Effect of Vaginal Progesterone Treatment on Incidence of Glucose Intol-erance and Birth Weight in Pregnant Females with Threatened Abortion

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ABSTRACT

Background: Preterm birth is an important health problem for neonates, families and societies. High risk patients for spontaneous preterm birth due to short cervix benefit from prophylactic use of progesterone. Progesterone has diabetogenic properties by affecting on insulin release and pancreatic function, and may cause gestational diabetes mellitus. The aim of this study was to evaluate whether the usage of vaginal progesterone would increase the incidence of glucose intolerance, and affect the birth weight in pregnancy or not. **Material and methods:** 49 women treated with vaginal progesterone and 49 healthy not treated pregnant women participated in this prospective cohort study. Fasting blood sugar (FBS), glucose challenge test (GCT), and serum progesterone level in all women were checked at 28th week of gestation. An abnormal GCT was followed by the subsequent glucose tolerance test (GTT). **Results:** Progesterone levels showed statistically significant higher levels in the cyclogest exposed group compared to the control group (P<0.001). Furthermore, the Mean GCTs levels were higher in the cyclogest exposed group in comparison to the control group (P=0.007). Nevertheless, Mean FBS levels and Mean GCTs were higher in the cyclogest group, but the FBS differences were not statistically significant (P>0.05). The frequency of women with abnormal FBS, GCT and GTT did not show statistically significant differences between the two groups (P>0.05). **Conclusion:** The daily use of vaginal progesterone caused higher incidence of glucose intolerance but it was not statistically significant; therefore, unnecessary use of cyclogest during pregnancy should be avoided.

Key Words: *Cyclogest, Glucose intolerance, Preterm labor, Vaginal progesterone.*

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INTRODUCTION

Preterm birth is an important health problem for neonates, families, and societies [1]. A variety of morbidities complicate the neonates mostly because of organ immaturity in preterm infants [2]. Many risk factors have been identified for preterm birth [3], such as shortened cervical length that is a powerful predictor of preterm delivery [4]. Short cervix may be caused by previous trauma to the cervix such as conization, dilation and curettage (D&C), although the etiology may be unknown [2]. High risk patients for spontaneous preterm birth due to short cervix benefited from prophylactic use of progesterone [5]. Progesterone administration in the first trimester of pregnancy supported corpus luteum function, and prevented spontaneous abortion [5, 6].

Progesterone has several routs of administration including vaginal, oral, and by injection [1]. It has been reported that vaginal progesterone reduced the rate of preterm labor by 44% in patients with short cervix [7]. Vaginal

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progesterone had a high uterine bioavailability due to uterine exposure before the first pass through the liver and less systemic side effects [8]. Progesterone administration should be started between 16 and 20 weeks of gestation and continued till 36 weeks [8]. In previous reports on 2000 pregnancies using progesterone, no increase in birth defects or genitalia anomalies has been reported, so it can be considered completely safe [9]. Progesterone had diabetogenic properties by affecting on insulin release and pancreatic function, and might cause gestational diabetes mellitus [6, 10]. Gestational diabetes mellitus increased macrosommia, dystocia, and prenatal mortality [11].

Abnormal glucose metabolism in pregnancy has been one of the most important diseases which would complicate the pregnancy. Because vaginal progesterone for prevention of preterm delivery and threatened abortion is widely used by obstetricians, the aim of this study was to evaluate whether the usage of vaginal progesterone would increase the incidence of glucose intolerance, and affect the birth weight in pregnancy or not.

METHODS

Study Population and Design

This was a prospective cohort study performed during September 2012 and December 2013 in the department of obstetrics and gynecology at Shiraz University of Medical Sciences. 49 women treated with vaginal progesterone with a history of previous abortion, preterm birth or due to short cervix, participated in this study. All these women used vaginal progesterone with the trade mark of cyclogest, 400 milligram daily from maximum of 16-20 week of gestation till 36 week of pregnancy. Inclusion criteria were singleton pregnancies , and healthy women without any medical diseases. Women with irregular using cyclogest, smoking and using drugs (not including iron, folic acid and prenatal supplements), abnormal fetus detected by sonography, preterm birth (delivery before 37 weeks of gestation), history of overt diabetes, gestational diabetes and other systemic diseases, macrosomia in previous pregnancy(birth weight > 5000gr), and a history of previous polycystic ovarian syndrome were excluded from this study.

49 healthy not treated pregnant women with mentioned criteria were selected as the control group. These two groups were matched by maternal age and body mass index (BMI) before pregnancy. Gestational age was calculated by the first trimester sonography and last regular menstruation date. Sample size was calculated to be 49 pregnant women in each case and control group. All the women were checked for diabetes in pre-conceptional counseling.

Study Measurements

10 ml blood sample from fasting participants was taken between 7:30 am and 8:30 am. Serum and plasma were separated by centrifugation at 800 × g. Fasting blood sugar (FBS), glucose challenge test (GCT), serum progesterone level in all women were checked at 28th week of gestation. Serum levels of progesterone were measured by enzyme-linked immunosorbent assay (ELISA) kits (DRG, Marburg, Germany). FBS≥ 100mg/dl was accepted as abnormal FBS. GCT was performed by giving 50 gram oral glucose and checking 1hour serum glucose. An abnormal test was defined as GCT≥ 130 mg/dl followed by subsequent glucose tolerance test (GTT).

An abnormal 3-hour 100 gram GTT was defined as two or serum glucose levels that met or exceeded the standards of Carpenter-Coustan criteria. (FBS≥95mg/dl, 1hour≥180mg/dl, 2hour≥155mg/dl, 3hour≥140mg/dl). GCT≥200mg/dl was accepted as diabetes mellitus, and further GTT test was not required. All above laboratory tests were performed in one laboratory.

Statistical Analysis

The data were analyzed using Chi-square, T- test, Fisher's exact test and Man Whitney in SPSS, version 1.b statistical software. The level of significance was considered 5% in all cases.

RESULTS

There were 49 cases of pregnant women treated with cyclogest, and 49 untreated pregnant women fulfilling the inclusion criteria. There were no significant differences in gestational age at delivery between the two groups. Women were matched by maternal age and BMI before pregnancy. Mean birth weights did not show statistically significant differences between the two groups (Table 1).

Comparison of progesterone levels (at 28th week of gestation) between the two groups showed statistically significant differences between them (P<0.001). The mean progesterone levels were 48.9ng/ml and 43.6ng/ml in the exposed and control groups; respectively.

Mean FBS levels were 82 mg/dl in the cyclogest exposed group and 79 mg/dl in the control group (P= 0.222). In the cyclogest exposed group, 4 women had FBS≥100, but there was no abnormal FBS in the control group (P=0.117).

Mean GCTs levels were 129mg/dl and 116 mg/dl in the cyclogest exposed and control groups; respectively (P=0.007). 19 women in the cyclogest exposed group had abnormal GCT, and in the control group, 11 women had abnormal GCT but the difference was not statically significant (P=0.08)

Six women (12.2%) had abnormal GTT the same as gestational diabetes in the cyclogest exposed group and 3 cases (6.1%) in the control group (*P*=0.478). Three women (6.1%) in the cyclogest exposed group, and one (2%) in the control group required insulin therapy for controlling blood sugar (P= 0.617).

Table 1: Demographic characteristics in the cyclogest exposed and unexposed groups.

variables	Cyclogest exposed (n=49)	control (n=49)	P value
Maternal age(y)	28.4(5.7)	28.7(5.08)	0.75
Maternal weight(kg)	61.7(9.13)	64.2(10.3)	0.21
Maternal height(cm)	160.4(5.9)	161.6(6.02)	0.3
Maternal BMI(kg/)	23.9(3.1)	24.5(3.6)	0.38
gestational age at delivery (w)	37-40	37-40	0.232
birth weights(kg)	3.01	3.12	0.08

DISCUSSION

Gestational diabetes mellitus (GDM) has been defined as abnormal glucose tolerance which is first time diagnosed during pregnancy [12]. In normal pregnancy, increase in glucose metabolism is accompanied by increased secretion of insulin from the pancreas but in women with gestational diabetes, glucose metabolism cannot compensate the insulin secretion [13]. GDM is the most prevalent disease during pregnancy. The prevalence has ranged from 1 to 14% in different parts of the world [12]. The prevalence of GDM has been reported from 1.3% to 10% in different parts of Iran [12].

Women with GDM have been the high risk group for some adverse pregnancy outcomes such as macrosomia, shoulder dystochia, cesarean delivery, infections, hypertensive disorders, and other prenatal mortality [10, 11].

Use of progesterone at the beginning of the mid gestation of pregnancy in patients with previous preterm labor reduced the recurrence of preterm delivery by 50% [7]. The importance of using progesterone in the first trimester of pregnancy to support corpus luteum and to prevent abortion has been well established [5, 6]. Also using progesterone in women with short cervix and high risk for preterm birth to prevent spontaneous preterm delivery has been a frequent clinical practice [5, 6, 14].

A randomized control trial study done by Fonseca *et al.* [7] reported that the daily administration of vaginal progesterone in pregnancy significantly reduced the rate of spontaneous preterm birth. Progesterone has some diabetogenic properties due to signaling in insulin release and pancreatic function with reduction of glucose transporter4 (GLUT4) in the adipose tissue and skeletal muscle [6]. As pregnancy progresses, the increased levels of progesterone would lead to insulin resistance [15]. The onset of GDM typically occurs in the second trimester of pregnancy, when progesterone levels are high [16]. Due to the frequent prescription of vaginal progesterone in pregnancy by obstetricians, the evaluation of the effect of progesterone on glucose metabolism has great importance.

In the retrospective cohort study conducted by Waters *et al.* [10] about the effect of weekly intramuscular injections of 17-α hydroxy progesterone caproate (17OHP-C) on glucose intolerance, the diagnosis of GDM was significantly higher in the 17-α hydroxy progesterone caproate exposed patients but they said that their study as a retrospective chart review was open to ascertainment bias. Also, a prospective study by Rebarber *et al.* [17] reported a higher incidence of GDM in intramuscular 17OHP-C treated women. In addition, Köşüş *et al.* [6] reported that FBS and GCT in the oral micronized progesterone exposed group were significantly higher. Duan *et al.* [18] found that the use of high dose intramuscular progesterone resulted in slightly higher incidence of GDM but it was not statistically significant. In this cohort study, the effect of vaginal progesterone on the GDM was evaluated, and a higher frequency of abnormal FBS, GCT and GTT in the cyclogest treated group was found, but there was no statistically significant difference in comparison to the control group. Similar to this study, Klein *et al.* [19] found no significant difference between the group treated with vaginal micronized progesterone and placebo group about the risk of preterm delivery in high-risk twin pregnancies.

The differences between the results of the mentioned studies might be due to the different routes of administration. The majority of studies using progesterone supplement intramuscular or orally showed significantly higher incidence of glucose intolerance. But in the Klein's study [19] and also the current study with vaginal progesterone, the incidence of glucose intolerance was not significant. It might be due to the uterine first pass effect and lower progesterone level in circulation with vaginal use in comparison to the oral and intramuscular use.

It was found that with the daily use of 400 mg cyclogest vaginaly, progesterone level was higher than the unexposed group (*P*<0.001), but the mentioned studies did not check progesterone level with oral and intramuscular administration, so the comparison between them was impossible. The approval of the FDA of the commercial preparation of 17OHP-C intramuscular injection was with a warning that the administration of this agent might increase the frequency of gestational

diabetes [4]. On the other hand, Bagis *et al.* [20] in a prospective study on 28 non-pregnant patients with polycystic ovary syndrome showed that the short term oral micronized progesterone and micronized progesterone acetate ameliorate insulin sensitivity in patients with polycystic ovarian syndrome. The small number of this study's group was the important limitation of this study. This result was contradictory because polycystic ovarian syndrome has been the known cause of insulin resistance, and management of PCO with progesterone would lead to the improvement in insulin sensitivity. In this study, all women with a history of PCO were excluded.

Maternal hyperglycemia leads to excess fetal insulin, which is a growth hormone for the fetus. Thus, offspring of mothers with gestational diabetes mellitus had higher birth weights [21]. In the study by Köşüş *et al.* [6], the median birth weight was significantly higher in the micronized progesterone exposed group for a similar gestational age. In contrast, Duan *et al*. [18] concluded that the mean birth weight at delivery time had no differences related to progesterone treatment in boys and girls. In this study, the difference between the birth weights of the cyclogest exposed and unexposed groups were not statistically significant. However, the comparison of birth weight between the two groups could not show the exact effect of cyclogest on birth weight, because most of cyclogest exposed group were women with high risk pregnancy and poor obstetric history, although women were matched by BMI and age.

The limitations of the present study were the fact that the patient compliance could not be monitored; and also the sample size was small.

CONCLUSION

This study indicated that the daily use of vaginal progesterone slightly increased serum progesterone level. The daily use of vaginal progesterone caused higher incidence of glucose intolerance but it was not statistically significant. A higher abnormal level of GCTs in the progesterone exposed women revealed the fact that unnecessary use of vaginal progesterone during pregnancy should be avoided.

REFERENCES

[1] Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk ofpreterm birth. Cochrane Database Syst Rev. 2013; 31(7). doi: 10.1002/14651858.

[2] Cunningham F, Leveno K , Bloom S, Spong CY,Dashe J. Williams Obstetrics, 24thed, McGraw Hill USA; 2010, 1383 p.

[3] Khandelwal M. Vaginal progesterone in risk reduction of preterm birth in women with short cervix in the midtrimester of pregnancy.Int J Women's Health. 2012;4:481-490. doi: 10.2147/IJWH.S28944.

[4] Romero R, Yeo L, Miranda J, Hassan SS, Conde-Agudelo A, Chaiworapongsa T. A blueprint for the prevention of preterm birth: vaginal progesterone in women with a short cervix. J Perinat Med. 2013; 41 (1):27-44.

[5] Romero R. Prevention of spontaneous preterm birth: the role of sonographic cervical length in identifying patients who may benefit from progesterone treatment. Ultrasound ObstetGynecol. 2007; 30 (5): 675-686.

[6] Köşüş A, Köşüş N, Haktankaçmaz SA, Ak D, Turhan NÖ. Effect of dose and duration of micronized progesterone treatment during the first trimester on incidence of glucose intolerance and on birth weight. FetalDiagnTher. 2012; 31 (1):49-54.

[7] Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. 2007;357 (5) :462-469.

[8] NorwitzE, CaugheyA. Progesterone Supplementation and the Prevention of Preterm Birth. Rev ObstetGynecol 2011; 4 (2): 60–72.

[9] Thomas W. Hilgers. The Medical and Surgical Practice of NaProTECHNOLOGY, Pope Paul VI Institute Press, Omaha; 2004. 770 p.

[10] Waters TP, Schultz BA, Mercer BM, Catalano PM. Effect of 17alpha-hydroxyprogesterone caproate on glucose intolerance in pregnancy.ObstetGynecol. 2009;114 (1):45-49.

[11] Mohammadbeigi A, Tabatabaee S H, Mohammadsalehi N, Yazdani M. Gestational diabetes and its association with unpleasant outcome. Pak J med Sci. 2008; 24 (4):566-570.

[12] Khoshnniat NM, Abbaszadeh AS, Larijani B. A review on the prevalence of gestational diabetes mellitus (GDM) in different regions of Iran. Iranian journal of Diabetes and Lipid Disorders. 2009. 8. 47-56.

[13] Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of diabetes; a systematic review. Diabetes Care. 2002; 25 (10): 1862-1868.

[14] Sugaya A, Sugiyama T, Yanase S, Shen XX, Minoura H, Toyoda N. Expression of glucose

transporter 4 mRNA in adipose tissue and skeletal muscle of ovariectomized rats treated with sex steroid hormones. Life sci. 2000; 66 (7): 640-648.

[15] Picard F, Wanatabe M, Schoonjans K, Lydon J, O'Malley BW, Auwerx J. Progesterone receptor knockout mice have an improved glucose homeostasis secondary to beta -cell proliferation. ProcNatlAcadSci U S A, 2002;99 (24):15644-8.

[16] Daya S. Efficacy of progesterone support for pregnancy in women with recurrent miscarriage. A meta-analysis of controlled trials.Br J ObstetGynaecol, 1989;96 (3) :275-280.

[17] Rebarber A, Istwan NB, Russo-Stieglitz K, Cleary-Goldman J, Rhea DJ, Stanziano GJ, Saltzman DH. Increased incidence of gestational diabetes in women receiving prophylactic 17alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery.Diabetes Care. 2007; 30(9) :2277-2280.

[18] Duan L, Yan D, Zeng W, Yang X, Wei Q. Effect of progesterone treatment due to threatened abortion in early pregnancy for obstetric and perinatal outcomes. Early Hum Dev. 2010; 86 (1) :41-43.

[19] Klein K, Rode L, Nicolaides KH, Krampl-Bettelheim E, Tabor A. Vaginal micronized progesterone and risk of preterm delivery in high-risk twin pregnancies: secondary analysis of a placebo-controlled randomized trial and meta-analysis. Ultrasound ObstetGynecol. 2011; 38 (3):281-287.

[20] Bagis T, Gokcel A, Zeyneloglu HB, Tarim E, Kilicdag EB, Haydardedeoglu B. The effects of short-term medroxyprogesterone acetate and micronized progesterone on glucose metabolism and lipid profiles in patients with polycystic ovary syndrome: a prospective randomized study. J ClinEndocrinolMetab 2002; 87 (10) :4536-4540.

[21] Silverman BL, Rizzo T, Cho NH, et al. Long-term prospective evaluation of offspring of diabetic mothers. Diabetes. 1991; 40 (2):121–125.

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