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Indexes of Insulin Resistance in Hyperinsulinemic Polycystic Ovary Syndrome in a Macedonian Cohort of Women of Reproductive Age: A Cross-Sectional Study

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Abstract

BACKGROUND: Polycystic ovary syndrome (PCOS) is complex hormonal, metabolic and reproductive disorder and is a leading cause of female infertility. Hyperinsulinemia secondary to insulin resistance plays important role in the pathogenesis of PCOS.

AIM: To assess the sensitivity of different indices of insulin resistance and their relevance in a clinical setting.

MATERIAL AND METHODS: A cross-sectional study of 43 patients with PCOS and 29 noromo ovulatory women as a control group was conducted. Standard clinical, anthropometrical and hormonal testing for hyperandrogenism was conducted, as well as oral glucose tolerance test with determination of basal and stimulated glucose and insulin values.

RESULTS: The dynamic I/G index showed the highest sensitivity and specificity, but the static indexes HOMA-IR and QUICKI, although based on only basal glycemic and insulinemic values, showed good sensitivity, 90.38% and 94.01% respectively. HOMA-IR showed significant positive correlation with the stimulated insulin values.

CONCLUSIONS: Our results support the use of static indexes in the evaluation of insulin resistance in women with PCOS in a clinical setting, offering a simple assessment of insulin resistance in PCOS, which holds great prognostic and treatment implications.

Introduction

Polycystic ovary syndrome (PCOS) is complex hormonal, metabolic and reproductive disorder affecting 10% of females of reproductive age and is a leading cause of female infertility [1]. PCOS is one of the most frequent endocrinologic dysfunctions in women of reproductive age, characterised by the association of polycystic ovaries, hyperandrogenism and chronic anovulation [2], [3]. Its aetiology remains unknown, but it is clear that hyperinsulinemia secondary to insulin resistance plays an important role in the pathogenesis of reproductive abnormalities [4]. PCOS is a diagnosis of exclusion and is defined by the Rotterdam classification from 2003 requiring at least 2 out of 3 criteria: oligo-ovulation and/or anovulation, clinical and/or biochemical hyperandrogenism and polycystic ovaries on ultrasound [5].

As early as 1980, Burgen reported that women with PCOS have basal and glucose-stimulated hyperinsulinemia and noted a significant positive linear correlation between the insulin and androgen concentrations in women with polycystic ovarian syndrome [6]. Insulin resistance and hyperinsulinemia is evident both in lean and obese patients with PCOS [7], [8]. The prevalence of insulin resistance in PCOS is approximatively 50-60%, compared to 10-20% in the general population [9]. It is still controversial

whether the hyperinsulinemic state stimulates the excessive ovarian production of androgens or if the chronic hyperandrogenemic milieu promotes insulin resistance. Despite obesity, present in more than half of the patients, decreased insulin-stimulated glucose utilisation regardless of body mass index has been demonstrated in polycystic ovary syndrome [8].

Several mechanisms have been postulated to explain the correlation between the hyperinsulinemia and hyperandrogenemia in PCOS. Studies have shown a strong negative correlation of basal insulin with the levels of sex hormone binding globulin (SHBG), suggesting that the insulin has an inhibitory effect on the hepatic production of SHBG, decreasing its levels and leading to increased bioactivity of testosterone in its free unbound form that emphasises the hyperandrogenic characteristics. Insulin resistance also predisposes to a visceral type of adiposity, reflecting the androgen-like phenotype of PCOS [10], [11]. The latest studies revealed unique post-receptor defects in the insulin signalling pathways in PCOS. Fibroblast cell lines from women with PCOS have significantly decreased insulin-stimulated glucose incorporation into glycogen, but similar insulin-stimulated thymidine incorporation, compared to cell lines from reproductively normal control women. This suggests that there is a selective defect in insulin action in PCOS that affects the metabolic, but not the mitogenic actions of insulin [4].

Insulin resistance imposes not only disturbances of the glucose metabolism but is also associated with a tendency towards atherogenic dyslipidaemia and vascular endothelial dysfunction. Approximately, 25% to 30% of women with PCOS will show impaired glucose tolerance by the age of 30 and 8% of affected women will develop type 2 diabetes annually [12]. Women with PCOS are seen to have more extensive coronary artery disease by angiography. Hypertension is also observed more frequently in these women [13]. Therefore the testing for insulin resistance becomes important and integral part of the evaluation of patients with PCOS.

The aim of this study was to assess the sensitivity of different indices of insulin resistance and their relevance in a cross-sectional study of patients with PCOS and noromo ovulatory women as a control group.

Material and Methods

A cross-sectional study was conducted at the University Clinic of Endocrinology, Diabetes and Metabolic Disorders in Skopje, Macedonia, in the period between October 2012 and May 2014. In this study, 43 patients were enrolled with hyperinsulinemic PCOS and a control group of 29 noromo ovulatory women with regular menstrual cycles, without clinical or biochemical signs of hyperandrogenism and no prior known endocrinologic diseases. PCOS was diagnosed according to the criteria from The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group [5]. Patients presenting with thyroid disorders or neoplastic causes of hyperandrogenemia such as androgen-secreting tumours, congenital adrenal hyperplasia and Cushing's syndrome were excluded from the study.

Patients with PCOS were grouped according to body mass index (BMI) into PCOS with normal BMI ≤ 25 kg/m^2 (PCOS N) and PCOS with high BMI > 25 kg/m^2 (PCOS H).

Hormonal parameters were assessed in the follicular phase of the menstrual cycle or at any given day in women with absent menstrual cycle in the previous two or more months. Blood samples for hormonal and biochemical analyses were obtained by venipuncture between 08:00 and 10:00 h, after an overnight fast of 12 hours. Anthropometrical measurements and clinical assessment of signs of hyperandrogenism were conducted at the visit. Transvaginal ultrasound scan of the ovaries was performed at the University clinic of Gynaecology using a 6,5 MHz transducer in order to determine the total number of early antral follicles. All patients underwent an oral 75g glucose tolerance test (OGTT) after an overnight fast of at least 12 hours during which basal values of glucose and insulin were measured at baseline, as well as post-load glucose and insulin values at 60 and 120 minutes.

Serum estradiol (E_2), luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone (T), androstenedione (A), dehidroepiandrostenedione-sulphate (DHEA-s) and prolactin (PRL) levels were measured by electrochemiluminescence immunoassay on a Roche Elecsys 1010/2010 automated immunoassay analyser. Sex hormone binding globulin (SHBG) measurements were performed by enzyme-linked immunosorbent assay on an IMX Abbott semiautomatic analyser (values of these tests are not shown in results section). Insulin was measured in serum with microparticle enzymatic assay (MEA) on the semiautomatic analyser IMX Abbot. Glucose was determined in plasma with glucose-oxidase method on the glycemic analyser Beckmann. Free androgen index (FAI) was calculated using the standard formula: testosterone/SHBG × 100 (values of these tests are not shown in results section).

Established direct methods for measuring insulin sensitivity in vivo are relatively complex. Therefore, simple surrogate indexes for insulin sensitivity/resistance which is derived from blood insulin and glucose concentrations under fasting conditions (steady state) or in the postprandial state (dynamic) was calculated. Based on the results of

basal and post-load glucose and insulin levels obtained during OGTT, several indexes of insulin resistance were calculated for all of the patients. Homoeostasis model of insulin resistance (HOMA-IR) was calculated using the formula: (fasting insulin (μU/ml) x basal glucose (mmol/l))/22.5. The quantitative insulin sensitivity check index (QUICKI) was derived using the inverse of the sum of the logarithms of the fasting insulin and fasting glucose, using the formula: 1/(log(fasting insulin μU/mL) + log(fasting glucose mmol/l)). The sum of insulin measured at 0, 60 and 120 minutes divided by the sum of glucose at 0, 60 and 120 minutes was calculated as a dynamic index I/G [14].

All statistical procedures were run using the StatSoft Statistica 7 software. Statistical significance was set at $p < 0.05$. Normality of distribution was evaluated with the one-sample Kolmogorov-Smirnoff test. Comparisons of means were performed with one-way ANOVA and general linear model multi-variance. Correlations were evaluated with the calculation of the Spearman coefficient.

Results

In this study, 43 patients were diagnosed as having PCOS according to the Rotterdam diagnostic criteria and had basal or stimulated hyperinsulinemia during OGTT while the control group consisted of 29 women with normal glucose and insulin values during OGTT and normal hormonal status. The basic clinical data for the patient groups (PCOS N, PCOS H and control group) as well the results for insulinemia and glycaemia during the OGTT are shown in Table 1.

Table 1: Basal clinical, anthropometrical, hormonal and metabolic values in the three groups

	Control group	PCOS N BMI ≤ 25 kg/m^2	PCOS H BMI >25 kg/m^2
n	29	12	31
Age (years)	22.36 ± 3.82	21.42 ± 3.94	24.97 ± 6.29
BMI (kg/m^2)	23.16 ± 3.24	23.75 ± 1.22	33.13 ± 5.56*
Menstrual cycle length (days)	49 ± 2.6	77.92 ± 64.39	67.76 ± 45.29
Testosterone (ng/ml)	1.32 ± 0.77	1.5 ± 1.4	1.72 ± 0.95
Fasting insulin (μU/ml)	10.45 ± 2.63	24.15 ± 35.57	22.89 ± 7.77
Stimulated insulin at 60 min (μU/ml)	44.95 ± 20.11	148.74 ± 80.87	166.95 ± 96.68
Stimulated insulin at 120 min (μU/ml)	28.85 ± 9.17	102.65 ± 78.6	148.96 ± 102.66
Fasting glucose (mmol/L)	4.43 ± 0.58	4.75 ± 0.7	4.84 ± 0.63
Stimulated glucose at 60 min (mmol/L)	5.65 ± 1.04	6.96 ± 1.66	8.26 ± 2.32
Stimulated glucose at 120 min (mmol/L)	4.85 ± 072	5.75 ± 1.05	6.63 ± 2.06

*, $p < 0.001$.

Most of the patients were in the 21 to 30 years age group, with an average age of the patients in the PCOS H group higher (24.97 ± 6.29 years) in comparison to the PCOS N group, but not statistically significant. A statistically significant difference ($p<0.001$) was found in the BMI of patients with PCOS H in comparison to the control group. There was no statistically significant difference in the glycemic status between the groups, but still, the PCOS H group had higher average basal glycaemia values and more markedly higher glycemic excursions post load (Fig. 1).

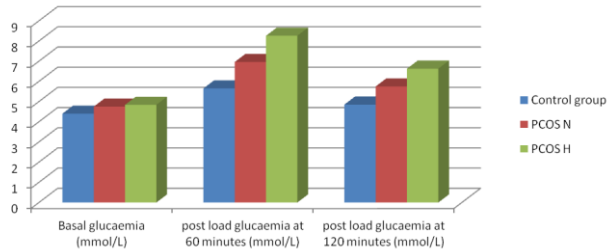

Figure 1: Basal and post load glycemic values in the groups

The PCOS group showed both basal and post-load hyperinsulinemia. The stimulated insulin values were significantly higher both in PCOS N and PCOS H groups compared to the controls, independent of obesity status, which was used as criteria for group division (Fig. 2).

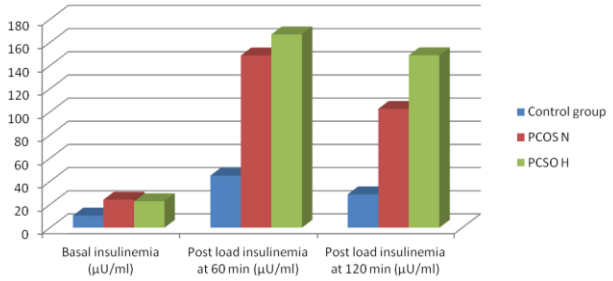

Figure 2: Basal and stimulated insulin values in the groups

There was no statistically significant difference between the values of fasting glycaemia between the groups, although higher post load glycemic excursions were noted in PCOS patients, especially at 60 minutes during OGTT. There was no significant difference in the degree of stimulated hyperinsulinemia in lean and obese patients with PCOS (Table 2).

Table 2: Statistical difference in the basal and stimulated glucemic and insulinemic values between lean and obese PCOS patients

	Mean PCOS N	Mean PCOS H	St.D. PCOS N	St.D. PCOS H	t-value	p
Age	21.42	24.97	3.94	6.29	-1.81	0.076
BMI	23.75	33.13	1.21	5.56	-5.75	<0.001*
MNZ	77.92	67.76	64.38	45.30	0.57	0.568
Testosterone	1.50	1.72	1.40	0.95	-0.56	0.579
Basal insulin	24.15	22.90	35.57	7.77	0.19	0.851
Stimulated insulin at 60'	148.74	166.95	80.87	96.69	-0.58	0.566
Stimulated insulin at 120'	102.65	148.96	78.61	102.66	-1.41	0.166
Basal glucose	4.74	4.84	0.70	0.63	-0.42	0.674
Stimulated glucose at 60'	6.94	8.26	1.67	2.32	-1.74	0.090
Stimulated glucose at 120'	5.75	6.63	1.06	2.06	-1.34	0.189

*, $p < 0.001$.

For the PCOS groups, three indexes of insulin resistance were calculated: homoeostasis model of

insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) as static indexes and the sum of insulinemia versus the sum of glycaemia (I/G) as a dynamic index. All of the values were compared to the values obtained in the control group and sensitivity and specificity were calculated for each index. The results for sensitivity and specificity of insulin indexes in the entire PCOS group are given in Table 3.

Table 3: Sensitivity and specificity of indexes of insulin resistance

	I/G	HOMA-IR	QUICKI
Control group	5.65 ± 1.47	2.06 ± 0.65	0.61 ± 0.04
PCOS N	15.78 ± 11.13	5.02 ± 7.2	0.59 ± 0.14
PCOS H	17.17 ± 9.6	4.92 ± 1.75	0.49 ± 0.03
PCOS all	17.42 ± 9.91	4.2 ± 3.84	0.51 ± 0.07
Sensitivity%	96.02	90.38	94.01
Specificity%	92.64	84.09	86.21

The I/G index showed the highest sensitivity and specificity, being derived from both basal and post load values of glycaemia and insulinemia. Although the static indexes HOMA-IR (90.38%) and QUICKI (94.01%) are based on only basal glycemic and insulinemic values, they showed good sensitivity. HOMA-IR values also showed significant positive correlation with the insulin values at 60 minutes ($r = 0.42$; $p < 0.005$) and at 120 minutes post load ($r = 0.52$; $p < 0.0003$) during OGTT (Fig. 3).

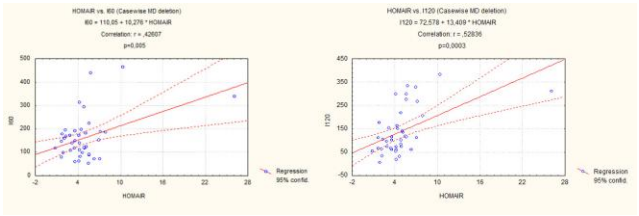

Figure 3: Correlation of HOMA-IR with post-load insulinemic values at 60 and 120 minutes

Discussion

The polycystic ovary syndrome is not only the most common underlying cause of anovulation in women in the reproductive period but is also associated with characteristic dysfunctions of the insulin action that have an important impact on the possible metabolic disturbances appearing later in life in women with PCOS. The association between the impaired carbohydrate metabolism and hyperandrogenism was first described in 1921 by Archard and Thiers as “diabetes in a bearded female” [15]. Kierland in 1947 described the characteristic skin lesion, acanthosis nigricans, which can be seen in women with hyperandrogenism and in patients with diabetes, as an epiphenomenon of the insulin resistance [16]. Dunaif et al investigated the characteristics of hyperandrogenic women with acanthosis nigricans; they found impaired glucose tolerance in 20% of the patients [17]. According to the revised criteria of the world health organisation (WHO), later studies determined the prevalence of impaired glucose tolerance of 20-40% in women with PCOS, compared to 5.3% prevalence of impaired glucose tolerance in the control population [18]. This high incidence led towards more extensive research of the role of insulin resistance in PCOS.

Insulin resistance is seen in 50-60% of women with PCOS, while almost 10% of them have a certain degree of glucose intolerance or diabetes at the time of diagnosing the syndrome [9], [19]. Pesant et al, reported that during three years follow-up period, up to 25% of women with PCOS, initially with normal glucose metabolism, will develop some degree of glucose metabolism abnormalities [20]. In our study, we have demonstrated that the fasting glycaemia is not a marker of metabolic dysregulation, since there was no statistically significant difference between the values of fasting glycaemia between the groups, although higher post load glycemic excursions were noted in PCOS patients, especially at 60 minutes during OGTT. Our data confirm that insulin resistance is not exclusively seen in obese patients with PCOS, but marked post load hyperinsulinemia was also noted in lean patients with PCOS. There was no significant difference in the degree of stimulated hyperinsulinemia in lean and obese patients with PCOS, confirming the fact that insulin resistance in PCOS is independent of obesity, which was taken as a group dividing factor.

Insulin resistance is characterised by an inability of normal amounts of insulin to achieve the normal predicted response, often in the clinical setting of central adiposity. To achieve euglycemia, the pancreas over secretes insulin [21]. Investigators define insulin resistance based on hyperinsulinemic-euglycemic clamp techniques. Hyperinsulinemic-euglycemic clamp techniques rely on an intravenous insulin infusion to maintain steady serum glucose concentrations at fasting levels to measure glucose uptake. Lower glucose uptake signifies resistance to insulin action (insulin resistance). Since the technique requires intravenous infusions, frequent blood sampling, extensive time and significant financial resources, it is experimentally useful but rarely applicable in a clinical setting [22]. Therefore, many derived indexes for assessment of insulin resistance have been proposed. Clamp techniques have been used as comparisons to validate other modes of assessment of insulin resistance.

The homeostatic model assessment of insulin resistance (HOMA-IR) has been compared to clamp techniques with good results [22]. One major limitation of HOMA rests on the fact that many adolescents with PCOS display stimulated but not fasting metabolic abnormalities. In fact, HOMA in young PCOS patients missed 50% of insulin resistance as compared to

OGTT with insulin-AUC calculations [23]. I/G ratio correlated strongly with clamp-demonstrated insulin resistance in a small study of PCOS women, showing evidence of insulin resistance in both lean and obese women with PCOS [24]. Quantitative insulin sensitivity check index (QUICKI) was developed to improve the sensitivity of fasting measurements. QUICKI has been shown to correlate well to clamp measurements in obese and non-obese patients [25]. QUICKI also demonstrates correlation with HOMA-IR. In our study, the I/G ratio showed the highest sensitivity, which was expected because the index calculations are based on both basal and simulated values of insulin and glucose, but the static indexes showed also very high sensitivity. The sensitivity and specificity of HOMA-IR were comparable to the QUICKI index, bearing in mind the fact that our studied population did not include adolescents. The correlation of HOMA-IR with the stimulated insulin values indicates that this index gives a relevant value of the level of insulin resistance in women with PCOS.

Our results are in accordance with several studies that support the use of static indexes of insulin resistance in the evaluation of insulin resistance in women with PCOS in a clinical setting. Furthermore, the method is simple, quick and easy to execute in contrast to the complicated and expensive hyperinsulinemic-euglycemic clamp. The diagnosis of insulin resistance holds great prognostic and treatment implications. All women with PCOS should be screened for the presence of insulin resistance as well as assessed for other stigmata of the insulin resistance syndrome such as hypertension, dyslipidemia, central obesity, and glucose intolerance.

References

1. Slowey MJ. Polycystic ovary syndrome: new perspective on an old problem. South Med J. 2001;94(2):190-6. http://dx.doi.org/10.1097/00007611-200194020-00004 PMid:11235033

2. Franks S. Polycystic ovary syndrome. N Engl J Med. 1995;333(13):853-61. Erratum in: N Engl J Med. 1995;333(21):1435. http://dx.doi.org/10.1056/NEJM199509283331307 PMid:7651477

3. Futterweit W. Polycystic ovary syndrome: clinical perspectives and management. Obstetrical & gynecological survey. 1999;54(6):403-13. http://dx.doi.org/10.1097/00006254-199906000-00024

4. Book CB, Dunaif A. Selective Insulin Resistance in the Polycystic Ovary Syndrome 1. The Journal of Clinical Endocrinology & Metabolism. 1999;84(9):3110-6. http://dx.doi.org/10.1210/jc.84.9.3110

5. ESHRE TR, Group AS. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertility and sterility. 2004;81(1):19-25. http://dx.doi.org/10.1016/j.fertnstert.2003.10.004

6. Burghen GA, Givens JR, Kitabchi AE. Correlation of Hyperandrogenism with Hyperinsulinism in Polycystic Ovarian Disease. The Journal of Clinical Endocrinology & Metabolism. 1980;50(1):113-6. http://dx.doi.org/10.1210/jcem-50-1-113 PMid:7350174

7. Nestler JE, Jakubowicz DJ. Lean women with polycystic ovary syndrome respond to insulin reduction with decreases in ovarian P450c17 alpha activity and serum androgens. J Clin Endocrinol Metab. 1997;82(12):4075-9. PMid:9398716

8. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes. 1989;38(9):1165-74. http://dx.doi.org/10.2337/diab.38.9.1165 PMid:2670645

9. Dunaif A, Thomas A. Current concepts in the polycystic ovary syndrome. Annual review of medicine. 2001;52(1):401-19. http://dx.doi.org/10.1146/annurev.med.52.1.401 PMid:11160786

10. Sørensen K, Aksglaede L, Munch-Andersen T, Aachmann-Andersen NJ, Petersen JH, Hilsted L, Helge JW, Juul A. Sex hormone–binding globulin levels predict insulin sensitivity, disposition index, and cardiovascular risk during puberty. Diabetes care. 2009;32(5):909-14. http://dx.doi.org/10.2337/dc08-1618 PMid:19196890 PMCid:PMC2671098

11. Wallace IR, McKinley MC, Bell PM, Hunter SJ. Sex hormone binding globulin and insulin resistance. Clinical endocrinology. 2013;78(3):321-9. http://dx.doi.org/10.1111/cen.12086 PMid:23121642

12. Broekmans FJ, Knauff EA, Valkenburg O, Laven JS, Eijkemans MJ, Fauser BC. PCOS according to the Rotterdam consensus criteria: change in prevalence among WHO-II anovulation and association with metabolic factors. BJOG: An International Journal of Obstetrics & Gynaecology. 2006;113(10):1210-7. http://dx.doi.org/10.1111/j.1471-0528.2006.01008.x PMid:16972863

13. Daniilidis A, Dinas K. Long term health consequences of polycystic ovarian syndrome: a review analysis. Hippokratia. 2009;13(2):90-2. PMid:19561777 PMCid:PMC2683463

14. Patarrão RS, Lautt WW, Macedo MP. Assessment of methods and indexes of insulin sensitivity. Revista Portuguesa de Endocrinologia, Diabetes e Metabolismo. 2014;9(1):65-73. http://dx.doi.org/10.1016/j.rpedm.2013.10.004

15. Achard C, Thiers J. Le virilisme pilaire et son association a l'insuffisance glycolytique (diabete des femmes a barbe). Bull Acad Natl Med. 1921;86(29):51-66.

16. Kierland RR. Acanthosis nigricans: An analysis of data in twenty-two cases and a study of its frequency in necropsy material. Journal of Investigative Dermatology. 1947;9(6):299-305. http://dx.doi.org/10.1038/jid.1947.102 PMid:18918924

17. Dunaif A, Graf M, Mandeli J, Laumas V, Dobrjansky A. Characterization of Groups of Hyperaiidrogenic Women with Acanthosis Nigricans, Impaired Glucose Tolerance, and/or Hyperinsulinemia. The Journal of Clinical Endocrinology & Metabolism. 1987;65(3):499-507. http://dx.doi.org/10.1210/jcem-65-3-499 PMid:3305551

18. Harris MI, Hadden WC, Knowler WC, Bennett PH. Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in US population aged 20–74 yr. Diabetes. 1987;36(4):523-34. http://dx.doi.org/10.2337/diab.36.4.523 PMid:3817306

19. Ovalle F, Azziz R. Insulin resistance, polycystic ovary syndrome, and type 2 diabetes mellitus. Fertility and sterility. 2002;77(6):1095-105. http://dx.doi.org/10.1016/S0015-0282(02)03111-4

20. Pesant MH, Baillargeon JP. Clinically useful predictors of conversion to abnormal glucose tolerance in women with polycystic ovary syndrome. Fertility and sterility. 2011;95(1):210-5. http://dx.doi.org/10.1016/j.fertnstert.2010.06.036 PMid:20655529

21. Garruti G, Depalo R, Vita MG, Lorusso F, Giampetruzzi F, Damato AB, Giorgino F. Adipose tissue, metabolic syndrome and polycystic ovary syndrome: from pathophysiology to treatment. Reproductive biomedicine online. 2009;19(4):552-63. http://dx.doi.org/10.1016/j.rbmo.2009.05.010 PMid:19909598

22. Legro RS, Castracane VD, Kauffman RP. Detecting insulin resistance in polycystic ovary syndrome: purposes and pitfalls. Obstetrical & gynecological survey. 2004;59(2):141-54.

http://dx.doi.org/10.1097/01.OGX.0000109523.25076.E2
PMid:14752302

23. Fulghesu AM, Angioni S, Portoghese E, Milano F, Batetta B, Paoletti AM, Melis GB. Failure of the homeostatic model assessment calculation score for detecting metabolic deterioration in young patients with polycystic ovary syndrome. Fertility and sterility. 2006;86(2):398-404. http://dx.doi.org/10.1016/j.fertnstert.2006.01.024 PMid:16769061

24. Ducluzeau PH, Cousin P, Malvoisin E, Bornet H, Vidal H, Laville M, Pugeat M. Glucose-to-insulin ratio rather than sex hormone-binding globulin and adiponectin levels is the best predictor of insulin resistance in nonobese women with polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism. 2003;88(8):3626-31. http://dx.doi.org/10.1210/jc.2003-030219 PMid:12915646

25. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. The Journal of Clinical Endocrinology & Metabolism. 2000;85(7):2402-10. http://dx.doi.org/10.1210/jcem.85.7.6661 PMid:10902785