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Research Article

Use of Anticoagulants During Pregnancy Prevent Gestational Diabetes?

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Abstract

Background: Nowadays, the use of anticoagulants during pregnancy has increased It is used nearly in all of the advanced maternal age and multifetal pregnancies. It is important to study the effects of this increasingly popular treatment modality on other diseases. The purpose of this study is to research the effect of the usage of anticoagulants on the prevalence of gestational diabetes.

Material and Methods: Our study is retrospective. The participants consist of a group of pregnant women. Pregnant women using anticoagulants formed the case, and randomly selected pregnant women not using anticoagulants formed the control group. The study consisted of 800 participants, 400 case and 400 control. The descriptive statistics are age, number of pregnancies and body mass index. A Chi-Square test was performed to study the effect of the usage of anticoagulants on gestational diabetes.

Results: Other than the body mass index of the groups, other descriptive statistics are similar There was no relationship between the participants with and without gestational diabetes in the case group in terms of gestational age, number of pregnancies and body mass index ($p > 0.05$). In the control group, statistically significant relationship was found ($p < 0.01$). A statistically significant relationship was found between the case and control groups in terms of gestational diabetes frequency ($p < 0.01$).

Conclusions: Our study is one of the first studies to research the effect of anticoagulants had on the development of gestational diabetes. The findings of our study show that the usage of anticoagulants decrease the gestational diabetes development rate.

Keywords: Pregnancy; Anticoagulant Drugs; Gestational Diabetes; Low Molecular Weight Heparin; Acetylsalicylic Acid

Introduction

During pregnancy, the risk of venous thromboembolism increases significantly [1]. The reason behind this is the increase in coagulation factor levels to decrease the risk of postpartum hemorrhage. Thromboembolic diseases during pregnancy and puerperium are the leading causes of maternal mortality [2]. Anticoagulant drugs are used to prevent vascular/cardiac pathologies likely to arise in the mother and decrease placental complications like preeclampsia [3].

Nowadays, the user indication of anticoagulant drugs in pregnant women has expanded, and the use of anticoagulants during pregnancy has increased. The usage of anticoagulants in both pregnancies delivered through assisted reproductive techniques and on patients with recurrent pregnancy loss has become a routine in most clinics [4]. It is used nearly in advanced maternal age pregnancies and multifetal pregnancies. It is essential to study the effects of this increasingly popular treatment modality on other diseases [5].

Gestational diabetes (GDM) is a carbohydrate intolerance seen during pregnancy or first diagnosed during pregnancy. It complicates 8-9% of pregnancies and is two times more likely to happen in high-risk pregnancies. A normal pregnancy progresses with insulin resistance, hyperinsulinemia, and mild postprandial hyperglycemia affected by the growth hormone, corticotropin-releasing hormone, placental lactogen, tumor necrosis factor-α (TNF-α), and progesterone released from the placenta. This situation prepares the mother to supply, especially during the second half of the pregnancy, the fetus' increasing need for amino acids and glucose. It is believed that there is a subclinical metabolic disfunction in mothers who had average glucose resistance before pregnancy but developed GDM during the late stages of the pregnancy. The effect anticoagulants affecting the placenta have on this metabolic change should be discussed [6].

This study aims to research the effect of the usage of anticoagulants on the prevalence of gestational diabetes.

Materials and Methods

Study design

Our study is retrospective. The participants consist of a group of pregnant women in a tertiary health center from January 2011 - to October 2021. Pregnant women using low molecular weight heparin (LMWH) or acetylsalicylic acid (ASA) alongside LMWH as anticoagulants were included in this study as the case group. On the contrary, pregnant women that did not use randomly chosen anticoagulants constituted the control group.

The study consisted of 800 participants, 400 cases, and 400 controls. Any file with missing information was omitted. The information on the participants was acquired through their files. The study was voluntary-based. All participants were fully informed about the study and gave their consent. The required ethical permissions were obtained from the relevant councils.

Studies show that the best age range for pregnancy is 24-35 [7]. Participants were separated into two groups according to their age ranges. Studies show that as parity increases, GDM also increases. Thus, participants were separated into two groups based on whether it was their first pregnancy. Participants were weighed to calculate their body mass index (BMI). Participants were separated into two groups as, participants with average weights (BMI ≤ 25) and overweight participants (BMI > 25).

Inclusion/exclusion criteria

Criteria to be included in the study:

- The case group consists of participants that used LMWH or LMWH + ASA during pregnancy and do not have any missing information in their files.
- The control group consists of randomly chosen participants that did not use LMWH or LMWH + ASA during pregnancy and do not have any missing information in their files

Criteria to be excluded from the study:

- Pregnant women that have missing information in their files.

GDM diagnosis

Fasting blood glucose levels of pregnant women in their 24th-28th weeks of pregnancy that did not have pre-diagnosed diabetes were measured after at least 8 hours of night fasting. After that, the women were given 75 grams of glucose, and during the 1st and 2nd hours, oral glucose tolerance tests (OGTT) were done through plasma glucose measurements. If encountered with any of the plasma glucose levels mentioned below, a GDM diagnosis was made:

- Fasting blood glucose level ≥ 92 mg/dL
- First-hour blood glucose level ≥ 180 mg/dL
- Second-hour blood glucose level ≥ 153 mg/dL [8].

Power analysis

A power analysis was done to calculate the sample size of the study. According to the calculations, the sample size has to be 176 (Table 1).

t tests - Means: Difference between two independent means (two groups)		
Analysis:	A priori: Compute required sample size	
Input:	Tail(s)	= One
	Effect size d	= 0.5
	α err prob	= 0.05
	Power (1-β err prob)	= 0.95
	Allocation ratio N2/N1	= 1
Output:	Noncentrality parameter δ	= 33.166.248
	Critical t	= 16.536.580

	Df	= 174
	Sample size group 1	= 88
	Sample size group 2	= 88
	Total sample size	= 176
	Actual power	= 0.9514254

Table 1: Sample Calculation (G Power Analysis).

Statistical analysis

The descriptive statistics used are the participants' demographic characteristics. These are age, number of pregnancies, and BMI. Additionally, the control group's fasting blood glucose levels, OGTT 1st, and 2nd-hour measurements, and LMWH or LMWH + ASA as anticoagulants were used as descriptive statistics.

A Chi-square test was performed to determine whether there was a significant relationship between the case and control groups in terms of GDM, age, number of pregnancies, and BMI values of the participants.

A Chi-Square test was done to study the effect of the usage of anticoagulants on GDM, which is the primary aim of our study and to determine whether there is a significant relationship between the prevalence of GDM in the case and control groups. The effects of LMWH or LMWH + ASA as anticoagulants had on the potential development of GDM was also studied.

Results

The descriptive statistics of the case and control groups are shown in table 2. Other than BMI values, other descriptive statistics seem to be similar to this information. While 218 (54.5%) participants in the case group are overweight, 35 (83.8%) participants in the control group are overweight.

	Case		Control	
Pregnancy Age	**Frequency**	**Percent**	**Frequency**	**Percent**
24-35	293	73.2	256	64.0
<24 or >35	107	26.8	144	36.0
Number of Pregnancies				
First Pregnancy	293	73.2	231	57.8
More than One Pregnancy	107	26.8	169	42.2
Weight				
BMI<25	182	45.5	65	16.2
BMI>25	218	54.5	335	83.8
GDM				
Exists	281	70.2	249	62.2
Doesn't Exist	119	29.8	151	37.8
Fasting Blood Glucose				
Normal	326	81.5	295	73.8
High	74	18.5	105	26.2
OGTT 1st Hour				
Normal	335	83.8	330	82.5
High	65	16.2	70	17.5
OGTT 2nd Hour				
Normal	335	83.8	326	81.5
High	65	16.2	74	18.5
Anticoagulants				
LMWH	358	89.5		
LMWH + ASA	42	10.5		
Total	400	100.0	400	100.0

Table 2: Descriptive Statistics.

In the study, the participants in the case and control groups were compared among themselves in terms of GDM, gestational age, number of pregnancies, and BMI values. The results obtained are presented in table 3. According to the results, it was determined that there was no statistically significant relationship between the participants with and without GDM in the case group in terms of gestational age, several pregnancies, and BMI ($p > 0.05$). A statistically significant relationship was found between the participants with and without GDM in terms of gestational age, the number of pregnancies, and BMI ($p < 0.01$) in the control group.

	GDM (Case)		x^2	SD	p
Age	**Exists**	**Doesn't Exist**			
24-35	209 (74.4%)	84 (70.6%)	0.613	1	0.459
<24 or >35	72 (25.6%)	35 (29.4%)			
Number of Pregnancies					

First Pregnancy	199 (70.8%)	94 (79%)	2.850	1	0.108
More than One Pregnancy	82 (29.2%)	25 (21%)			
Weight					
BMI<25	129 (45.9%)	53 (44.5%)	38.811	1	0.827
BMI>25	152 (54.1%)	66 (55.5%)			
Total	281 (100%)	119 (100%)			
	GDM (Control)		**x^2**	**SD**	**p**
Age	**Exists**	**Doesn't Exist**			
24-35	71 (28.5%)	73 (48.3%)	16.043	1	0.000
<24 or >35	178 (71.5%)	78 (51.7%)			
Number of Pregnancies					
First Pregnancy	118 (47.4%)	51 (33.8%)	7.141	1	0.009
More than One Pregnancy	131 (52.5%)	100 (66.2%)			
Weight					
BMI<25	51 (20.5%)	14 (9.3%)	13.071	1	0.002
BMI>25	198 (79.5%)	137 (90.7%)			
Total	249 (100%)	151 (100%)			

Table 3: Comparison of the Case and Control Groups' Descriptive Statistics.

The case and control groups were compared with the chi-square test in terms of GDM frequency in the study. The results are presented in table 4. These results determined that the incidence of GDM was lower in the case group than in the control group (x^2 = 5.725; $p < 0.05$).

In the group that used anticoagulants, the effect of LMWH and LMWH + ASA as anticoagulants on GDM development was studied. No significant difference statistically was founded between the groups.

GDM	Case Group	Control Group	x^2	SD	p
Exists	281 (70.3%)	249 (62.3%)	5.725	1	0.020
Doesn't Exist	119 (29.8%)	151 (37.8%)			
Total	400 (100%)	400 (100%)			

Table 4: Comparison between the Case and Control Group according to GDM Prevalence.

Discussion

According to the findings of our study, GDM prevalence was 29.8% in the group that used anticoagulants and 37.8% in the control group. The frequency of pregnant women between 24-35 was 75% in the case group. Pregnancy age in the control group was at a similar rate. It was the first pregnancy of most of the participants from the case group. Nearly half of the participants from this group were overweight. This value is higher in the control group (83.8%). About 90% of the anticoagulant agents were LWMH.

According to the 2020 official statistics of Turkey, the highest fertility rate is between the ages of 25-29. This is followed by the ages 30-34. About 60% of all childbirths are done between 25-34 [9]. On average, 7% of all pregnant women experience GDM. This rate can increase up to 22% depending on different regions and the usage of different diagnostic methods. These findings are parallel to the findings of our study [10].

According to the official statistics, the rate of obesity in women in Turkey is 70% [11]. The findings of our study are close to that rate. Interestingly, the rate of participants with a BMI higher than 25 in the control group is 80%, significantly higher than the 54.5% found in the case group. This may be because the participants in the control group had more pregnancies and were older. Because it is expected that obesity increases with age and the number of pregnancies. There are plenty of studies that confirm this finding [12,13].

According to the results of our study, there is not a significant difference in the basis of age, the number of pregnancies, and BMI between the case group participants that were detected with GDM and not detected with GDM. However, the exact opposite is

valid for the control group. It is estimated that this is the usage of anticoagulants in the case group. The findings of our study show that the usage of anticoagulants decreases the GDM development rate. The prevalence of GDM is lower in the case group than in the control group, and its statistical significance is proof of this finding.

Placental dysfunction in patients with GDM is caused by hyperglycemia. Insulin therapy does not cure the metabolic consequences [14,15]. This indicates that factors other than glucose play a part in GDM's pathophysiology. These factors are advanced glycation end products (AGE). It is thought that these products are essential for fetal pathology. AGE shows its harmful effects by connecting to specific receptors (RAGE) [16]. It was concluded that in response to AGE levels, the RAGE/NF-κB pathway gets activated in the placenta of women with GDM. This activation results in increased permeability in the placenta [17].

A study was done to research the AGE levels in the plasma of pregnant women, its dynamic changes, and to determine the relationship between GDM and these levels. The study was conducted on 90 pregnant women with GDM in the case group and 90 healthy pregnant women in the control group. The AGE levels during pregnancy of both groups were analyzed. The results showed that the plasma levels of AGE were related to GDM [18].

In a study conducted on mice, GDM was associated with increased permeability in the placenta. It was stated that increased permeability might be related to the changes happening in the tight junctions. Animals with GDM were given LMWH; LMWH was connected to RAGE to prevent the placental permeability from failing. This was done by repressing the nuclear factor-kappa B signal and inhibiting the AGE-RAGE signal pathway. The study results showed that protecting the placental barrier in GDM could represent a new target in treatment and that LMWH could be a potential drug for treatment [19]. Other studies confirm that LMWH has an antagonistic effect on the RAGE axis. Some studies emphasize LMWH's antitumor effect beyond its anticoagulant activity [20].

In a similar study, the effect of ursolic acid on the fetal development of GDM in mice and its potential mechanisms were researched. According to the study's findings, ursolic acid showed a protective effect from diabetes on mice with GDM. It was stated that this effect happened in the AGE-RAGE axis. It was reported that ursolic acid might be a protective drug for gestational diabetes treatment [21]. In another study about ursolic acid, the effect mechanism was studied. It was reported that it operated by repressing the nuclear factor-kappa B signal and inhibiting the AGE-RAGE signal pathway. This mechanism is the same one as the LMWH mechanism [22].

In our study, both LMWH and LMWH + ASA as anticoagulants were studied. While the studies on the preventive effect of LMWH on GDM increased [18,19], the studies on ASA mainly prevent the cardiac complications that may happen in pregnant women [23,24]. Our analysis shows no significant statistical difference between LMWH or LMWH + ASA usage in GDM development. This may be because the number of pregnant women who used LMWH + ASA was significantly lower than those who used LMWH.

Conclusion

Our study is one of the first studies to research the effect the usage of anticoagulants had on the development of GDM in pregnant women. Most of the studies in this field are conducted as animal experiments. Moreover, in most human studies, the pathophysiology of the development of GDM was researched.

Having enough participants is an essential advantage of our study. The power analysis done showed that 176 participants would be enough. To ensure data reliability, a 400-person case and control group was put together to respond to this. This is important in terms of the reliability of the findings of our study.

One of the drawbacks of our study is that the AGE levels in the mom's plasma during pregnancy and its dynamic changes were not analyzed. In our retrospective study, that was not possible. It is estimated that analyzing the AGE levels, its use with anticoagulants, and the changes observed would contribute to the literature.

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