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Impaired Glucose Tolerance Test in Pregnant Woman Receiving Vaginal Progesterone: A 1-Year Cohort Study

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KEYWORDS

Gestational diabetes, Pregnant, Vaginal progesterone

A B S T R A C T

Gestational diabetes is the most common metabolic disorders during pregnancy, which can cause serious complications in mother and fetus. Progesterone is a known diabetogenic hormone used in the treatment of preterm labor. The aim of this study was to assess the incidence of gestational diabetes after taking progesterone suppositories by using the Glucose Tolerance Test (GTT). In this Cohort study, 84 pregnant patients who referred to Fatemieh Hospital in the first trimester were evaluated. Among them, 42 patients were treated with vaginal progesterone suppositories with any causes (400 mg daily until 20 weeks of gestational age) and 42 patients in a control group did not receive progesterone.Changes in glucose levels (GTT) in the case group before and after the treatment and also in the control groups were compared using SPSS software Ver.18 and statistical tests such as Paired T-test, Mann – Whitney. The mean age in the case group was 26.97±4.53 and in the control group was 26.64±5.01 years, (P=0.75). The FBS means in the treatment group was 79.29±8.88 and the control group was 81.55±8.89, (P=0.229). In the case group of 42 patients, 10 patients (23.8%) and in a control group of the same number of patients, 7 patients (16.7%) had impaired GTT (P=0.415). The results showed that although the incidence of gestational diabetes in patients who received progesterone was more than patients in the control group. But this difference was not statistically significant and this while the patients participating in this study in terms of age, weight and other characteristics were consistent with each other.

Introduction

Gestational diabetes (GDM) is one of the most common metabolic disorders during pregnancy which causes serious complications for maternal and fetal ones (1). Therefore, identifying risk factors for GDM is so important since by such recognition, screening programs can be conducted in prone women and complications can be prevented on mother and fetus by early diagnosis and proper control of blood sugar. Maternal complications of diabetes are as following: preeclampsia, polyhydramnios, preterm birth, birth canal injuries and increase rate of cesarean section (2). Fetal complications also are as following: macrosomia, intrauterine fetal death, causeless neonatal death, hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia and respiratory distress syndrome of neonatal period (3). Progesterone is one of the most basic hormones of human endogenous, which has been used during recent years for treatment of premenstrual syndrome, pregnancy depression, recurrent threatened abortion, preterm birth prevention and support of the luteal phase (4,5). Since 1960, Progesterone has been hired to assess and study safety and effectiveness in preventing preterm labor. Recent studies show that progesterone composites (like intramuscular 17-hydroxyprogesterone caproate and natural progesterone vaginal suppositories which are used daily) reduce preterm labor (6). Other special applications of progesterone include supporting the pregnancy cycles by Assisted Reproductive Technology (ART), controlling irregular uterine bleeding and contraception. In addition, it seems that progesterone is also effective on personal behavior (7,8). It may also lead to some unsuitable effects, including increased insulin resistance, changes in hemostasis, carbohydrates and continued diabetes during pregnancy (9). Progesterone may affect adaptation of normal cells and insulin secretion. This effect is applied through reduction of appearance of transporter 4 (GLUT4) in peripheral tissues particularly in muscle and fatty tissue. In other words, Progesterone- with direct effectiveness on Progesterone receptors- is effective on insulin secretion and pancreatic islet cell proliferation in carbohydrate metabolism (10). Due to pregnant women's hormonal situation, this population are subject to metabolic disorders and on top of them gestational diabetes. When a person is not able to secrete enough insulin to compensate for the increased nutritional needs during pregnancy, risk of gestational diabetes will be increased by also increased production of anti-insulin hormones such as human chorionic hormone, prolactin, cortisol and progesterone (11-13). In this regard, a special attention should be paid to Progesterone's role in increased possibility of gestational diabetes incidence because this medicine is known as one of the effective drugs in treatment and prevention of preterm labor and threatened abortion (5). However, there have been conflicting results in previous studies. The results of some studies indicate lack of gestational diabetes incidence after weekly use of Progesterone. Nevertheless, there are also some findings that report the relationship between parenteral administration of Progesterone and gestational diabetes and use of Progesterone has been known as a risk factor for gestational diabetes incidence (14-16). But, a precise look to such studies shows that the relationship between use of Progesterone and gestational diabetes needs more researches and more studies in this regard seem to be necessary. Since in case of this issue's proof, more precision should be applied for Progesterone administration in order to prevent gestational diabetes, which gives rise to maternal and fetal

complications and lots of costs, the present study was conducted to investigate such an important issue.

Material and Methods

A Cohort study was conducted in Fatemieh hospital of Hamedan in Iran during 2012–2013. This study was conducted on pregnant women in first pregnancy trimester that were under treatment by Progesterone vaginal suppositories (400 mg daily until the 20th week of pregnancy) as the subject group. The control group included the ones without Progesterone vaginal suppositories. This project was approved by the Ethics Committee of Hamedan University of Medical Sciences. Before the project implantation, the objective was explained for the participants (pregnant women) and they entered the study with awareness and satisfaction. The possible problem during the study was the participants' lack of follow up that reduced through researcher's precise track and trace. Also, before the study, probable side effects of the medicines were explained for patients and with complete details, the likelihood of the study exclusion was decreased. The inclusion criteria were as follows: singleton pregnancy, healthy women without serious medical condition and Fasting blood sugar (FBS) less than 92. Furthermore, the exclusion criteria included experience of stillbirth, experience of recurrent abortion, fetal malformation experience in previous pregnancy, experience of macrosomia (birth weight of 4 kg or more), presence of diabetes for the subject for her level 1 relatives, lack of keeping track of patients in the study, presence of the diseases requiring treatment, such as high blood pressure, cancer, seizures, thromboembolic disease, liver disease, treatment with beta-adrenergic drugs for asthma, transfer of vaginal suppository progesterone into injections and Body mass index (BMI) greater than 30. All these people were taken a morning venous blood samples to evaluate the FBS and in case of FBS<92 and having above mentioned conditions, the subjects entered the study. All measurements were performed in the morning after 8 hours overnight fasting. Give the above criteria, 84 patients were evaluated among whom 42 ones were placed in subject group and 42 ones in control group. In order to calculate sample number, the study power and confidence level were considered as 99% and 95%, respectively. All the participants were under sonography at first pregnancy trimester and gestational age was specified based on biometry. Weight and height of participants as well as their BMI were measured and calculated. In order to evaluate variables into two groups and comparing them, a questionnaire was designed and collected. The patients of both subject and control groups were followed up by weeks 24-28. Incidence of Gestational Diabetes and disorder were investigated in Oral Glucose Tolerance Test (OGTT) after follow up. 2 hours OGTT was measured by feeding 75grams of glucose. Given the definition of the American College of Obstetricians and Gynecologists, fasting blood glucose less than 92 for one and two hours are considered natural as 153 and 180, respectively. During the study, in case of any abnormal item, the Gestational Diabetes was diagnosed.

Statistical analysis

Data resulted from the study was entered SPSS v.16 and after an assessment on data distribution normality, Student's T-test and Mann – Whitney were used to compare mean values between subject and control groups. Qualitative variables' frequency comparison was also performed using "Chi-Square" Statistical test. Central indices were

also used. Also, in order to investigate the impact of such variables as BMI, Age and gravity on disorder incidence at OGTT, the logistic regression test was used. P-Value <0.05 were taken significant into account in these tests.

Results and Discussion

In the present study, totally 84 participants were evaluated among whom 42 ones were in subject group and 42 ones in the control group. Total mean age of all studied patients was 26.80 ± 4.75. Separately, mean age of case group and control group members were 26.97 ± 4.53 and 26.64 ± 5.01, respectively (P=0.75) (Table 1). FBS mean assessment showed generally such a mean as 80.42 ± 8.88. This mean for case and control groups was 81.55 ± 8.89 and 79.29 ± 8.88, respectively (P=0.229) (Table 1). OGTT showed that 17 patients (20.2%) have impaired OGTT among whom 10 patients (23.8%) and 7 patients (16.7%) were in case group and the control group, respectively (P=0.415). Furthermore, BMI mean, gravidity and FBS mean as well as an hour later blood sugar and two hours later blood sugar of all patients are separately presented in table 1. Mean difference of BMI, age and gravity among the people with impaired GTT and normal GTT was not statistically significant. The relationship between BMI and impaired GTT was investigated. The findings showed that in subject group, 16 patients had a BMI greater than 25 among whom 5 patients (31.2%) had impaired GTT. Also in control group, 15 patients had a BMI greater than 25 among whom 4 patients (26.7%) were with impaired GTT (Table 2). Given the assessment, the relationship between mean age and GTT disorder among the patients at both groups was not statistically significant (P=0.469). The results indicated that in the case group, 21 patients were older than 25 years among them 6 patients (28.6%) had impaired GTT. However, 23 patients in the control group were older than 25 years that 4 patients (17.4%) were with impaired GTT (Table 3). Also, the relationship between gravidity and GTT disturbance was statistically insignificant (P=0.654). Frequency percentage of impaired GTT cases for both control and subject groups are presented in table 4.

The present study was conducted aiming to determine incidence of impaired GTT among pregnant women treated with progesterone vaginal suppository. So far, lots of studies have investigated the relationship between gestational diabetes and Progesterone consumption that most of them have used injection of progesterone to prevent preterm labor, often in the third trimester and sometimes in the second trimester (17, 18). Gestational diabetes is a common complication of pregnancy which engages about 2-5% of the population. This disease is accompanied by maternal, fetal and neonatal complications (2, 8). In the present study, totally 42 patients were studied among pregnant women treated with vaginal progesterone in the first trimester of pregnancy. No significant difference was seen between mean age, FBS and BMI of subject and control groups.

The main purpose of this study was to investigate the incidence of gestational diabetes among the studied patients. For this purpose, GTT was used. As mentioned in the results section, impaired GTT was seen more in the case group compared to control group, though such a difference was not statistically significant. Rebarber *et al.* (19) also studied the relationship between progesterone consumption and incidence of gestational diabetes. In their study, the mothers with experience of preterm labor who were treated with weekly injections of

progesterone from week 27 were compared with the ones with similar conditions but receiving placebo medicine. They indicated that after week 28 of pregnancy, in the group receiving progesterone and the placebo group incidence of gestational diabetes was 9.12% and 4.9%, respectively, which shows a significant difference in terms of statistical analyses. Although the results of Rebarber *et al.* (19) are not in line with those of present study, amount of incidence of gestational diabetes in the group receiving was also higher compared to control group. However, this should be paid into attention that studied patients in Rebarber *et al.* (19) study were investigated from week 27 of pregnancy. Present work studied patients in the first trimester, which may be the cause of observed differences in the results. Rebarber *et al* only studied the mothers with preterm labor. Our studied population was different in these terms that the pregnant women were also enrolled who were also treated by progesterone in addition to ones with preterm labor. However, it does not seem that this difference has an effect on the results. In another study, incidence of impaired GTT after weekly Progesterone injection was compared in case group with the control group. The corresponding results indicated that impaired GCT in Progesterone group was 6.2%, while it was 2.1% for the control group which indicates a significant statistical difference (20). The results of this study are not also parallel with our results. This finding of Rebarber (19) which both-like our findings- address Progesterone consumption as a risk factor for Gestational Diabetes, suggest this hypothesis that in different races, Progesterone can be known as a risk factor for Gestational Diabetes. Therefore, it needs more assessment that in which race Progesterone consumption has higher risk for incidence of Gestational Diabetes (21-23). Supporters of the concept which refers to the impact of Progesterone on Gestational Diabetes relate cause of this finding to the impact of Progesterone hormone as one of the anti-insulin hormones (24). During the pregnancy, with increased production of anti-insulin hormones like HCG hormone, prolactin, cortisol and progesterone, Gestational Diabetes risk will be increased (25–27). In fact, progesterone causes to eliminate sensitivity to insulin. These changes can result in reduced incidence of GLUT-4 at skeletal muscle and adipose tissue and impairs insulin release (28). Progesterone is known as a factor of Gestational Diabetes incidence. Mentioned mechanism includes increased resistance to insulin through decreased incidence if GLUT-4 or impaired beta adaptive response to increased insulin secretion (29). Incidence of Gestational Diabetes after weekly treatment by alpha hydroxyprogesterone caproate 17 was investigated by Gyamfi *et al.* (30).

Incidence of Gestational Diabetes in singleton pregnant women who had received hydroxyprogesterone was 8.5% and it was 4.7% among placebo group mothers that showed no significant statistical difference. Their results are in line with ours. Effects of progesterone vaginal suppositories in the incidence of gestational diabetes were also studied by Kheiri *et al.* (31). In terms of methodology, their study is the closest study to present work since it also worked on pregnant women before week 18 of pregnancy that were treated by progesterone vaginal suppositories for any reason. However, their results are not parallel with those of present paper. In this study, a significant difference was reported between incidence of impaired GTT among the patients of subject and control groups. It seems that duration of contact progesterone, its dose and method of use may increase risk of Gestational Diabetes by different amounts which need more studies for assessment.

Table.1 Baseline and clinical characteristics of patients in case and control groups

Mean Variable	Case	Control	P-value*
Age	26.97 ± 4.53	26.64 ± 5.01	0.75
FBS	81.55 ± 8.89	79.29 ± 8.88	0.22
1 h BS	144.72	135.31	0.19
2h BS	112.36	108.29	0.54
BMI	24.78 ± 2.8	24.77 ± 2.2	0.98
Gravity	1.84 ± 1.02	1.6 ± 0.74	0.22

*P-Value less than 0.05 considered significant

Table.2 Incidence of GTT impairment in case and control groups with different BMI levels

Groups		BMI<=25	BMI>25	P-Value
Case	Impaired GTT	5(19.2)	8(31.2)	0.46
	Normal GTT	21(80.8)	11(68.8)	
Control	Impaired GTT	3 (11.1)	4(26.7)	0.22
	Normal GTT	24 (88.9)	11(73.7)	

Table.3 Incidence of GTT impairment in case and control groups by different age ranges

Groups		Age <=25	Age>25	P-Value
Case	Impaired GTT	4(19)	6(28.6)	0.46
	Normal GTT	17(81)	15(71.4)	
Control	Impaired GTT	3 (15.8)	4(17.4)	0.22
	Normal GTT	16(84.2)	19(82.6)	

Table.4 GTT impairment in case and control groups with different gravities

		Gravity				P-Value
		1	2	3	4	
Case	Impaired GTT	5(23.8)	3(27.3)	2(33.3)	0	0.65
	Normal GTT	16(76.2)	8(72.7)	4(66.7)	4(100)	
Control	Impaired GTT	3(13)	2(15.4)	2(33.3)	0	0.48
	Normal GTT	20(87)	11(84.6)	4(66.7)	0	

Totally, the present study showed that although the amount of Gestational Diabetes incidence was higher among the patients who had progesterone compared to control group, this higher amount was insignificant. And this is while that the participants in present study were parallel in terms of age, weight and other specifications. But as mentioned, in many studied progesterone consumption can be a risk factor for Gestational Diabetes that shows need to more studies in this regard. Besides, discrepancy of results of present study with former ones can be due to such factors as different methods of use to conduct different studied and different sample sizes. One of the limitations here can be low number of samples. This issue along with existing differences in project methods of use can somewhat convinces some cases in present study that have shown no statistical difference. Therefore, in order to approve or reject impact of progesterone on Gestational Diabetes incidence, we should conduct more studies as clinical trials or cohort with more frequent samples as well as multi-center projects in this regard.

Conclusion

Given the results here, it can be concluded that use of vaginal progesterone suppositories has probably no considerable impact on make GTT impaired and Gestational Diabetes incidence. However, according to importance of pregnancy period and possible side effects of this medicinal composition, it seems that gynecologists and even other disciplines should take these cases into account at the time of prescribing these medications.

Conflict of interests

None of the contributing authors have any conflict of interests, including any specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

References

1. Gary Cunningham, F., Norman, F., Kenneth, J., Larry, C., Johns, C., Katharine, D. 2001. Willams obstetrics, 21th edn, Vol. 2. Mc Graw Hill, New York. Pp. 1359–79.
2. American Diabets Association, 1997. Report of the expert committee on the diagnoses and classification of diabetes mellitus. *Diabets Care*, 20: 1183–97.
3. Deitra, L., Low dermilk, S., Perry, BoBak, I. 2000. Maternity & women's health care, 7th edn. Mosby Co., St. Louis. Pp. 863–4.
4. Braun, W., Fauci, K., Tango, J. 2001. Harrison's principles of internal medicine, 15th edn. McGraw Hill, New York. Pp. 2109–12.
5. Sayehmiri, F., Bakhtiari, S., Darvishi, P., Sayehmiri, K. 2013. Prevalence of gestational diabetes mellitus in Iran: A systematic review and meta-analysis study. *IJOGI*, 15(40): 16–23
6. Saram, K., Memarzadeh, M. (Assessment of gestational diabetes prevalance in women referred to Akbar Abady hospital in Tehran). Phd Thesis. Iran University of Medical Sciences, Tehran. 1381.(Persian)
7. Daniela, C. 2004. Obstetricans and gynecologists, gestational diabetes [online][cited 2004]. Available from URL: http:// www. Med students. Com.br/ginob/ginob4.htm
8. Engelgau, M.M., Herman, H., Smith, P.J. 1995. The epidemiology of diabetes and pregnancy in US 1988. *Diabetes care*, 18: 1059.
9. American college of obstetricians and gynecologists, 2001. Gestational diabetes. American College of obsterician and Gynecologists, Practice- bulletin, Washington (DC). 30 Pp.
10. Hare, C., Johan, W. 1994. Diabetic complications of diabetic pregnancies. *J. Perinatol.*, 18: 451–6.
11. Persson, B., Hanson, V. 1998. Neonatal morbidities in gestational diabetes mellitus. *Diabetes Care*, 21(Suppl.): B 79–84.
12. Metzger, B.E., Coustan, D.R. 1998. Summary and recommendation of the fourth international workshop conference on gestational diabetes mellitus. *Diabetes Care*, 21(Suppl.): B 161–7.
13. American diabetes association, 1999. Gestational diabetes mellitus. *Diabetes Care*, 22(Suppl.1): s74– s76.
14. John Schorge, J.S., Lisa Halvorson, Barbara Hoffman, Karen Bradshaw, Cunningham, F. 2008. Williams gynecology. McGraw Hill Medical, NY.
15. Wikimedia Foundation, I., 2012. Progesterone. Retrieved 10, 28.
16. Vergnaud, S.A. 1982. Progesterone and glucose metabolism in the female rat adipocyte: effect on hexokinase activity. *J. Endocrinol.*, 95(3): 369–375.
17. Sagaya, A., Sugiyama, T., Yanase, S., Shen, X.X., Minoura, H., Toyoda, N. 2000. Expression of glucose transporter 4 mRNA in adipose tissue and skeletal

muscle of ovariectomized rats treated with sex steroid hormones. *Life Sci.*, 66: 641–648.
18. Thaddeus, P., Waters, B., Brian, M., Mercer, A., Catalano, P.M. 2009. Effect of 17 alpha-hydroxyprogesterone caproate on glucose intolerance in pregnancy. *Obstet. Gynecol.*, 114: 45–49.
19. Rebarber, A., Istwan, N.B., Russo-Stieglitz, K., Cleary-Goldman, J., Rhea, D.J., Stanziano, G.J., *et al.* 2007. Increased incidence of gestational diabetes in women receiving prophylactic 17 alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery. *Diabetes Care*, 30(9): 2277–80.
20. Aydin Kosus, Seval, A., Haktankacmaz, Dilek, A.K., Nilgun, O., Turhan, 2012. Effect of dose and duration of micronized progesterone treatment during the first trimester on incidence of glucose intolerance and on birth weight. S. Kragr AG, basal 31.
21. Wolf, K., How, H., Henderson, Z.T., Sibai, B. 2011. The rates of abnormal glucose challenge test and gestational diabetes in women receiving 17 alpha-hydroxyprogesterone caprate. *Am. J. Perinatol.*, 28(10): 741–746.
22. Caritis, S.N. 2011. Pharmacokinetics of 17-hydroxyprogesteronecaproate in multifetal gestation. *Am. J. Obstet. Gynecol.*, 205(1): 40.e1–8.
23. Franz, M.J., Horton, E.S. Sr., Bantle, J.P., Beebe, C.A., Brunzell, J.D., Coulston, A.M. *et al.* 1994. Nutrition principles for the managementof diabetes and related complications. *Diabetes Care*, 17(5): 490–518.
24. Hillier, T.A., Vesco, K.K., Pedula, K.L., Beil, T.L., Whitlock, E.P., Pettitt, D.J. 2008. Screening for gestational diabetes mellitus: asystematic review for the U.S. Preventive Services Task Force. *Ann. Intern. Med.*, 148(10): 766–75.
25. Metzger, B.E., Buchanan, T.A., Coustan, D.R., de Leiva, A., Dunger, D.B., Hadden, D.R., *et al.* 2007. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care*, 30(Suppl. 2): S251–60.
26. Waters, T.P., Schultz, B.A., Mercer, B.M., Catalano, P.M. 2009. Effect of 17 alpha-hydroxyprogesterone caproate on glucose intolerance in pregnancy. *Obstet. Gynecol.*, 114(1): 45–9.
27. Mercer, B., Milluzzi, C., Collin, M. 2005. Periviable birth at 20 to 26weeks of gestation: proximate causes, previous obstetric history and recurrence risk. *Am. J. Obstet. Gynecol.*, 193(3): 1175–80.
28. Simhan, H., Canavan, T. 2005. Preterm premature rupture of membranes: diagnosis, evaluation and management strategies. *BJOG*, 112(1): 32–7.
29. Aagaard-Tillery, K., Nuthalapaty, F., Ramsey, P., Ramin, K. 2005. Preterm premature rupture of membranes: perspectives surrounding controversies in management. *Am. J. Perinatol.*, 22(6): 287–97.
30. Gyamfi, C., Horton, A.L., Momirova, V., Rouse, D.J., Caritis, S.N., Peaceman, A.M., *et al.* 2009. The effect of 17-alphahydroxyprogesterone caproate on the risk of gestational diabetes in singleton or twin pregnancies. *Am. J. Obstet. Gynecol.*, 201(4): 392 e1–5.
31. Kheyri, N., Anbarluei, M., Saleh, S., Sarfeju, F. 2013. Side effects of sustained-release vaginal suppository progesterone in pregnant women: gestational diabetes mellitus. *HBI J.*, 11(4): 300–306.