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Risk Factors for Gestatıonal Diabetes in Women with Polycystic Ovarian Syndrome

Senem Arda Duz, Ilgın Turkcuoglu

Inonu University School of Medicine, Department of Obstetrics and Gynecology, Malatya, Turkey

Abstract

We aimed to compare the pre-gestational metabolic states of the women who were previously diagnosed with policystic ovarian syndrome and had gestational diabetes mellitus in the subsequent pregnancy and who did not have gestational diabetes mellitus in subsequent pregnancy and to determine the independent variables that predict the gestational diabetes mellitus risk for policystic ovarian syndrome patients in the subsequent pregnancy. Between the dates 2007 and 2012, the patients who were diagnosed with policystic ovarian syndrome in our outpatient gynecology clinic were searched retrospectively. Then these patients were called for pregnancy states. All of these patients have pregnancy spontaneously. The patients' pre-gestational mean age, body mass index, metabolic and hormonal profiles and pregnancy outcomes were compared between policystic ovarian syndrome cases who developed gestational diabetes mellitus or not. We found some differences in pregestational metabolic states between the policystic ovarian syndrome patients who developed gestational diabetes mellitus in pregnancy or not. The mean age, body mass index, very low density lipoprotein, triglyceride, fasting insulin, fasting c-peptide levels, 1st and 2nd hour glucose levels in 75 gr oral glucose tolerance test, homeostatsis model assessment –insulin resistance measures and neonates' birth weights were higher in gestational diabetes mellitus group than non-gestational diabetes mellitus group. But high density lipoprotein was lower in gestational diabetes mellitus group than non- gestational diabetes mellitus group. There were no differences between the mean levels C-reactive protein, hormonal profile, mean fasting glucose, low density lipoprotein cholesterol, total cholesterol levels and mode of delivery. Glucose intolerance was significantly higher in the gestational diabetes mellitus group (%74,07 vs %6,66). With the multipl logistic regression analysis we found the body mass index as the strongest independent predictor of gestational diabetes mellitus in policystic ovarian syndrome patients (OR: 2,831, %95 CI: 1,234-6,495). The second independent predictor was the high 2nd hour glucose level in oral glucose tolerance test (OR: 1,119, %95 CI: 1,026-1,221). The pre-gestational metabolic variables including the age, body mass index, lipid profile, and glucose metabolism are significantly different in the gestational diabetes mellitus group than the non-gestational diabetes mellitus group. The obesity and glucose intolerance are the independent predictors of gestational diabetes mellitus in policystic ovarian syndrome cases.

Keywords: Polycystic ovarian syndrome, gestational diabetes mellitus, glucose intolerance, insulin resistance, obesity

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Corresponding Author*:* Senem Arda Duz, Inonu University School of Medicine, Department of Obstetrics and Gynecology, Malatya, Turkey

E-mail: senem_arda@yahoo.com **Phone:** +90533 277 64 01

Introduction

Gestational diabetes mellitus (GDM) is a diabetes or impaired glucose tolerance that occurs first time during pregnancy [1]. The frequence of the disease varies between 0.2-14% by ethnicity and diagnose criteria [2-4]. This disease has two clinical patterns. Greater than 90% of these cases involve diabetes limited to the pregnancy and greater than one half of women with GDM will have overt diabetes during the next 20 years [4,5].

Also increasing evidence has suggested that long term complications, such as obesity and diabetes, occur in the children of mothers with GDM [6-9]. Underlying pathogenic mechanism is the imbalance between hiperinsulinemia and pancreatic β cells capasity that occurs secondary to decreased insulin sensitivity in pregnancy [10-13].

Macrosomia and its obstetrical consequences, and neonatal hipoglisemia are the major complications of GDM. The risk factors for GDM are obesity, a familial history of type 2 diabetes mellitus, gestational diabetes during a previous pregnancy and glucosuria [14]. Recent studies have shown that a history of policystic ovarian syndrome (PCOS) may be a risk factor for GDM [15].

Policystic ovarian syndrome (PCOS) is the most common endocrine disorder in women during the reproductive ages and is often accompanied by insulin resistance and hyperinsulinemia [16]. Although the disordered carbohydrate metabolism and greater than 20% of PCOS occurs in premenopause women, the possible relationship between GDM has not been studied sufficiently yet. The familial transmission of PCOS, severe insuline resistance and GDM had been reported [17]. A recent study reported a relationship between GDM and PCOS but another recent study reported that there is no relationship between GDM and PCOS [18,19].

Early diagnose is very important to prevent the negative consequences of GDM. If there is a relationship between GDM and PCOS we will screen the PCOS patients during pregnancy earlier than the non-PCOS women. It will be so useful to find some markers that predict the GDM risk in PCOS patients. The purpose of the present study was to determine the independent variables that increase GDM risk by comparing the pre gestational anthropometric, biochemical, matabolic, hormonal measurements and pregnancy outcomes between the patients who previously diagnosed PCOS and in subsequent pregnancy diagnosed and did not diagnose GDM.

Materials and Methods

Between the dates 2007 and 2012, the patients who were diagnosed with PCOS in our outpatient gynecology clinics were searched retrospectively. Then these patients were called for pregnancy states. All of these patients have pregnancy spontaneously not later than one year after outpatient visits. This study was approved by the ethics committee of Inonu University Faculty of Medicine (06.13.2013 dated and 2013/60 protocol coded).

The inclusion criterias were: (a) the women between 18-40 years old, (b) absence of drug use in last 3 months that will affect hormonal, lipid or insuline metabolism, (c) absence of systemic and/or metabolic disease. The exclusion criteria were: (a) thyroid disfonction, hyperprolactinemia, congenital adrenal hyperplasia or adrenal tumors, (b) chronic systemic disorder like type 1 or 2 DM or hypertension, (c) body mass index >35 kg/m^2, (d) pregnancies that achieved by asisted reproductive technology.

The diagnosis of PCOS in patients was considered according to presence of at least 2 criterias of Rotterdam: (a) oligo- and/or anovulation, (b) the presence of the clinical and/or biochemical markers of hyperandrogenism, (c) policystic ovaries in ultrasonography (USG) [20].

Oligomenorrhea was defined as menstrual cycles longer than 35 days and amenorrhea was defined as no menstrual bleeding for 3 consecutive cycles. Hirsutism is a clinical symptom of hyperandrogenism and in this study evaluated with Ferriman- Gallwey method and > 8 score is defined as hirsutism. By USG 2-9 mm, at least 12 periferic placed follicule is determined as policystic ovaries.

Age, heigth, weight of the patients were acquired from hospital files. Body mass index (BMI) was calculated as:

BMI=weight in kilograms/square of height in meters

On the 3rd day of menstrual cycle, at 8:00-9:00 am, after a 3 day of normal carbohydrate diet and an at least 10 h overnight fasting plasma lipid profile, insulin and glucose levels, c-peptide and hormonal profile were evaluated. On the same day, after the blood samples were taken, 75 g 120-min OGTT was performed and fasting and 2nd hour blood glucose levels were determined for each patient.

IR was determined with homeostatsis model assessment (HOMA-IR) as:

HOMA-IR=fasting glucose (mg/dL) x fasting insulin 8pmol/l)/405

Impaired glucose tolerance (IGT) was diagnosed if the blood glucose level on the 2nd hour of OGTT was more than or equal to 140 mg/dL and less than 199 mg/dL [21]. When pregnancy was achieved, subjects received obstetric care according to national guidelines. According to these guidelines, no metformin was used in these patients, neither was it given before conception. GDM was diagnosed or ruled out in the second trimester, at a gestational age of 24-28 weeks, when all women underwent an oral glucose tolerance test (75 g glucose load, 2 hours follow up). When one or more plasma glucose levels exceeded the given treshold after a 75 g glucose load, GDM was diagnosed: fasting glucose ≥92mg/dl, 1st hour glucose ≥180mg/dl and 2nd hour glucose ≥153mg/dl (HAPO).

Gestational week at birth was calculated with last menstrual period date for the patients who have regular menstrual cycle. For the patients who did not know the last menstrual period date or the patients who have irregular menstrual cycle, CRL was used for calculating. The neonates' birth weight more than or equal to 4500 g was determined as macrosomia. The birth weight according to birth gestational age is more than 90% is determined as Large for Gestational Age (LGA).

Plasma fasting glucose, postprandial 1st and 2nd hour glucose, high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), total cholesterol, triglyceride and C reactive protein (CRP) levels were determined by spectrophotometric method (Aeroset, Abbott Laboratories, Abbott Park, IL).

Plasma c-peptide, follicule stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2), prolactin, thyroid stimulating hormone (TSH), total testosteron, sex hormone binding globuline (SHBG) and fasting insulin levels were determined by chemiluminescence method (Immulite 2000, Siemens Medical Solutions Diagnostics, Los Angeles, CA). Free testosterone was determined with free androgen index (FAI) as:

FAI = 100 x total testosterone (ng/dL) / SHBG (nmol/mL)

The data were analyzed using the Statistical Package for Social Sciences soft-ware 17.0 (SPSS, Inc., Chicago, IL). The normality of distribution of variables was tested by using Kolmogorov-Smirnov test. Becouse of the variables distribution was not normal, Chi-square, Mann-Whitney-U and Wilcoxon tests were used for comparing the groups. All datas were refered to median (minimum-maximum) and mean ± standard deviation (SD). To analyse the categorical datas Chi-square test was used. The relation between GDM and the variables age, BMI, LH/FSH ratio, FAI, CRP, HDL, LDL, total cholesterol, triglyceride, HOMA-IR, c-peptide, OGTT 1st and 2nd hour levels was analyzed with multinomial logistic regression analysis. The concordance of the model was detected with Hosmer and Lemeshow and Omnibus tests. A p value < 0.05 was considered as statistically significant. The specifity of the model was 93.3%, the sensitivity was 92.6% and accuracy was 93%.

Results

A total of 57 patients were enrolled to the study. 27 of these patients had GDM in subsequent pregnancy and 30 patients had not. There were statistical differance between the two groups about age and BMI. The age and BMI is significantly more in GDM group compared to non-GDM group, but hormonal profiles and FAI were similar in two groups (Table 1).

CRP, LDL cholesterol, total cholesterol and fasting glucose levels were similar in two groups. HDL cholesterol was significantly lower in GDM group (p = 0.023), but VLDL cholesterol and triglyceride were significantly higher in GDM group (p = 0.017 and p = 0.001 respectively). Fasting c-peptide and insuline levels were significantly more in GDM group compared to non-GDM group (p = 0.000 and p = 0.005 respectively). OGTT 1st and 2nd hour glucose levels and HOMA-IR were higher in GDM group too (8p = 0.000, p = 0.000 and p = 0,009 respectively) (Table 1).

Table 1. The differences between GDM and non-GDM groups

	Non-GDM(n= 30) (mean ± SD)	GDM (n = 27) (mean ± SD)	*P*
Age (years)	28,0 ± 5,21	30,9 ± 4,19	0,029*
BMI (kg/m^2)	23,5 ± 3,5	28,29 ± 4,37	0,000*
FSH (mIU/ml)	5,30 ± 1,81	6,19 ± 2,56	0,240
LH (mIU/ml)	7,86 ± 5,59	7,99 ± 4,58	0,533
LH/FSH	1,66 ± 1,38	1,40 ± 0,74	0,943
E_2 (pg/ml)	80,3 ± 44,83	65,29 ± 40,32	0,106
PRL (ng/ml)	9,69 ± 4,89	11,4 ± 10,83	0,502
TSH (µIU/ml)	1,69 ± 1,22	1,66 ± 0,86	0,533
Total Testosterone (ng/dl)	44,87 ± 22,81	57,67 ± 39,64	0,642
FAI	120,42 ± 149,26	151,51 ± 200,53	0,543
SHBG (nmol/ml)	39,57 ± 25,12	33,22 ± 15,18	0,397
CRP (mg/dl)	4,63 ± 2,55	4,15 ± 2,16	0,330
HDL (mg/dl)	46,6 ± 11,9	40,03 ± 6,08	0,023*
LDL (mg/dl)	103,66 ± 18,21	106,9 ± 30,13	0,930
VLDL (mg/dl)	17,19 ± 7,69	26,29 ± 16,85	0,017*
Total Cholesterol (mg/dl)	158,76 ± 32,59	164,7 ± 42,1	0,767
Triglyceride (mg/dl)	87,06 ± 42,87	156,66 ± 83,23	0,001*
c-peptide (ng/ml)	2,26 ± 1.05	4,22 ± 1,81	0,000*
Fasting insulin (µIU/ml)	6,92 ± 4,10	13,44 ± 6,96	0,005*
Fasting glucose (mg/dl)	86,86 ± 8,38	92,33 ± 25,43	0,586
HOMA-IR	1,70 ± 1,11	3,40 ± 2,84	0,009*
OGTT 1st hour (mg/dl)	134,13 ± 24,33	179,25 ± 33,54	0,000*
OGTT 2nd hour (mg/dl)	113,23 ± 22,7	151,5 ± 27,79	0,000*
Gestational age at birth (week)	38,16 ± 1,44	37,07 ± 1,77	0,002*
Birth weight (g)	3107 ± 416	3409 ± 600	0,013*
Oligo and/or amneorrhea			0,137
Present (n,%)	22 (%73,3)	24 (%88,9)	
Absent (n,%)	8 (%26,7)	3 (%11,1)	
PCO in USG			0,061
Present (n,%)	30 (%100)	24 (%88,9)	
Absent (n,%)	0 (%0)	3 (%11,1)	
Hirsutism			0,764
Present (n,%)	20 (%66,7)	19 (%70,4)	
Absent (n,%)	10 (%33,3)	8 (%29,6)	
Mode of delivery			0,889
NVD (n,%)	15 (%50)	14 (%51,9)	
C/S (n,%)	15 (%50)	13 (%48,1)	
Sex of neonate			0,288
Female (n,%)	16 (%53,3)	14 (%51,9)	
Male (n,%)	14 (%46,7)	13 (%48,1)	
Neonatal intensive care unit need			0,033*
Present (n,%)	3 (%10,0)	9 (%33,3)	
Absent (n,%)	27 (%90)	18 (%66,7)	
Live birth			0,288
Present (n,%)	30 (%100)	26 (%98,2)	
Absent (n,%)	0 (%0)	1 (%1,8)	

* Statistically significant

Glucose intolerance in GDM group was 74.07% and in non-GDM group 6.66% (p = 0.000).

Presence of oligo and/or amenorrhea, policystic ovaries in USG and hirsutism were similar in two groups (Table 1).

Normal vaginal delivery rate was 50% and cesarean delivery rate was 50% in non-GDM group. In GDM group these rates were 51.9% and 48.1% respectively. So there is no statistical difference between the groups about the mode of delivery. Also there were no difference between the groups about neonates' sex. Neonatal intensive care unit need was significantly more in GDM group compared to non- GDM group (p = 0.033). All pregnancies were resulted with live births in non-GDM group but there was a stillbirth in GDM group at 36th gastational week in present study. But there was no statistical difference between two groups about live births (Table 1). There were statistically significant difference between the two groups about gestational age at birth (p =0.002) and birth weight of neonates (p =0.013) (Table 1).

Although LGA rate in GDM group was 44.44% and non-GDM group 6.66% (p =0.01), there was no macrosomic neonate in this present study.

The risk of elevated BMI and OGTT 2nd hour glucose level were associated with the presence of GDM with the crude OR of 2.831 (95% CI:1.234-6.495) and 1.119 (95% CI:1.026-1.221) respectively in multinomial logistic regression analysis. There were inverse relationship between increasing HDL cholesterol (OR = 0.788, 95% CI:0.629-0.988), LH/FSH ratio (OR = 0.142, 95% CI:0.025-0.798) and CRP (OR = 0.365, 95% CI:0.167-0.799) (Table 2).

Table 2. Multinomial logistic regression analysis of the variables that may have a role in the GDM risk in PCOS

	OR (%95 CI)	*P*
BMI	2,831 (1,234-6,495)	0,014
LH/FSH	0,142 (0,025-0,798)	0,027
CRP	0,365 (0,167-0,799)	0,012
HDL	0,788 (0,629-0,988)	0,039
OGTT 2nd hour	1,119 (1,026-1,221)	0,011

Discussion

The PCOS patients had been studied in terms of insulin resistance and GDM, a lot of times until now. Although we know that PCOS is a risk factor for GDM, that is not clear that which PCOS patients will be diagnosed GDM in subsequent pregnancy.

In our study, the pregestational metabolic states of the women who had been diagnosed PCOS according to revised Rotterdam criterias and in subsequent pregnancy had been diagnosed or not diagnosed GDM, were compared.

We reported that age and BMI of GDM group is more than the non-GDM group as Falluca et al. [22]. Holte et al. studied with PCOS and GDM patients. They reported that BMI was higher in GDM group. In addition fasting glucose, fasting insulin and fasting c-peptide were significantly higher in GDM group too. Neonates' birth weight, FSH, LH, FSH/LH ratio, androstenedione, testosterone, dihydroepiandosterone sulphate (DHEAS), SHBG, growth hormone (GH) and FAI were similar in two groups [15]. In contrast we found that neonates' birth weight higher in GDM group, but hormonal profile was similar with Holte et al. Fasting insulin and similar in two groups unlike Holte. While we were used revised Rotterdam criterias for diagnose of PCOS, Holte was used only policystic ovaries in USG as a diagnose c- were peptide significantly different in our study as Holte et al. but fasting glucose was criteria. So the two groups were significantly different about hirsutism and menstrual irregularity. Unlike our study each group were not similar about Rotterdam fenotype.

Mikola et al. have reported in a community-based study that the incidence of GDM was higher in patients with PCOS. Advanced maternal age and multiparity were found to increase the risk of GDM [23,24].

Kashanian et al. studied about the relationship between PCOS history and devlopment of GDM. They reported that there was no difference in terms of the patients age, parity, infertility states and hyperandrogenism. Pregnancy induced hypertension rates and APGAR scores were similar too. However BMI, oligomenorrhea, cesarean delivery, birth weight and gestational age at birth were different significantly [25]. In our study GDM was not a risk factor for cesarean delivery. On the other hand Kashanian et al. were enrolled total 21 patients, in GDM group n=15 and in non- GDM group n=6. Also Rotterdam fenotypes were different in two groups.

At a study that research about the effect of insulin resistance on pregnency outcomes, PCOS was found as a risk factor for GDM [26]. In another study that there were no difference between the patients about pregestational BMI and weight gain in pregnancy, PCOS was reported as a risk factor for GDM too. A difference in terms of birth weights was not determined in the same study [27]. Another study reported that metformin therapy for PCOS patients decrease GDM risk 10 times [28].

De Wilde et al. studied with 72 pregnant women, that 22 developed GDM. They found both insulin levels and HOMA-IR were significantly higher at each sampling point in women with PCOS who developed GDM. Also they reported that SHBG levels were significantly higher before conception and in the second trimester compared with women who developed GDM. Testosterone concentrations were significantly lower before conception in women who developed GDM. After adjusting for BMI, waist circumference and waist/hip ratio, the differences in insulin, HOMA-IR, SHBG and testosterone levels remained largely the same [29].

Ashrafi et al. compared spontaneous pregnant women without PCOS, PCOS and non-PCOS women who had pregnancy with ART. They reported menstrual irregularity, serum triglycerides level ≥150mg/dL and pregestational metformin use as risk factors of GDM in PCOS women [30].

In contrast all studies aforementioned, a study reported that there was no relationship between PCOS and GDM, but GDM patients’ BMI were higher than others. There were no difference in terms of pregnancy outcomes. Only they reported a relationship between mothers’ BMI and birthweight of neonates [31]. Further an another study was reported the risk of GDM did not differ between PCOS and controls. They suggested that the main predictor of GDM development was BMI>25 kg/m^2. However they added that impaired glucose tolerance rate was higher in PCOS patients. The outcomes about gestational age at birth, preterm delivery prevalance, mode of delivery, mean birth weight, 5th minute APGAR score and neonatal intensive care unit need were similar [32].

There are numerous studies that suggest PCOS is a risk factor for GDM. But which PCOS patients are at high risk for GDM has not been studied sufficiently yet. If the markers that increase the GDM risk in PCOS patients can be determined, GDM associated negative fetal and maternal outcomes will be decreased. Our study is important in terms of comparement of metabolic states of PCOS patients who diagnosed or not diagnose GDM in subsequent pregnancy.

References

1. American Diabetes Association. Clinical Practice Recommendations 2001. Diabetes Care. 2001;24(Suppl. 1):S1-133.
2. Hadden DR. Screening for abnormalities of carbohydrate metabolism in pregnancy. Diabetes Care. 1980;3(3):440-6.
3. Hadden DR. Geographic, ethnic and racial variation in the incidence of gestational diabetes mellitus. Diabetes. 1985,34(Suppl 2):8-12.
4. Jovanovic L, Pettitt D. Gestational diabetes mellitus. JAMA, 2001;286(20):2516-8.
5. Damm P, Kuhl C, Bertelsen A, Molsted-Pedersen L. Predictive factors for the development of diabetes in women with previous gestational diabetes mellitus. Am J Obstet Gynecol. 1992;167(3):607-16.
6. Cunningham GF, leveno KJ, Bloom SL, Hauth JC, Gilstrap LC, Wenstrom KD. Williams Obstetrics, 22nd edition. MC Graw-Hill, New York, 2005;1170-5.
7. Dabelea D. The predisposition to obesity and diabetes in offspring of diabetic mothers. Diabetes Care. 2007;30(Suppl. 2):S169-74.
8. Damm P. Future risk of diabetes in mother and child after gestational diabetes mellitus. Int J Gynaecol Obstet. 2009;104(Suppl. 1):S25-6.
9. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care. 2002;25(10):1862-8.
10. Ryan EA, O'Sullivan MJ, Skyler JS. Insulin action during pregnancy: Studies with the euglycemic clamp technique. Diabetes. 1985;34(4):380-9.
11. Buchanan TA, Metzger BE, Freinkel N, Bergman RN. Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. Am J Obstet Gynecol. 1990;162(4):1008-14.
12. Catalano PM, Tyzbir ED, Roman NM, Amini SB, Sims EAH. Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. Am J Obstet Gynecol. 1991;165(6 Pt 1):1667-72.

13. Ryan EA, Imes S, Liu D, McManus R, Finegood DT, Polonsky KS, Sturis J. Defects in insulin secretion and action in women with a history of gestational diabetes. Diabetes. 1995;44(5):506-12.
14. Metzger BE. Summary and recommendations of the third international workshop-conference on gestational diabetes. Diabetes. 1991;40(Suppl 2):197-201.
15. Holte J, Gennarelli G, Wide L, Lithell H, Berne C. High prevalence of polycystic ovaries and associated clinical, endocrine, and metabolic features in women with previous gestational diabetes mellitus. J Clin Endocrinol Metab. 1998;83(4):1143-50.
16. Speroff L, Fritz MA. Clinical Gynecologic Endocrinology and Infertility, 7th edition. Lippincott Williams & Wilkins, Philadelphia, 2005;465-89.
17. Plehwe WE, Maitland JE, Williams PF, Shearman RP, Turtle JR. Familial hyperinsulinemia complicated by extreme insulin resistance during pregnancy: a probable postreceptor defect. J Clin Endocrinol Metab. 1985;61(1):68-77.
18. Lanzone A, Caruso A, Di Simone N, De Carolis S, Fulghesu AM, Mancuso S. Polycystic ovary disease. A risk factor for gestational diabetes? J Reprod Med. 1995,40(4):312-6.
19. Wortsman J, de Angeles S, Futterweit W, Singh KB, Kaufmann RC. Gestational diabetes and neonatal macrosomia in the polycystic ovary syndrome. J Reprod Med. 1991;36(9):659-61.
20. Revised 2003 consensus on diagnostic criteria and long-term health risksrelated to polycystic ovary syndrome Rotterdam ESHRE/ASRM-SponsoredPCOS Consensus Workshop Group Fertil Steril. 2004;81(1):19-25.
21. American Diabetes Association. Standards of medical care in diabetes-2007. Diabetes Care. 2007;30 Suppl 1:S4-S41.
22. Fallucca F, Dalfrà MG, Sciullo E, Masin M, Buongiorno AM, Napoli A, Fedele D, Lapolla A. Polymorphisms of insulin receptor substrate 1 and beta3-adrenergic receptor genes in gestational diabetes and normal pregnancy. Metabolism. 2006;55(11):1451-6.
23. Mikola M, Hiilesmaa U, Halttunen M, Suhonen L, Tiitinen A. Obstetric Outcome in women with polycystic ovarian syndrome. Hum Reprod. 2001;16(2):226-9.
24. Lo J C, Feigenbaum SL, Escobar GJ, Yang J, Crites YM, Ferrara A. Increased Prevalence Of Gestational Diabetes Mellitus Among Women With Diagnosed Polycystic Ovary Syndrome. Diabetes Care. 2006;29(8):1915-7.
25. Kashanian M, Fazy Z, Pirak A. Evaluation of the relationship between gestational diabetes and a history of polycystic ovarian syndrome. Diabetes Res Clin Pract. 2008;80(2):289-92.
26. Bjercke S, Dale PO, Tanbo T, Storeng R, Ertzeid G, Abyholm T. Impact of insulin resistance on pregnancy complications and outcome in women with polycystic ovary syndrome. Gynecol Obstet Invest. 2002;54(2):94-8.
27. Anttila L, Karjala K, Penttila RA, Ruutiainen K, Ekblad U, Polycystic ovaries in women with gestational diabetes. Obstet Gynecol. 1998;92(1):13-6.
28. Glueck CJ, Wang P, Kobayashi S, Phillips H, Sieve-Smith L. Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome. Fertil Steril. 2002;77(3):520-5.
29. de Wilde MA, Goverde AJ, Veltman-Verhulst SM, Eijkemans MJ, Franx A, Fauser BC, Koster MP. Insulin action in women with polycystic ovary syndrome and its relation to gestational diabetes. Hum Reprod. 2015;30(6):1447-53.

30. Ashrafi M, Sheikhan F, Arabipoor A, Hosseini R, Nourbakhsh F, Zolfaghari Z. Gestational diabetes mellitus risk factors in women with polycystic ovary syndrome (PCOS). Eur J Obstet Gynecol Reprod Biol. 2014,181:195-9.
31. Vollenhoven B, Claric S, Kovacs G, Burger H, Healy D. Prevalence of gestational diabetes mellitus in polycystic ovarian syndrome (PCOS) patients pregnant after ovulation induction with gonadotrophins, Aust N Z J Obstet Gynaecol. 2000;40(1):54-8.
32. Weerakiet S, Srisombut C, Rojanasakul A, Panburana P, Thakkinstian A, Herabutya Y. Prevalence of gestational diabetes mellitus and pregnancy outcomes in Asian women with polycystic ovary syndrome. Gynecol Endocrinol. 2004 Sep;19(3):134-40.