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Distribution of normal and pathological OGTTs among pregnant population and non-pregnant women with PCOS – the cross-sectional study

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Abstract

Both pregnancy, as physiological, and polycystic ovary syndrome (PCOS), as a pathological condition, carry the risk for developing glucose metabolism abnormalities. In this retrospective cross-sectional study, we hypothesized that pregnancy as a physiological condition carries a higher likelihood for abnormal oral glucose tolerance test (OGTT) results than PCOS as a pathological condition.

We have compared the prevalence and likelihood ratios for abnormal OGTT results between non-pregnant women with PCOS (Group A) and pregnant women at 24 to 28 weeks of gestation (Group B). Participants of both study groups underwent glucose tolerance testing with 75 g glucose OGTT. During the study period, 7411 women were tested, 3932 women encompassed Group A, and 3479 women comprised Group B.

The numbers of yearly tested pregnant women and the corresponding proportion of tested women among all study participants have decreased during the study period, from 766 to 131 and 89.1% to 20.5%, respectively. Group A had a significantly lower prevalence (4.4%) of pathological OGTT results compared to Group B (8.1%). This has resulted in a 45.427 likelihood ratio ($P < .001$) for abnormal OGTT results in pregnant women compared to non-pregnant women with PCOS.

We might conclude that pregnancy could have a more challenging influence on glucose metabolism and that carries higher risks for abnormal glucose metabolism than PCOS. The awareness of obstetricians regarding physiological changes during pregnancy that predisposes abnormal glucose metabolism is decreasing over time and the compliance concerning OGTT testing of pregnant women is decreasing too.

Abbreviations: BMI = body mass index, GDM = gestational diabetes mellitus, LR = likelihood ratio, OGTT = oral glucose tolerance test, PCOS = polycystic ovary syndrome.

Keywords: glycemia, polycystic ovary syndrome, pregnancy

1. Introduction

Common features of an altered metabolic and immune milieu in women with polycystic ovary syndrome (PCOS) and women during pregnancy are characterized by increased insulin resistance[1–3] and altered immune tolerance to the fetus and placenta in pregnant women[1,2] and to pancreatic islet cell in PCOS.[3] Therefore, both conditions, pregnancy as a physiological state and PCOS as a disorder carry the risk for the development of abnormal metabolism of glucose.

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PCOS is the most common endocrine-metabolic condition in women of the reproductive period,[4] with a prevalence varying from 5% to 20% depending on the diagnostic criteria used and the population evaluated.[5] Women with PCOS also frequently manifest metabolic alterations such as insulin resistance, advocated to be intrinsic of PCOS and play a significant role in its pathogenesis.[6] Such intrinsic insulin resistance places women with PCOS at increased risk of dysglycemia, type 2 diabetes,[7] and when women with PCOS become pregnant, this results in an increased risk of gestational diabetes mellitus (GDM).[8] On the other hand, GDM carries not only risks for ongoing pregnancy and delivery but also carries long-term health risks (hypertension, type 2 diabetes, and obesity) for both women affected by GDM and their offspring. This explains the significance of PCOS and GDM and underlines the importance of prediction, diagnosis, and management of these entities for the prevention of future non-communicable diseases.[9]

The risk for abnormal glucose metabolism in women with PCOS might be better identified by oral glucose tolerance test (OGTT) than fasting glucose level alone, since fasting glucose alone may miss approximately 50% of pre-diabetes and more than 10% of diabetes as diagnosed by OGTT.[10,11] Screening for dysglycemia by OGTT is endorsed in all women with PCOS to screen diabetes and pre-diabetes conditions.[12] Furthermore, preconceptual OGTT is recommended by reputable Endocrine Societies for infertile women who are seeking fertility treatments.[13]

Despite recognized all-encompassing and profound physiological changes in pregnancy which may affect glucose metabolism, we have an impression that the awareness of pregnancy as a challenging and risk-carrying condition is not at the appropriate level and that number of OGTT tested women is decreasing. Although pregnancy is considered a physiological condition we hypothesized that it carries higher risks for abnormal OGTT results than PCOS which is considered a pathological condition. We also aimed to compare prevalence and likelihood ratios for abnormal OGTT results between pregnant women and non-pregnant women with PCOS. The rates of OGTT testing over time will also be compared.

2. Material and method

2.1. Study design

This retrospective cross-sectional study analyzed trends in OGTT testing and prevalence and likelihood ratios for abnormal OGTT among non-pregnant nulliparous women with PCOS and pregnant women who were evaluated at the Clinic for Gynaecology and Obstetrics, Clinical Centre of Serbia, from January 1st, 2012 to December 31st, 2019. All women (both pregnant women and non-pregnant women with PCOS) with pathological OGTT were further evaluated and treated at the Clinic for Gynaecology and Obstetrics, Clinical Centre of Serbia and at the Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Serbia, either as outpatients or inpatients. These 2 clinics are the biggest tertiary healthcare institutions for Obstetrics and Gynaecology and Endocrinology in Serbia and they both are parts of the Clinical Centre of Serbia. Data were collected from paper and electronic medical records (Heliant Healthcare Information System, Heliant d.o.o., Belgrade, Serbia) from the above-mentioned period.

The primary study goals were to evaluate whether pregnancy carries higher likelihood ratios for abnormal glucose metabolism than PCOS. Secondary study aims were to evaluate the prevalence of abnormal OGTT among non-pregnant women with PCOS and pregnant women. Furthermore, we aimed to estimate the trends regarding the numbers and corresponding proportion of OGTT performed per year in study groups, as well as whether there were differences in glycemia during OGTT between study groups.

The research was approved by the Ethical Committee of Faculty of Medicine, University of Belgrade (approval number 1322/VII-52, date of approval: July 29th, 2020).

2.2. Study participants

Group A included all women with PCOS referred as outpatients to undergo screening for impaired glucose tolerance with a 75 g OGTT and further follow-up and eventually further diagnostic evaluation and treatment. Eligibility criteria for group A were PCOS and nulliparity. Exclusion criteria for group A were pregnancy, other endocrine disorders, and diseases, body mass index (BMI) over 30. Group B encompassed all pregnant women referred to as outpatients for universal glucose tolerance testing by 75 g OGTT at 24 to 28 weeks of gestation according to the American Diabetes Association/The International Association of the Diabetes and Pregnancy Study Groups recommendations.[14] Eligibility criteria for group B were singleton pregnancy and primiparity. Exclusion criteria were pregnancy achieved by in vitro fertilisation, multiple pregnancies, fetal growth restriction, sudden fetal intrauterine death, congenital fetal anomalies, placental abruption, pregnancy-related risk factors for glucose metabolism abnormalities, and GDM, such as pre-pregnancy BMI over 30, acanthosis nigricans, and pregnancy-related risk factors for GDM, such as fetal macrosomia and polyhydramnion.

All women referred to OGTT testing at our clinic underwent anthropometric evaluation which included measurement of height (cm) and body weight (kg), with the calculation of BMI (kg/m^2).

According to previously mentioned recommendations and criteria,[14] glycemia cutoff values were 5.1 mmol/L (fasting), 10.0 mmol/L (1 hour after glucose load), and 8.6 mmol/L (2 hours after glucose load). Among potential exposures, predictors, potential confounders, and effect modifiers, race, age, BMI, and consumption of nicotine were analyzed.

The standard protocol for the OGTT was used. After 12 hours overnight fast with a usual diet for the preceding 72 hours, venous plasma samples were collected to measure glucose levels at fasting, 1 and 2 hours after the administration of 75-g of glucose. Although there are other eligible tests to measure the body's response to sugar (glucose) and to screen for type 2 diabetes and GDM we have used only the 75-g OGTT due to the protocols of our 2 clinics. The oral glucose load was administered chilled to minimize nausea, vomiting, and abdominal distension.[15] In women with PCOS, if possible, blood samples were collected during the early follicular phase of the spontaneous menstrual cycle in regularly menstruating women or any day in amenorrheic women.

The diagnosis of abnormal OGTT was based on the criteria of the American Diabetes Association and International Association of the Diabetes and Pregnancy Study Groups.[14] Plasma glucose was estimated via the electrochemical method GOD-PAP (BIOSEN C-line; EFK DIAGNOSTIK Instruments, Brea, CA). The overall coefficient of variation of day-to-day imprecision for glucose was 2.4%. The clinical laboratory subscribes to external quality control from Serbian National External Quality Assessment

Table 1

Number of OGTTs performed per year in study groups during study period.

Year	2012	2013	2014	2015	2016	2017	2018	2019	Total
Total	860	723	1171	1149	1204	1008	657	639	7411
Group A	94 (10.9)	27 (3.7)	360 (30.7)	788 (68.6)	862 (71.6)	791 (78.5)	502 (76.4)	508 (79.5)	3932 (53.1)
Group B	766 (89.1)	696 (66.3)	811 (69.3)	361 (31.4)	342 (28.8)	217 (21.5)	155 (23.6)	131 (20.5)	3479 (56.9)

Data are presented as absolute numbers and/or percentages (in brackets). Group A: non-pregnant women with PCOS and Group B: pregnant women. OGTT = oral glucose tolerance test, PCOS = polycystic ovarian syndrome.

Scheme. The average deviation of glucose laboratory results from the target mean was 2.4%. Thus, the laboratory met the standards for both internal and external quality assurance for glucose.

2.3. Statistical analysis

Data were analyzed using SPSS version 20.0 (Statistical Package for Social Sciences, Chicago, IL). Results are presented as figures and tables. *P* values less than .05 were considered statistically significant. The student *t* test was used to test differences between study groups for numerical data. Fisher test of exact probability and Pearson Chi-square tests were used to testing differences between study groups for categorical data.

3. Results

During the study period a total of 7411 women were tested at our Clinic, 3932 women encompassed Group A, and 3479 women comprised Group B. Our study has demonstrated that compliance to recommendations regarding referral of PCOS women and pregnant women to OGTT testing has been lowered as regards pregnant women. The numbers of tested pregnant women and the proportion of tested pregnant women among all study participants have decreased during the study period, from 766 to 131 and 89.1% to 20.5%, respectively. Circumstances were opposite in PCOS women where these figures were increasing, from 94 to 508 yearly tested women and from 10.9% to 79.5% of pregnant women among all tested women (Table 1). In the light of these results, it is important to mention that the numbers of followed up, treated, and/or delivered pregnant women have not decreased during the study period.

All study participants in both groups were Caucasians. The mean age of participants in group A was 25.65 ± 7.31, while in group B was 24.02 ± 6.06. Mean BMI in group A was 25.26 ± 1.72 while in group B was 24.91 ± 1.89. In group A 31.12% of participants were smokers, while 29.28% of participants were smokers in group B. Significant differences in all evaluated potential confounders and effect modifiers such as age, BMI, and consumption of nicotine were not found, *P* values were .431, .123, and .087, respectively.

Significant differences were found in glycemia levels during OGTT in study groups (Table 2). While fasting glycemia was higher in group A, glycemia values 1 and 2 hours after oral glucose load were higher in Group B.

In Group A 172 women (4.4%) had pathological OGTT results, while in Group B 283 women (8.1%) had pathological OGTT results and the difference was significant (Chi-square 45.288, $P < .001$). Significantly higher prevalence of pathological OGTT results in pregnant women compared to PCOS women resulted in a 45.427 likelihood ratio ($P < .001$) for abnormal OGTT. We have also observed that the prevalence of abnormal OGTT has decreased in Group A during the study period while the prevalence of abnormal OGTT in group B has increased (Fig. 1).

The prevalence of abnormal glycemia values during OGTT was significantly different between study groups (Table 3).

All values of serum glucose were classified as normal and abnormal according to previously mentioned criteria and analyzed for each glycemia value during OGTT for both study groups. The numbers and percentages of abnormal OGTT glycemia values are presented in Table 4.

Analysis of perinatal outcomes among 172 pregnant women with abnormal OGTT results revealed the prevalence of caesarean delivery to be15.59%, premature delivery 10.47%, gestational hypertension 5.23%, postpartum hemorrhage 4.07%, preeclampsia 8.72%, polyhydramnios 6.97%, PROM 17.44%, and placental abruption 1.16% as maternal outcomes and macrosomia 14.53%, stillbirth 0.58%, and fetal growth restriction 1.16% as neonatal outcomes. Investigation of co-morbidities related to PCOS was limited due to exclusion criteria in our study. Therefore we have identified hypertension in 24%, metabolic syndrome in 48%, and nonalcoholic fatty liver disease in 0% of our study participants.

4. Discussion

Although recommendations regarding referral of PCOS women and pregnant women to OGTT testing have not changed during the past 10 years in Serbia, regrettably our study has demonstrated that compliance to those guidelines has been

Table 2

Glycemia values during OGTT in study groups.

	Fasting glycemia		1 hour		2 hours	
OGTT	Mean ± SD	CI	Mean ± SD	CI	Mean ± SD	CI
Group A	4.6618 ± 0.44435	4.6479–4.6757	7.2213 ± 2.02376	7.1580 ± 7.2846	5.8496 ± 1.58754	5.8000–5.8992
Group B	4.4388 ± 0.60885	4.4186–4.4591	7.8658 ± 2.00363	7.7992 ± 7.9324	6.6306 ± 1.74619	6.5726–6.6887
t^* (*P*)	18.143 (<.001)**		−13.754 (<.001)**		−20.167 (<.001)**	

*Student *t* test was used to test differences between study groups; SD: standard deviation; and CI: 95% confidence interval for mean lower bound upper bound.

**A *P* value less than .05 is statistically significant; Group A: non-pregnant women with PCOS; and Group B: pregnant women.

OGTT = oral glucose tolerance test, PCOS = polycystic ovarian syndrome.

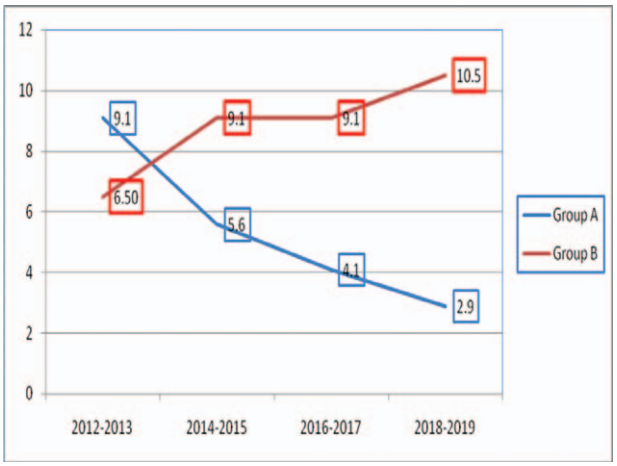

Figure 1. Prevalence of abnormal OGTT testing results in study groups during the study period. The prevalence of abnormal OGTT has decreased in Group A during the study period while the prevalence of abnormal OGTT in Group B has increased. Group A: non-pregnant women with PCOS and Group B: all pregnant women. OGTT = oral glucose tolerance test, PCOS = polycystic ovarian syndrome.

lowered in regards to pregnant women. Conveniently, the number of OGTT tested women with PCOS has increased. Given this finding, it is important to mention that during the study period, numbers of treated non-pregnant women with PCOS and pregnant women followed up, evaluated, and treated at 2 study centers have remained stable, without significant increase or decrease. Gynecologists and obstetricians have a privileged position and significant role in the prevention of long-term morbidities of patients and their offspring. This is particularly true regarding the management of pregnant and women with PCOS. Both PCOS as a pathological[16] and pregnancy as a physiological condition carry a risk for the development of dysglycemia, glucose metabolism abnormalities, and diabetes[17] and could have a negative impact on the future health of patients and their offspring. However, this privileged position is often insufficiently used,[18,19] which is to a certain degree confirmed by the results of our study. Although the overall proportion of OGTT tested pregnant women among all women tested according to previously mentioned recommendations in our study was 56.9% and it is similar to the corresponding percentage in the previous report (56%),[20] the worrisome finding is that testing among pregnant women had decreasing trend, ranging from 89.1% in 2012 to 20.5% in the year 2019. The usage of OGTT is now moving with the times and trends in medicine, resulting in paying more attention to PCOS than to GDM. Moreover, the prevalence of abnormal OGTT results among pregnant women increased during the study period. This fact represents another important reason to increase compliance to recommended OGTT testing of pregnant women. On the contrary, the overall proportion of OGTT tested PCOS women among all women tested were 53.1% and perceived trends seem to be favorable, with an increase from 10.9% in 2012 to 79.5% in the year 2019. This finding is of great importance because of the impact of PCOS on future diseases.[21] It seems that this fact is recognized and not ignored in Serbia, since we have reported the rising trend of the number of OGTT tested PCOS women. Reputable professional associations endorse the implementation of prevention strategies in PCOS women, stating that such policies should be given high priority, both locally and globally.[4,18]

Our results revealed significantly lower fasting glycemia in pregnant women compared to PCOS women. Plasma volume expansion as an essential physiologic change across gestation has the steepest rate of increase in the second trimester and that fact could explain this finding.[22] On the other hand, although some physical properties of blood are altered in PCOS, changes in plasma volume have not been observed.[23] Furthermore, despite increased insulin resistance in pregnancy, fasting glucose levels in maternal blood normally remain relatively stable until the end of pregnancy.[24] This could be further explained by the phenomenon of high glucose utilization by the fetus, although postprandial glucose levels tend to be higher.[25] Mean glycemia levels are significantly lower in the second trimester and the third trimester than non-pregnant women, including those with PCOS. To understand these results, one needs to keep in mind that the mechanisms driving insulin resistance in a healthy pregnancy, as well as in a pregnancy complicated by hyperglycemia, are complex and differ from the non-pregnant scenario.[26] Cousins et al have performed a longitudinal study to quantify the progressive effects of the second and third trimesters of normal pregnancy on the levels of plasma glucose and insulin and to compare it with non-pregnant controls. During pregnancy, the peak anabolic values for both plasma glucose and insulin were significantly increased and consequently, the 2-hour postprandial glucose and insulin levels were significantly elevated after meal ingestion and higher compared to non-pregnant controls.[27] Since 75 g OGTT to some extent imitates postprandial glycemia, it is considered as the conventional method for the detection of postprandial hyperglycemia.[28] From this standpoint, our results confirm the findings of Cousins et al and explain higher glycemia levels 60 and 120 min after glucose load during OGTT compared to PCOS women. In addition, Tao et al have determined the features of postprandial glycemic excursions in patients with PCOS and have compared it with healthy, age-matched women

Table 3

Prevalence of abnormal glycemia values during OGTT values.

Abnormal OGTT glycemia	Group A	Group B	χ^2	*P*	LR
Fasting	193 (4.9%)	192 (5.5%)	1.396	.237	1.394
1 hour	376 (9.6%)	496 (14.3%)	39.181	.000	39.135
2 hours	216 (5.5%)	436 (12.5%)	113.980	.000	115.125

Pearson Chi-square was used to test differences. Data are presented as counts and % within the group in brackets; χ^2: Pearson Chi-square value. A *P* value less than .05 is statistically significant; Group A: non-pregnant women with PCOS; and Group B: pregnant women.

LR = likelihood ratio, OGTT = oral glucose tolerance test, PCOS = polycystic ovarian syndrome.

Table 4

The numbers and percentages of abnormal OGTT glycemia values.

	Abnormal glycemia (fasting)	Chi square (*P*)	Abnormal glycemia (60 min)	Chi square (*P*)	Abnormal glycemia (120 min)	Chi square (*P*)
Group A	198 (5.03%)	1.138 (.286)	383 (9.74%)	38.085 (<.001)	222 (5.64%)	109.782 (<.001)
Group B	196 (5.63%)		502 (14.42%)		438 (12.58%)	

Pearson Chi-square was used to test differences. Data are presented as Counts and % within group in brackets; a *P* value less than .05 is statistically significant; Group A: non-pregnant women with PCOS and Group B: pregnant women.

OGTT = oral glucose tolerance test, PCOS = polycystic ovarian syndrome.

during a 3-day period using a continuous glucose monitoring system. The amplitude of postprandial glycemic excursions was higher in PCOS women only after breakfast, while no significant differences were found after lunch and dinner.[29] Analysis of perinatal outcomes among pregnant women with abnormal OGTT results demonstrated mostly similar results with those reported by Ding et al[30]

The prevalence of abnormal OGTT in PCOS women in our study (4.4%) is lower than those reported by others 9.4% and 10.3%.[10,31] However, these studies were performed in all PCOS women regardless of BMI. Obesity had a positive correlation with insulin resistance and the prevalence of abnormal OGTT testing results.[32] The fact that we have excluded obese women from our study could explain the discrepancy of our results with data obtained in mentioned studies. Although we have previously reported a higher prevalence of abnormal OGTT in pregnant women in Serbia,[15,33,34] our current results are in accordance with other studies performed worldwide.[24,25] The explanation of disagreement between previously and currently reported prevalence of abnormal OGTT in pregnant Serbian women is the fact that the prevalence in our earlier studies has been assessed among pregnant women with a high risk for GDM.

To the best of our knowledge, our study is the first one to simultaneously investigate the trends in OGTT testing both in pregnant women and women with PCOS. Additionally, we have evaluated all primiparous pregnant women and all nulliparous non-pregnant women with PCOS referred for OGTT testing in our Clinic. These strict inclusion criteria were used to avoid previous pregnancies as potential confounders which could influence the study results. Moreover, our study clinics are referral centers for the whole country, Serbia. Serbia has a similar prevalence of PCOS with other countries of South-Eastern Europe. Therefore, we believe the generalizability of our findings is strong regarding this part of Europe. All these facts we consider as the strengths of our study.

However, our study has several limitations. The exclusion of obese women has omitted an important population among both pregnant women and non-pregnant women with PCOS. Obesity has a potentially significant influence on the course of pregnancy and clinical features of PCOS. Therefore, this fact has to be kept in mind during the interpretation of our study results. Moreover, data regarding insulinemia during OGTT are lacking and this data could provide more profound insight regarding issues addressed in this study.

Against this background, presented by our results and other published data on this issue, we might conclude that pregnancy could have a more challenging influence on glucose metabolism and that might carry higher risks for abnormal glucose metabolism than PCOS. It seems that the awareness of obstetricians regarding physiological changes during pregnancy that predisposes abnormal glucose metabolism is lowering over time and that compliance concerning OGTT testing of pregnant women is lowering too. Future studies with more insightful data are needed to confirm or to prove our assumptions false.

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