

The Effect of Previous Covid-19 Infection on Gestational Diabetes Mellitus

Geçirilmiş Covid-19 Enfeksiyonunun Gestasyonel Diabetes Mellitus Üzerine Etkisi

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ABSTRACT

Aim: This study aims to investigate the effect of Covid-19 infection in the first trimester of pregnancy on Gestational Diabetes Mellitus.

Material-Method: The retrospective descriptive study was conducted by scanning the files of pregnant women who applied to the Obstetrics outpatient clinic of the Obstetrics and Gynecology Department of Ankara Dr. Sami Ulus Gynecology, Child Health and Diseases E.A.H. between 11.03.2020, the pandemic start date, and 30.05.2022. The study group consisted of single pregnant women (n=150), aged 18-45 years, who did not have any additional disease, and who were not vaccinated against Covid-19, who had a 50 gr Oral Glucose Tolerance Test. The next single pregnant woman applying to the clinic, who did not have the Covid-19 infection, had a 50 g Oral Glucose Tolerance Test, was aged between 18-45 years, had no additional disease, and was not vaccinated against Covid-19, was enrolled in the study control group (n=150). The rates of gestational diabetes diagnosis of pregnant women in the study and control groups were compared.

Results: It was determined that 12 (8.0%) of 150 pregnant women in the study group and only 4 (2.7%) of 150 pregnant women in the control group were diagnosed with GDM, and the difference was found to be statistically significant (p=0.040). As a result of logistic regression analysis; it was determined that the diagnosis of Covid-19 was an important parameter affecting the risk of gestational diabetes (p<0.05), and the risk of gestational diabetes was found to be 3.174 times higher in those diagnosed with Covid-19 (OR=3.174).

Conclusion: It is obvious that stress caused by covid-19 infection in pregnant women, acute damage to pancreatic islets, and resulting hypercoagulability may increase GDM by disrupting glucose metabolism. Considering that GDM is a disease that brings not only perinatal risks but also long-term chronic metabolic complications, it is clear that special attention should be paid to vaccination and prevention measures to protect pregnant women from extra risk factors such as Covid-19 infection.

Keywords: Covid-19, gestational diabetes

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ÖZET

Amaç: Bu çalışmanın amacı, gebeliğin ilk trimesterinde geçirilmiş Covid-19 enfeksiyonunun Gestasyonel Diabetes Mellitus üzerine etkisinin araştırılmasıdır.

Materyal-Metod: Çalışma retrospektif tanımlayıcı bir çalışma olup, pandemi başlangıç tarihi olan 11.03.2020 ile 30.05.2022 tarihleri arasında Ankara Dr Sami Ulus Kadın Doğum, Çocuk Sağlığı ve Hastalıkları E.A.H. Kadın Hastalıkları ve Doğum Bölümü Obstetrik Polikliniği'ne başvuran gebelerin dosyalarının taranması ile yürütülmüştür. 50 gr Oral Glukoz Tolerans Testi bakılmış olan, 18-45 yaş aralığındaki, ek hastalığı olmayan, Covid-19 aşısı yapılmamış olan tekil gebeler çalışma grubunu (n=150) oluşturmuştur. Çalışma grubuna dahil edilen her gebeden bir sonraki Covid-19 enfeksiyonu geçirmemiş, 50 gr Oral Glukoz Tolerans Testi bakılmış olan, 18-45 yaş aralığındaki, ek hastalığı olmayan, Covid-19 aşısı yapılmamış olan tekil gebeler de kontrol grubunu oluşturmuştur (n=150). Çalışma ve kontrol grubunu oluşturan gebelerin gestasyonel diabet saptanma oranları karşılaştırılmıştır.

Results: Çalışma grubundaki 150 gebeden 12'sinin (%8,0), kontrol grubundaki 150 gebeden ise sadece 4'ünün (%2,7) GDM tanısı aldığı saptanmış olup, aradaki farkın istatistiksel olarak anlamlı olduğu bulunmuştur (p=0,040). Lojistik regresyon analizi sonucunda; Covid-19 tanısı alma durumunun, gestasyonel diyabet riski durumunu etkileyen önemli bir parametre olduğu tespit edilmiş olup (p<0,05), Covid-19 tanısı alanların gestasyonel diyabet riskinin 3,174 kat daha fazla olduğu saptanmıştır (OR=3,174).

Conclusion: Gebelerde covid-19 enfeksiyonunun neden olduğu stres, pankreas adacıklarında yol açabileceği akut hasar ve ortaya çıkan hiperkoagülabilitenin glukoz metabolizmasına bozarak GDM'yi arttırabileceği açıktır. GDM' sadece perinatal riskleri değil uzun süreli kronik metabolik komplikasyonları da beraberinde getiren bir hastalık olduğu göz önünde bulundurulduğunda gebeleri Covid-19 enfeksiyonu gibi ekstra risk faktörlerinden korumada aşılama ve korunma tedbirlerine özellikle önem verilmesi gerektiği açıktır.

Anahtar Sözcükler: Covid-19, gestasyonel diabet

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INTRODUCTION

The coronavirus disease (Covid19) has led to a serious pandemic that has negative consequences for human health all over the world. Although the main target of the virus is the respiratory tract, it has been shown that SARS-CoV also affects many organs such as the heart, kidney, ovaries, uterus, vagina, placenta, testis, and gastrointestinal system by binding to the receptor Angiotensin-Converting Enzyme 2 (ACE2) (1,2). It is also known that ACE2 is intensely expressed in the pancreas. Studies show that the invasion of SARS-CoV into pancreatic islets can cause beta-cell dysfunction and cause acute hyperglycemic states, and this contributes to increased mortality even in healthy individuals without diabetes mellitus (DM) (3,4). At the same time, the increase in pancreatic enzymes is considered to be a finding that supports that this virus causes secondary DM (5). Although the data are limited in patients with Type 1 Diabetes, even in patients with Type 2 Diabetes without accompanying comorbidities, COVID-19 causes more severe pneumonia than patients without diabetes. Hypercoagulation is more common due to dysregulation of glucose metabolism. The need for intensive care rates was higher and it is known to increase the length of stay and mortality rates (6,7). It has been found that serum levels of inflammation-related biomarkers such as IL-6, C-reactive protein, serum ferritin, coagulation index, and D-dimer were also significantly higher in patients with diabetes (8). It has been reported that SARS coronavirus can cause acute diabetes by acute damage to the pancreatic islets in people who did not have diabetes before (4). Although the increased pancreatic enzyme level is considered a finding supporting that the virus causes secondary DM, studies with long-term results are still insufficient.

Especially due to the changes in the cardiovascular and immune systems, more research is being conducted on pregnant women who are at high risk for both COVID-19 infection and severe illness and death due to COVID-19 infection. Due to the placental infection of Covid-19, its effects on pregnancy and childbirth have recently begun to be emphasized, and it is seen that Covid-19 infection in pregnant women is associated with preeclampsia, preterm birth, stillbirth, and low birth weight, and it has been reported that complications are more common in severe Covid-19 cases compared to mild Covid-19 infection (9,10). Although it is known that Covid-19 progresses more aggressively in pregnant women with gestational diabetes mellitus (GDM), especially in groups that use insulin and have a high body mass index, studies on the effect of Covid-19 during pregnancy on GDM are limited (11). Our aim in this study is to investigate the effect of Covid-19 infection in the first trimester of pregnancy on Gestational Diabetes Mellitus.

METHOD

The study is a retrospective descriptive study conducted by scanning the files of pregnant women who applied to the obstetrics outpatient clinic of the Obstetrics and Gynecology Department between 11.03.2020, the pandemic start date, and 30.05.2022, in Ankara Dr. Sami Ulus Gynecology, Child Health, and Diseases Training and Research Hospital.

Table 1. Comparison of some parameters according to groups

Variable	Study Group (n=150)		Control Group (n=150)		Statistical analysis* Probability
	$\bar{X} \pm S. D.$	Median [Min-Max]	$\bar{X} \pm S. D.$	Median [Min-Max]	
Age (year)	28,73±5,41	28,0 [18,0-41,0]	28,29±5,19	28,0 [18,0-42,0]	p=0,516
Gravidity	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 Screening Test					
• None	46	30,7	47	31,3	p=0,437
• Normal	97	64,7	100	66,7	
• High risk	7	4,6	3	2,0	

* "Mann-Whitney U" test (Z-table value)

The study was approved by the Ethics Committee (approval number E-2022/06-361) of the hospital and informed consent was obtained from all patients. In our hospital, there are two outpatient clinics in which approximately 50 pregnant women are examined per day. If the pregnant women who are constantly followed up and come for the results are excluded, there are approximately 10 new pregnant admissions per week. During this period, at approximately 116 weeks, 1160 new pregnant women applied. Among these patients, pregnant women who continued their follow-up regularly constituted the research population. The study group consisted of 750 pregnant women (n=150) who applied to the obstetric outpatient clinics of our hospital between the specified dates, had 50 g Oral Glucose Tolerance Test, were aged between 18-45 years, had no additional disease, and were not vaccinated against Covid-19. Single pregnant women included in the study group, who did not have the next Covid-19 infection, had a 50 g Oral Glucose Tolerance Test, were aged between 18-45 years, had no additional disease, and were not vaccinated against Covid-19, also formed the control group (n=150). Pregnant women who had Covid-19 infection before pregnancy, were vaccinated against Covid-19, had a history of chronic systemic diseases (diabetes, hypertension, cancer, autoimmune disease, etc.), did not come to regular follow-up, did not undergo OGT, had multiple pregnancies and fetal anomalies were excluded from the study. Gestational diabetes detection rates of pregnant women in the study and control groups were compared. In our hospital, 50 grams of Oral Glucose Tolerance Test (it does not matter whether the patient is fasting or not) is performed between 24-28 weeks as a gestational diabetes screening test. One hour after the patient drinks the solution containing glucose, the blood sample is taken and the glucose level is determined. Pregnant women demonstrating GCT exceeding or equal to 140 mg/dl at 1 h received a 100-g, 3-h OGTT. OGTT was performed after 3 days of diet (when the patient is fasting). A positive OGTT was defined as any of two values of plasma glucose equal to or greater than the following levels: fasting, 95 mg/dl; 1 h, 180 mg/dl; 2 h, 155 mg/dl; and 3 h, 140 mg/dl.

Statistical analyzes were performed using a package program called SPSS (IBM SPSS Statistics 24). Frequency tables and descriptive statistics were used to interpret the findings. Parametric methods were used for the values with normal distribution, and the "Independent Sample-t" test (t-table value) method was used to compare the values of two independent groups in accordance with the parametric methods. For the values with non-normal distribution, the "Mann-Whitney U" test (Z-table value method) was used as a non-parametric method in the comparison of the values of two independent groups. In the analysis of the relations between two qualitative variables, "Pearson- χ^2 " cross tables were used. $P < 0.05$ was accepted as significant.

RESULTS

There was no statistically significant difference between the study and control groups in terms of age, gravida, parity, number of live births, and double screening test values. It was observed that the groups were independent and homogeneous in terms of the specified characteristics ($p > 0.05$) (Table 1).

When the relationship between Covid-19 infection in the first trimester and gestational diabetes was examined, it was determined that 12 (8.0%) of 150 pregnant women in the study group and only 4 (2.7%) of 150 pregnant women

in the control group were diagnosed with GDM. The difference was found to be statistically significant ($p=0.040$). (Table 2)

Table 2. Examination of the relationship between gestational diabetes diagnosis and Covid-19

Covid-19 diagnosis Variable	Study Group (n=150)		Control Group (n=150)		Statistical analysis* Probability
	n	%	n	%	
Gestational diabetes					
None	138	92,0	146	97,3	p=0,040
Present	12	8,0	4	2,7	

*Pearson- χ^2 crosstabs

Median values of the 50 gram OGT and 100 gram OGTT values of the groups were given in Table 3. Although the median OGT 50 values of the control group was lower than the study group the difference was not statistically significant

($p=0,822$). Similarly, fasting, 1-2-3 hour values of OGTT 100 was lower in the control group but the difference was not statistically significant ($p<0,05$).

Table 3. OGTT 50 and 100 gram results of the groups

Covid-19 Variable	Evet (n=150)		Hayır (n=150)		Statistical analysis* Probability
	$\bar{X} \pm S. S.$	Median [Min-Max]	$\bar{X} \pm S. S.$	Median [Min-Max]	
OGTT 50	119,53 \pm 30,11	117,0 [72,0-225,0]	111,63 \pm 14,01	114,0 [67,0-191,0]	Z=-0,225 p=0,822
OGTT 100 (fasting)	91,09 \pm 14,62	90,0 [70,0-129,0]	88,82 \pm 9,94	88,5 [67,0-121,0]	t=1,076 p=0,286
OGTT 100 (1 hour)	172,06 \pm 34,50	170,0 [93,0-247,0]	157,75 \pm 22,09	158,0 [118,0-209,0]	t=1,968 p=0,054
OGTT 100 (2 hour)	143,00 \pm 29,58	140,0 [63,0-203,0]	134,94 \pm 23,86	136,5 [88,0-185,0]	t=1,195 p=0,238
OGTT 100 (3 hour)	124,13 \pm 27,33	124,0 [42,0-171,0]	111,84 \pm 27,57	117,5 [49,0-152,0]	Z=-1,554 p=0,120

*Nor "IndependentSample-t" test (t-value), "Mann-Whitney U" test (Z-value)

As a result of the Backward: LR logistic regression analysis based on the risk of Gestational Diabetes; it has been determined that the diagnosis of Covid-19 is an important parameter affecting the risk of gestational diabetes ($p<0.05$), and it

was determined that the risk of gestational diabetes is 3.174 times higher in those who were diagnosed with Covid-19 than those who were not diagnosed with Covid-19 (OR =3.174). (Table 4)

Table 4. Logistic Regression model based on gestational diabetes risk

Variable	B	S.E.	Wald	sd	p	OR	95% Confidence Interval (OR)	
							Upper	Lower
Covid-19 diagnosis*	1,115	0,589	5,767	1	0,049	3,174	2,111	4,567
Constant	-3,597	0,507	50,382	1	0,000	0,027		

*Reference category: No CCR=76.3% $\chi^2(8) =3.593$; $p=0.825$

S.E.: Standart error

DISCUSSION

The main consequences of gestational diabetes mellitus (GDM) are known to be preeclampsia, newborns large for gestational age, risks of cesarean delivery, and associated morbidities. When the diagnosis is not made and the appropriate approach is not taken, pregnant women with GDM are also candidates for being type 2 diabetes patients in the following years. In this study, in which we examined the effect of Covid-19 on gestational diabetes in early pregnancy, where early diagnosis and treatment seriously affected pregnancy outcomes, the risk of gestational diabetes in those who were diagnosed with Covid-19 in the first trimester of pregnancy was found to be 3.174 times higher compared to those who were not diagnosed with Covid-19. The literature supports that diabetes mellitus is a risk factor for the rapid progression of Covid-19 and poor prognosis, and that particular attention should be paid to the rapid deterioration in the general condition of these patients (8). It is known that severe pneumonia, excessive secretion of enzymes related to tissue damage, uncontrolled severe inflammatory reactions, and hypercoagulopathy are more common even in patients with diabetes mellitus without any accompanying comorbidities.

Extremely high blood levels of inflammatory markers (C-reactive protein, ferritin, interleukin 6) during Covid-19 infection in diabetic patients show that these patients are more susceptible to inflammatory storms and the clinical picture can deteriorate rapidly (8). In the study conducted by Yang et al., 39 SARS-CoV infected patients who did not have diabetes and did not receive steroid treatment before were compared with the same number of healthy individuals, and it was shown that diabetes developed in 14 of these patients three days after hospitalization, and diabetes developed in 20 of them two weeks later. It has been reported that SARS-CoV can cause diabetes by the mechanism of acute damage. It was emphasized that the damage to the islets by SARS-CoV was temporary since only two of 20 diabetic patients had diabetes after three years of follow-up (4).

There are many publications on the fact that pregnant women with Covid-19 infection have a more severe infection than non-pregnant women (11,12). It is stated that diabetes mellitus also increases the risk of COVID-19 infection in pregnant women, who are at high risk for both COVID-19 and severe illness and death due to COVID-19 infection, especially due to changes in the cardiovascular and immune systems (13). Although the data are limited, it is emphasized that hyperglycemia is a factor that increases the susceptibility to COVID-19 infection in pregnant women with diabetes mellitus by increasing viral replication and decreasing anti-viral response (14).

Gestational diabetes mellitus is a disease that affects approximately 3%-9% of all pregnancies and brings not only perinatal risks but also long-term chronic metabolic complications. In their study comparing the prevalence of GDM before and after the pandemic, Chelu et al. found that GDM was significantly higher during the epidemic period compared to the pre-COVID-19 period and stated that this increase in GDM could be explained by decreased physical activity, increased anxiety and changes in eating habits (15). In their study to investigate the prevalence of GDM and risk factors for serious infection in the pregnant population infected with SARS-CoV2, Radan et al. revealed that not only the risk of infection with COVID-19 increases in pregnant women with GDM, but also SARS-CoV-2 during pregnancy is a risk factor for the development of GDM, and they emphasized that vaccination and protection methods are particularly important in pregnant women (16). In our study, in accordance with the literature, 12 (8.0%) of 150 pregnant women who had Covid-19 infection in the first trimester, and only 4 (2.7%) of 150 women who did not have an infection were diagnosed with GDM, and the difference was found to be statistically significant. As a result of the regression analysis, it was determined that the diagnosis of Covid-19 is an important parameter affecting the risk of gestational diabetes, and it was determined that the risk of gestational diabetes in those diagnosed with Covid-19 was 3.174 times higher. Zanardo et al. conducted a study in 2022 with the hypothesis that the risk of GDM increases in pregnant women exposed to stressful conditions and traumatic events, and that the Covid-19 pandemic may have increased the prevalence of GDM in this context. The results of the study were consistent with our results, and they found that the prevalence of GDM increased during the pandemic, and as a result of logistic regression analysis, Covid infection in early pregnancy increased the risk of developing GDM by 1.34 times (17). In conclusion, it is clear that stress caused by covid-19 infection in pregnant women, acute damage to pancreatic islets, and resulting hypercoagulability may increase the risk of GDM by disrupting glucose metabolism. Considering that GDM is a disease that brings not only perinatal risks but also long-term chronic metabolic complications, it is clear that special attention should be paid to vaccination and prevention measures to protect pregnant women from extra risk factors such as Covid-19 infection.

Although the retrospective nature of our study, the homogeneity of the patient group, the small number of patients, and the fact that the Covid-19 infection of the patients could not be confirmed by looking for antibodies can be counted among the limitations of the study, the results of this study are important because little data on the effects of early covid-19 infection on GDM is available.

Conflict of interest

No conflict of interest was declared by the authors.

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