PERINATAL JOURNAL

Original Article

Perinatal Journal 2017;25(2):76–81

Investigating the effects of progesterone-derived medication during first and second trimesters on the gestational diabetes development and gestational outcomes

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Abstract

Objective: We aimed to compare newborn outcomes and blood glucose values of 75-g oral glucose tolerance test (OGTT) in pregnant women who were diagnosed gestational diabetes mellitus and did not receive progesterone in 1st and 2nd trimesters and the pregnant women who received progesterone for at least 4 weeks.

Methods: This single-center, retrospective, cross-sectional case study was conducted on pregnant women who were admitted to our obstetrics polyclinic between January 2014 and June 2016. A total of 337 pregnant women who were established with the diagnosis of gestational diabetes mellitus during their pregnancies followed up and delivered at our clinic were included in the study. The patients were separated into two groups as those received progesterone during 1st or 2nd trimester of their pregnancies (n=59) and those did not receive progesterone (n=278). The data were analyzed by SPSS software.

Results: While there was no statistically significant difference between the group not receiving progesterone-derived medication and the group receiving progesterone-derived medication in terms of mean 0-hour and 2-hour blood glucose values of 75-g OGTT, 1-hour blood glucose values were significantly higher in the group receiving progesterone ($p<0.05$). This high value was observed in pregnant women who received 17-OH progesterone caproate, which is a weekly injection form of progesterone derivatives. There was no statistically significant difference between the groups in terms of birth weight, and 1-minute and 5-minute APGAR scores.

Conclusion: We found significant increase in 1-hour values of 75-g OGTT in pregnant women who received 17-OH progesterone caproate for at least four weeks during first and second trimesters of their pregnancies. Further studies are required to compare our results since our population is small.

Keywords: Diabetes mellitus, insulin, pregnancy, progesterone.

Özet: Birinci ve ikinci trimesterde progesteron türevi ilaç kullanımının gestasyonel diyabet oluşumu ve gebelik sonuçlarına etkisinin araştırılması

Amaç: Gestasyonel diabetes mellitus tanısı almış olup 1. ve 2. trimesterde progesteron kullanmamış gebeler ile en az 4 hafta progesteron kullanmış gebelerin 75 g oral glukoz tolerans testi (OGTT) kan şekeri değerleri ile yenidoğan sonuçlarının karşılaştırılması amaçlanmıştır.

Yöntem: Bu tek merkezli, retrospektif, kesitsel, olgu çalışması Ocak 2014 – Haziran 2016 tarihleri arasında gebe polikliniğimize başvuran gebeler üzerinden yürütüldü. Takip edilen gebeliğinde gestasyonel diabetes mellitus tanısı konan ve doğumu kliniğimizde gerçekleşen 337 gebe çalışmaya dahil edildi. Hastalar gebeliğinin 1. veya 2. trimesterinde progesteron kullananlar (n=59) ve kullanmayanlar (n=278) olarak iki gruba ayrıldı. Veriler SPSS programı ile analiz edildi.

Bulgular: Progesteron türevi ilaç kullanmayan grup ile kullanan grup arasında 75 g OGTT 0. ve 2. saat ortalama kan şekeri değerleri açısından istatistiksel olarak anlamlı bir fark gözlenmezken; 1. saat kan şekeri değerleri progesteron kullanan grupta anlamlı yüksek bulundu ($p<0.05$). Bu yükseklik progesteron türevlerinden haftalık enjeksiyon formu olan 17-OH progesteron kaproat kullanan gebelerde gözlendi. Gruplar arasında doğum ağırlığı, 1. dakika APGAR skoru ve 5. dakika APGAR skoru açısından da istatistiksel anlamlı bir fark gözlenmedi.

Sonuç: Gebeliğin birinci ve ikinci trimesterinde en az dört hafta, intramüsküler 17- OH progesteron kaproat kullanan gebelerde 75 g OGTT 1. saat değerlerinde anlamlı yükselme tespit ettik. Popülasyonumuzun küçük olması sebebiyle sonuçlarımızın karşılaştırılabileceği yeni çalışmalara ihtiyaç duyulmaktadır.

Anahtar sözcükler: Diabetes mellitus, gebelik, insülin, progesteron.

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Received: July 10, 2017; **Accepted:** August 13, 2017

Please cite this article as: Taşdelen C, Dayangan Sayan C. Investigating the effects of progesterone-derived medication during first and second trimesters on the gestational diabetes development and gestational outcomes. Perinatal Journal 2017;25(2):76–81.

Available online at:
www.perinataljournal.com/20170252009
doi:10.2399/prn.17.0252009
QR (Quick Response) Code:

deomed

Introduction

Gestational diabetes mellitus (GDM) is the glucose intolerance which appears during pregnancy for the first time or diagnosed during pregnancy for the first time.[1] Although GDM can be seen in all periods of pregnancy, it is mostly diagnosed beginning from the 24 weeks of gestation. The reason is that the human placental lactogen (hPL), which is a placental hormone antagonizing the blood glucose-decreasing effect of insulin, reaches maximum level beginning from this period.[2,3] Therefore, GDM is a metabolic disorder which should be taken under control as of 24 weeks of gestation.[4,5] In various societies, 1–14% of pregnancies are established with the diagnosis of gestational diabetes while 0.5% of all pregnancies are established with the diagnosis of pregestational diabetes.[6] Pregnancies complicated with diabetes have various maternal and fetal risks compared to healthy pregnancies. While pregnancies complicated with diabetes had high rates of maternal mortality (45%) and perinatal mortality (60%) in the early periods of previous century, these rates decreased significantly when insulin began to be used in treatments in 1920s.[2]

Progesterone is a steroidal hormone which should be secreted sufficiently in order to provide embryonic implantation and maintain pregnancy and is produced in corpus luteum in the beginning, and placenta undertakes this duty as of the 9 weeks of gestation.[7,8] Progesterone has a key role to maintain the atonicity of the uterus; however, its mechanism has not been fully understood.[9–11] Although progesterone is prescribed widely for the treatment of imminent abortion in obstetric practice, the meta-analysis conducted by Wahabi et al. could not find any evidence showing that vaginal progesterone support is effective in the treatment of imminent abortion,[12] and some studies showing the efficacy of progesterone support to decrease preterm labor risk were published.[13,14] On the other hand, some studies reported that the use of progesterone increases the risk of developing GDM.[15,16]

In our study, we aimed to compare newborn outcomes and blood glucose values of 75-g oral glucose tolerance test (OGTT) in pregnant women who were diagnosed GDM in our clinic and did not receive progesterone in 1st or 2nd trimester and the pregnant women who received progesterone-derived medication for at least 4 weeks.

Methods

A total of 337 patients, who were admitted to our obstetrics polyclinic between January 2014 and June 2016, established with the diagnosis of GDM and delivered at our clinic, were included in this single-center, retrospective, cross-sectional case study.

The inclusion criteria were determined as being pregnant between 17- and 46-year-old, undergoing 75-g OGGT as GDM screening and diagnostic test between 24 and 29 weeks of gestation and being established with the diagnosis of GDM as a result, and receiving progesterone-derived medication for at least 4 weeks due to miscarriage risk or preterm labor threat.

The exclusion criteria were determined as having pregestational DM diagnosis, termination due to anomaly in pregnancy or intrauterine death of fetus, having any hepatic, renal or thyroid dysfunction during pregnancy which may affect glucose or protein metabolism, and discontinuing follow-up or control.

Age, gravida, parity, history of previous pregnancies, background, family history, history of current pregnancy, medication, and weight gained of pregnant women who included in the study were obtained through their medical records. Gestational ages of the patients were determined according to the first day of their last menstrual period and confirmed by CRL (crown-rump length) measurements established by first trimester ultrasonography. It was recorded whether each patient received progesterone during their pregnancies or not, and if they received, for how long did they receive progesterone-derived medication. Body mass index (BMI: weight [kg]/height^2 [m^2]) of each patient was calculated by prenatal weight and height. The birth weights and 1-minute and 5-minute APGAR scores of newborns were reached by their records.

For pregnant women who underwent 75-g OGTT, the diagnosis was deemed positive when either 0-hour blood glucose level was ≥92 mg/dL, 1-hour blood glucose level was ≥180 mg/dL or 2-hour blood glucose level was ≥153 mg/dL according to the criteria of American Congress of Obstetricians and Gynecologists (ACOG Practice Bulletin 2008) and American Diabetes Association (2003).[1,17]

The patients were separated into two groups as those receiving progesterone-derived medication during 1st or 2nd trimester of pregnancy and those not receiving

progesterone, and their OGTT values were compared. The pregnant women who were receiving progesterone-derived medication were also separated into 3 subgroups, which where oral progesterone (Progestan®, Koçak Farma, Istanbul, Turkey) (n=31), daily intramuscular progesterone (Progynex®, Farmako Eczacılık, Istanbul, Turkey) (n=16), and weekly intramuscular 17-OH progesterone caproate (Proluton®, Bayer, Istanbul, Turkey) (n=12).

SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. The data were presented as mean ± standard deviation. Independent two-sample t-test was used for comparisons between two groups, Kruskal-Wallis variance analysis was used for comparisons between more than two groups, and Mann-Whitney U test was used as post-hoc test to identifying the group causing the difference. Pearson correlation test was conducted to determine any relationship between newborn birth weight and APGAR scores and OGTT levels. In all comparisons, $p<0.05$ was considered statistically significant.

Results

Of 337 patients included in the study, 82.5% (n=278) did not receive any progesterone-derived medication during their pregnancies, and 17.5% (n=59) received any progesterone-derived medication for at least 4 weeks. The distribution of receiving progesterone-derived medication was 9.2% (n=31) for oral progesterone, 4.8% (n=16) for daily intramuscular progesterone, and 3.5% (n=12) for weekly intramuscular 17-OH progesterone caproate.

Of the patients not receiving progesterone-derived medication, the mean age was 30.8 years, mean weight was 80.2 kg and mean BMI was 30.6 kg/m^2. Of the patients receiving progesterone-derived medication, the mean age was 29.5 years, mean weight was 81.4 kg and mean BMI was 32.9 kg/m^2. There was no statistically significant difference between the groups in terms of age, gravida, parity, weight and BMI values (**Table 1**).

The groups receiving and not receiving progesterone-derived medication were compared in terms of 0-hour OGTT, 1-hour OGTT and 2-hour OGTT values. While no significant difference was observed between the groups in terms of 0-hour and 2-hour OGTT values, the values of 1-hour OGTT were significantly higher in the group receiving progesterone ($p=0.045$) (**Table 2**).

No difference was observed in 0-hour and 2-hour values when the patients receiving progesterone-derived medication were compared among themselves; however, 1-hour values of the group receiving 17-OH progesterone caproate were significantly higher the values of pregnant women receiving oral progesterone and daily intramuscular progesterone ($p<0.05$) (**Table 3**).

When 0-hour, 1-hour and 2-hour OGTT values of the patients not receiving progesterone-derived medication were compared with 0-hour, 1-hour and 2-hour OGTT values of the patients receiving oral proges-

Table 1. The comparison of the demographic data of two groups.*

	Group 1 (n=278)	Group 2 (n=59)	p-value
Age (year)	30.8±8.2	29.5±6.8	0.38
Weight (kg)	80.2±12.3	81.4±10.3	0.06
BMI (kg/m^2)	30.6±4.3	32.9±5.9	0.86
Gravida (number)	2 (1-6)	2 (0–6)	0.06
Parity (number)	2 (0–6)	1 (0–5)	0.05

*The data are presented as mean ± standard deviation and median (minimum–maximum). **Group 1:** The patient group not receiving progesterone-derived medication, **Group 2:** The patient group receiving progesterone-derived medication.

Table 2. The comparison of 0-hour OGTT, 1-hour OGTT and 2-hour OGTT values of two groups.*

	Group 1 (n=278)	Group 2 (n=59)	p-value
OGTT 0 (mg/dL)	96.0±14.3	94.1±10.3	0.83
OGTT 1 (mg/dL)	160.2±45.2	170.6±52.1	**0.045**
OGTT 2 (mg/dL)	131.5±38.1	133.2±29.9	0.11

*The data are presented as mean ± standard deviation. **Group 1:** The patient group not receiving progesterone-derived medication, **Group 2:** The patient group receiving progesterone-derived medication.

Table 3. The comparison of OGTT values of the pregnant women by progesterone derivation taken.*

	OP (n=31)	ImP (n=16)	17-OHP (n=12)	p-value
OGTT 0 (mg/dL)	93.1±15.2	95.8±16.2	93.4±13.8	0.66
OGTT 1 (mg/dL)	161.9±37.2[1]	169.9±42.1[1]	189.7±56.7[2]	0.04†
OGTT 2 (mg/dL)	131.2±39.9	132.3±42.9	136.9±33.1	0.09

*The data are presented as mean ± standard deviation. †Kruskal-Wallis variance analysis. The superscript numbers are presented to indicate the difference between the groups (Mann-Whitney U test, p=0.011). **17-OHP:** Weekly intramuscular 17-OH progesterone caproate, **ImP:** Daily intramuscular progesterone, **OGTT:** 75-g oral glucose tolerance test; **OP:** Oral progesterone.

Table 4. The comparison of the newborn data of two groups.*

	Group 1 (n=278)	Group 2 (n=59)			p-value
		OP (n=31)	ImP (n=16)	17-OHP (n=12)	
Birth weight (gram)	3201±584	3107±498	2988±793	3073±489	0.16
1-minute APGAR score	9.1±0.7	8.9±1.1	9.0±0.9	9.2±1.1	0.53
5-minute APGAR score	9.0±1.5	9.7±0.5	9.8±1.0	9.3±0.8	0.87

*The data are presented as mean ± standard deviation. **Group 1:** The patient group not receiving progesterone-derived medication, **Group 2:** The patient group receiving progesterone-derived medication. **17-OHP:** Weekly intramuscular 17-OH progesterone caproate, **ImP:** Daily intramuscular progesterone, **OP:** Oral progesterone

terone, intramuscular progesterone and weekly intramuscular 17-OH progesterone caproate, it was found that there was a significant difference between 1-hour values of the groups. In the inter-group sub-comparison, it was seen that the difference was caused by the patient group receiving intramuscular 17-OH progesterone caproate (p=0.011) (**Table 3**).

The newborn birth weights and 1-minute and 5-minute APGAR scores of the patients who were included in the study are presented in **Table 4**. No statistically significant difference was found between the groups in terms of birth weights and APGAR scores (p>0.05). No relationship was found in the correlation analysis conducted between 1-hour 75-g OGTT results and birth weight, and 1-minute and 5-minute APGAR scores.

Discussion

In our study, we found that 1-hour OGTT values of the patient group who were receiving intramuscular 17-OH progesterone caproate during 1st or 2nd trimester of pregnancy were significantly higher than those of the patients who did not receive progesterone-derived medication, but there was no significant difference in terms of 0-hour and 2-hour OGTT values. Also, there was no significant difference between the groups receiving oral progesterone and intramuscular progesterone and those not receiving progesterone-derived medication in terms of 0-hour, 1-hour and 2-hour OGTT values. In addition, we found no significant difference between the pregnant women with GDM who were receiving and not receiving in terms of birth weights and 1-minute and 5-minute APGAR scores.

Hormones synthesized during pregnancy such as estrogen, placental lactogen, human chorionic somatomammotropin and progesterone are responsible for the development of insulin resistance and hyperglycemia. It was shown that progesteron in particular decreased insulin sensitivity.[18] In a study conducted on pregnant rats, progesteron was shown to cause decreased insulin sensitivity.[19] In various studies, a relationship was also found between insulin resistance and oral contraceptives containing only progesterone.[20,21] In a recent study performed on adolescents, Aldhoon-Hainerová et al. investigated the relationship between insulin resistance (HOMA-IR) value and endogenous hormone levels, and found that endogenous progesterone level was in direct proportion to HOMA-IR values in female adolescents.[22] Nunes et al. showed in their cell culture study that progesterone caused apoptosis in the cells synthesizing insulin.[23]

Progesterone support in the treatment of imminent abortion and recurrent pregnancy wastage has become a common treatment option. Also, the recent studies showing the efficacy of progesterone treatment for the prevention of preterm labor have drawn attention. Meis et al. initiated 17-OH progesteron treatment on 16–20 weeks of gestation on 310 pregnant women who had high risk for preterm labor below 37 weeks of gestation. This group was compared to 153 pregnant women who also had high risk for preterm labor but not administered progesterone treatment. After the comparison, it was shown that 17-OH progesterone treatment was efficient to prevent preterm labor and to decrease perinatal morbidity.[13] In their study, Fonseca et al. compared a group consisting of 72 pregnant women who received vaginal progesterone to another group consisting of 70 pregnant women who received placebo and showed that vaginal progesterone is efficient in the prevention of preterm labor.[14] In 2008 after these two randomized controlled studies, ACOG recommended progesterone support for preterm labor prophylaxis in singleton pregnancies with the history of preterm labor.[1]

With the increased practice of progesterone treatment during pregnancy, the investigation of potential fetal and maternal side effects of this treatment was brought to agenda. It was brought to agenda that progesteron in particular may affect insulin resistance and may cause the development of gestational diabetes. In their retrospective study, Egerman et al. compared 491 obese pregnant women with GDM diagnosis to 408 obese pregnant women without GDM diagnosis. It was found out in the history of pregnant women with GDM diagnosis that the frequency of 17-OH treatment initiated at 16–20 weeks of gestation was higher.[24] In another retrospective study, 110 pregnant women who underwent weekly 17-OH progesterone treatment during their pregnancies were compared to the control group consisting of 330 pregnant women who did not receive progesterone during their pregnancies in terms of 1-hour 50-g OGTT blood values. In pregnant women who underwent progesterone treatment, 1-hour 50-g OGTT results were significantly higher than the control group.[15] Unlike this study, we did not have any control group in our study, and we only compared pregnant women, who were established with GDM diagnosis, and received and did not receive progesterone, in terms of 75-g OGTT values. We observed that 1-hour 75-g OGTT values were significantly higher in the group receiving progesterone-derived medication than those who did not receive. We found that this difference was caused by the group which underwent 17-OH progesterone treatment.

In the literature, there are studies with different results reporting that progesterone support increases GDM diagnosis frequency. In their prospective study, Rebarber et al. compared 557 pregnant women, who underwent weekly 17-OH progesterone treatment for the prevention of preterm labor, to 1524 healthy pregnant women who did not undergo progesterone treatment. In the group which underwent weekly 17-OH progesterone treatment, GDM incidence was significantly higher than the control group.[16] In the prospective study of Wolfe et al., 67 pregnant women who underwent 17-OH progesterone treatment for the purpose of preterm labor prophylaxis were compared to 140 healthy pregnant women who did not underwent progesterone treatment in terms of 1-hour 50-g OGTT values and GDM frequency. They reported that there was no significant difference between the groups in terms of preprandial blood glucose levels, 1-hour OGTT values and GDM diagnosis frequency.[25] Gyamfi et al. conducted a study to perform secondary analysis of two double-blind, randomized, controlled studies to investigate the effects of serial progesterone treatment on GDM risk on 1094 pregnant women. The population consisted of 441 singleton and 653 twin pregnancies. While 616 of the pregnant women underwent 17-OH progesterone treatment, 478 patients were in the placebo group. GDM incidence in singleton and twin pregnancies that underwent and did not undergo progesterone treatment was compared separately. While GDM incidence in singleton pregnancies receiving progesterone and placebo was 5.8% and 4.7%, respectively ($p>0.05$), it was 7.4% and 7.6% in twin pregnancies, respectively ($p>0.05$). Consequently, they reported that weekly progesterone treatment did not increase GDM rate in both singleton and twin pregnancies.[18]

In our study, unlike the studies investigating the relationship between progesterone and GDM to the best of our knowledge, we compared GDM cases only through the progesterone use and investigated the effects of oral natural progesterone and daily intramuscular natural progesterone on 75-g OGTT values. Small patient group receiving progesterone-derived medication and the lack of healthy control group seem to be the limitations of our study.

Conclusion

In conclusion, our study shows that receiving intramuscular 17-OH progesterone caproate causes a significant increase in 1-hour 75-g OGTT values compared to other progesterone derivatives and not receiving progesterone. In the obstetric practice where progesterone use increases gradually with the indication of preterm labor prophylaxis, further wide prospective studies investigating the relationship between GDM and all progesterone-derived preparations are needed.

Conflicts of Interest: No conflicts declared.

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