between increased nuchal thickness and pregnancy loss and Covid-19 infection. However, they noted that because of the presence of SARS-CoV-2 antibodies suggestive of prior infection in only 1.8% of the study population, the results of the study may apply to similar populations and patients who do not require hospitalization for infection (9). Cavalcante et al. (2021), in their review examining covid-19 infection in the first half of pregnancy and pregnancy loss at < 22 weeks, concluded that pregnancy loss rates in pregnant women with infection are similar to those in the normal population and noted that well-designed studies are needed to determine whether

SARS-CoV-2 infection increases the risk of pregnancy loss during periconception and early pregnancy (19). Rodriguez et al. (2022) compared the incidence of SARS-CoV-2 infection in women who miscarried in the first trimester and in women who delivered a child during the same period using a mixed-effects Poisson regression analysis and concluded that there was no association between first-trimester abortions and SARS-CoV-2 infection. They concluded that there was no association between first-trimester abortions and SARS-CoV-2 infection but found that the type of miscarriage differed between SARS-CoV-2-positive and negative pregnant women, and inevitable miscarriage was higher in the positive group (20). In their study in which Rotshenker-Olshinka et al (2021) examined 113 Covid-19-positive and 172 Covid-19-negative pregnant women in the first trimester, they concluded that the Covid-19 pandemic environment did not affect pregnancy losses in the first trimester, especially in asymptomatic patients (21). In their study conducted in our country, Saçintı et al (2021) found that the number of pregnancy losses per 100 pregnancies was significantly higher in 2020, when the pandemic peaked, than in 2019, but the rate of positive SARS-CoV-2 test results did not significantly affect the rate of pregnancy losses. They concluded that the high rate of pregnancy loss was related to the lower number of pregnancies in 2020 (22). Although it is generally considered in the literature that covid 19 infection does not affect early pregnancy loss, there are few studies indicating that placental inflammation occurring during viral infection increases the likelihood of pregnancy loss. Baud et al (2020), in their case report involving a patient with symptomatic coronavirus disease and miscarriage in the second trimester, could not explain fetal death for any other reason and found that pregnancy loss was related to SARS-CoV-2 placental infection. This was supported by virologic findings in the placenta (23). In their study, Hsu et al. (2021) demonstrated placental vasculopathy and the presence of SARS-CoV-2 virus in the placenta. They examined the placenta of a 29-year-old multigravid pregnant woman who had no symptoms such as fever and respiratory distress, had mild SARS-CoV-2 infection, and was hospitalized for induction of labor. They noted that the presence of covid-19 in the placenta can lead to complications such as early pregnancy loss and fetal growth restriction because it causes placental vasculopathy, and that pregnant women infected with covid-19 in early pregnancy in particular are at risk for possible vertical transmission (24).

In our study, no significant difference was found between the pregnant women who had been infected with Covid-19 before

pregnancy and the group who had not been infected in terms of the rate of early pregnancy loss. When we examined the association between the timing of Covid-19 infection before conception and pregnancy loss, no significant association was found between the timing of Covid-19 infection before pregnancy and pregnancy loss.

Although the results of our study are consistent with findings in the literature that there is no association between covid-19 infection and early pregnancy loss, they differ from the literature by assessing infection before pregnancy, not during pregnancy. The cross-sectional nature of our study, the homogeneity of the patient group, the small number of patients, and the fact that the patients' covid-19 infection could not be confirmed by antibody detection can be counted among the limitations of the study. As the decision of whether Covid-19 is present or not is based on the patients statement and not on objective evidence, there may be patients in the control group who experienced covid-19 asymptotically, and the covid-19 group is not subdivided by severity of disease. On the other hand, our study is valuable because there are not enough data on the effects of preconceptional covid-19 infection on pregnancy.

In conclusion, the effects of covid-19 infection on placental vasculopathy and its association with early pregnancy loss should be clarified by larger prospective studies, and at least in the preconception period, expectant mothers should be made aware of this issue and their fears alleviated.

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Ethics Committee Approval and Declaration of Helsinki: The study was approved by the Ethics Committee and was therefore conducted in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its subsequent amendments.

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