Research Report

Measurement of Glucose/Insulin Fasting Ratio (G:I Ratio) for Insulin Resistance Identification on Polycystic Ovary Syndrome Patients

Pengukuran Rasio Glukosa/Insulin Puasa (Rasio G:I) untuk identifikasi resistensi insulin pada pasien Sindroma Ovarium Polikistik

Fidel G. Siregar, Delfi Lutan, Thamrin Tanjung, Binarwan Halim

Division of Fertility and Reproductive Endocrinology
Department of Obstetrics and Gynecology
Medical Faculty of Sumatera Utara University/
H. Adam Malik Hospital
Medan

Abstract

Objective: To identify insulin resistance on PCOs patients and to know characteristics and clinical differences between PCOs patients with and without insulin resistance in Gynecologic Outpatient Clinic of H. Adam Malik Hospital, Clinic of Prof. Delfi Lutan, Clinic of Prof. Thamrin Tanjung and Clinic of Halim Fertility Center in Medan.

Method: This descriptive cross sectional study conducted from July 2008 - June 2009, diagnosis of PCOs based on Rotterdam's criteria was drawn for 5 ml blood samples, from mediana cubiti vein, after 10 - 12 hours fasting for determination of fasting glucose, fasting insulin, LH, FSH, prolactin and testosterone. Insulin resistance was determined by glucose/insulin fasting ratio < 4.5.

Result: From sixty one patients were divided into PCOs without insulin resistance (50 patients; 82%) and PCOs with insulin resistance (11 patients; 18%) group. No significant differences in clinico-biochemical characteristics, fasting glucose mean level, menstrual pattern, ovary volume, follicle number and reproductive hormone profile of two groups, except in BMI value, fasting insulin level and G:I ratio ($p < 0.05$).

Conclusion: There was significant correlation between fasting insulin level and insulin resistance with mean of fasting insulin level of 24.882 μU/ml. Insulin resistance was frequent on overweight group study according to WHO criteria (BMI 25 - 29.9 kg/m^2).

[Indones J Obstet Gynecol 2011; 35-2: 74-8]

Keywords: insulin resistance, polycystic ovary syndrome, G:I ratio

Abstrak

Tujuan: *Untuk mengidentifikasi resistensi insulin, perbedaan karakteristik dan klinis penderita SOPK dengan resistensi insulin dibandingkan dengan penderita SOPK tanpa resistensi insulin di Poliklinik Ginekologi RS H. Adam Malik dan Klinik Halim Fertility Center, Medan.*

Metode: *Penelitian ini merupakan penelitian deskriptif dengan rancangan potong lintang dari Juli 2008 - Juni 2009. Pasien yang didiagnosa SOPK berdasarkan kriteria Rotterdam diinstruksikan untuk berpuasa selama 10 - 12 jam semalam sebelum darah untuk sampel penelitian diambil. Diambil darah pasien yang telah dipuasakan sebanyak 5 cc dari vena mediana cubiti untuk dilakukan pemeriksaan kadar glukosa puasa, kadar insulin puasa, kadar LH, FSH, prolaktin, testosteron. Resistensi insulin ditandai dengan rasio glukosa insulin puasa (Rasio G:I) < 4,5.*

Hasil: *Dari 61 pasien dibagi atas 2 kelompok yaitu SOPK tanpa resistensi insulin (50 pasien, 82%) dan SOPK dengan resistensi insulin (11 pasien, 18%). Tidak terdapat perbedaan bermakna dalam hal karakteristik klinikobiokimia, kadar rata-rata glukosa puasa, pola menstruasi, volume ovarium, jumlah folikel dan profil hormone reproduksi dari kedua kelompok, kecuali pada nilai IMT, kadar insulin puasa, rasio G:I ($p < 0,05$).*

Kesimpulan: *Terdapat hubungan yang bermakna antara kadar insulin puasa terhadap terjadinya resistensi insulin dengan nilai mean kadar insulin puasa 25,386 μU/ml. Frekuensi terbanyak resistensi insulin pada penelitian ini ada pada kelompok dengan berat badan berlebih, menurut kriteria WHO. (BMI 25 - 29,9 kg/m^2).*

[Maj Obstet Ginekol Indones 2011; 35-2: 74-8]

Kata kunci: *resistensi insulin, sindroma ovarium polikistik, rasio G:I*

Correspondence: Fidel G. Siregar, Division of Fertility and Reproductive Endocrinology, Department of Obstetrics and Gynecology, Medical Faculty of Sumatera Utara University, H. Adam Malik Hospital, Jln. Bunga lau 17 Medan. Telp.: 061-8363760. Fax.: 061-8362292. Email: fgsiregar@gmail.com

INTRODUCTION

Polycystic ovary syndrome (PCOs) is an endocrine disorder mostly found in women of reproductive age, marked by the combination of several clinical manifestations such as hyperandrogenism, oligo-/amenorrhea, oligo-/anovulation, hirsutism, specific ovarian morphology, hyperinsulinemia, and insulin resistance.[1-4] In 1935, Stein and Leventhal for the first time elucidated the relationship between bilateral polycystic ovaries with amenorrhea, oligomenorrhea, hirsutism, obesity in women whom ovaries hypertrophy with multiple cystic follicles, and fibrotic thickening of the tunica albuginea and cortical stroma. Nonetheless, the clinical feature and pathology of polycystic or micropolycystic ovaries had been described by Antonio Vallisneri in 1721.[5] The term PCOs was first used in 1960 since both of clinical and histological differences of this syndrome was identified. Since 1960, ovarian enlargement or the presence of histological anomaly from specimen biopsy became important considerations for diagnosis.

Considering that the elevation of serum LH concentration and the increase of LH/FSH ratio are characteristics of this syndrome, the examination of serum gonadotrophin profile is an alternative approach to diagnose.

In 1970, the advance of ultrasound technology enabled non-invasive examination of ovarian morphology, which made possible visualization of a chariot wheel image with 12 or more follicles.[6]

The relationship between carbohydrate metabolic disorder and hyperandrogenism was explained in 1921 by Archard and Thiers.[7] Subsequently, numerous researches ascertained the relationship between hyperinsulinemia and hyperandrogenism.[8,9] In 1980, Burgen et al reported that women with PCOs exhibiting hyperinsulinemia were attributed to insulin resistance. The observation of this significant relationship between insulin and androgen levels strengthens the hypothesis of an etiologic relationship between these two conditions.[10] Furthermore, it is established that women with PCOs have hyperinsulinemia when compared with control based on age and body weight.[11-15] Consequently, 20% of women with PCOs tested with OGTT showed impaired glucose tolerance (IGT).[16]

Currently, it is well-accepted that obese women with PCOs have insulin resistance. Whether it is wholly attributable to PCOs or initially dependent on body weight or body fat distribution is still open to debate.[12] Although insulin resistance is not a disease, it is found in 50 - 70% of women with PCOs and is correlated with increased risk of cardiovascular disease and type-2 diabetes mellitus. That weight reduction in obese PCOs patients, especially reduced adiposity in the abdomen, normalizes insulin sensitivity, gives the impression that body fat distribution is an important determinant of insulin resistance in PCOs.[17]

Insulin resistance in PCOs is correlated with elevated level of androgen, particularly free testosterone.[4,7,9] Large doses of testosterone administered to healthy women may trigger insulin resistance. Nevertheless, the interaction between hyperandrogenemia and the definite etiology of insulin resistance remains undetermined.[17]

The cause of hyperinsulinemia in women with PCOs likewise remains unknown. This may be associated with increased insulin serine phosphorylation receptors which reduce the activity of tyrosine kinase protein and cause post-binding defect of insulin effect and/or abnormal insulin secretion. Metabolic disorder in PCOs may originate from early life, during the prenatal or prepubertal period; early exposure to androgen during the developmental phase of life may affect body fat distribution and work of insulin. Clinical implications to women with PCOs encompass the emergence of insulin resistance and/or hyperinsulinemia, especially in groups with anovulatory cycles and central obesity.[17]

Many earlier studies revealed that agents that improve insulin resistance and reduce circulating insulin level such as Troglitazone or Metformin may be new approaches to treating PCOs. Therefore, recognizing women with concomitant PCOs and severe insulin resistance using simple tests has become a relevant medical intervention that may improve insulin sensitivity in PCOs patients.[17]

Until now, the latest data of insulin resistance on PCOs patients in Indonesia as generally and newer data in Medan as specifically are still lacked. Therefore the author feels inclined to investigate this phenomenon.

METHOD

This research is an analytic descriptive study with cross-sectional approach conducted in the Department of Obstetrics and Gynecology of H. Adam Malik General Hospital and private practice in Medan from July 2008 until June 2009. Sixty-one female patients suffering from PCOs, and which fulfilled inclusion criteria, were designated as study subjects. They were divided into two groups, PCOs patients without insulin resistance and PCOs patients with insulin resistance group. Data were analyzed using Chi-square and Mann-Whitney U statistical test (SPSS version 15).

RESULTS

Distribution of study participants

Table 1. Distribution of study participants.

Group	Frequency (n)	Percentage (%)
Group of PCOs patients without insulin resistance	50	82.0
Group of PCOs patients with insulin resistance	11	18.0
Total	61	100

Clinical and biochemical characteristics, Carbohydrate metabolism profile, Reproductive Hormone Profile of group of PCOs patients without insulin resistance and with insulin resistance.

BMI parameters according WHO criteria, Menstrual cycle pattern, Ovarian volume, Number of follicles of group of PCOs patients without insulin resistance and with insulin resistance.

Table 2. Clinical and biochemical characteristics, Carbohydrate metabolism profile, Reproductive Hormone Profile of group of PCOs patients without insulin resistance and with insulin resistance.

	Group of PCOs patients without insulin resistance n = 50 (mean)	SD	Group of PCOs patients with insulin resistance n = 11 (mean)	SD	p
Characteristic:					
• Age (years)	27.8	3.5	30.5	6.0	0.127
• BMI (kg/m^2)	22.9	3.0	27	3.8	0.002
• LH/FSH	1.3	0.9	1.3	0.8	0.771
• Testosterone (ng/dl)	0.7	0.3	0.7	0.3	0.754
• Prolactin (ng/ml)	15.9	5.4	12.5	3.3	0.082
• Menarche (years)	12.3	1.2	12.3	0.8	0.702
Carbohydrate Metabolism Profile:					
• Blood sugar level (mg/dl)	84.9	9.8	88.1	4.4	0.239
• Fasting insulin level (μU/ml)	7.1	3.4	24.8	6.7	0.001
• G:I ratio	15.1	8.6	3.7	0.6	0.001
Reproductive Hormone Profile:					
• LH (IU/ml)	7.6	6.4	6.6	3.5	0.955
• FSH	5.2	1.1	5.2	1.0	0.969
• LH/FSH	1.3	0.9	1.3	0.8	0.771

Mann-Whitney U test

Table 3. BMI parameters according WHO criteria, Menstrual cycle pattern, Ovarian volume, Number of follicles of group of PCOs patients without insulin resistance and with insulin resistance.

	Group of PCOs patients without insulin resistance n = 50	(%)	Group of PCOs patients with insulin resistance n = 11	(%)	p
BMI (kg/m²):					
• < 18.5	1	2.0	0	0	0.004
• 18.5 - 24.9	39	78.0	3	27.3	
• 25 - 29.9	9	18.0	6	54.5	
• > 30	1	2.0	2	18.2	
Menstrual cycle pattern					
• Amenorrhea	24	48.0	5	47.5	0.878
• Oligomenorrhea	26	52.0	6	52.5	
Ovarian volume					
• < 20	2	4.0	0	0	0.792
• 20 - 29	21	42.0	5	45.5	
• > 30	27	54.0	6	54.5	
Number of follicles					
• 24 - 50	9	18.0	0	0	0.127
• ≥ 50	41	82.0	11	100	

Chi-square test

DISCUSSION

In this study, it was found that group of PCOs patients without insulin resistance was the majority of group (82.0%) compared to group of PCOs patients with insulin resistance (18.0%).

Meirow et al. reported that insulin resistance emerged in 50% of PCOs patients of their study.[18]

Dunaif et al. and Legro et al. in their study reported that the prevalence of insulin resistance varied between 25 - 70% depending on ethnicity and method of diagnosis.[19,20]

Meanwhile, Setiawan in the prior study in Medan reported that the prevalence of insulin resistance was 17.1%.[21]

No significant differences were found in both groups for clinical and biochemical characteristics, except for Body Mass Index (BMI). The BMI in the group of PCOs patients with resistance (27 kg/m^2) was greater compared to BMI in group of PCOs patients without insulin resistance (22.92 kg/m^2).

From the carbohydrate metabolism profile, no significant differences were found in both groups in

mean blood sugar level; group without insulin resistance (84.96 mg/dl) whereas group with insulin resistance (88.18 mg/dl).

Fasting glucose level in the group without insulin resistance ranged from 1.9 μU/ml to 16.5 μU/ml, with mean 7.192 μU/ml. In the group of PCOs patients with insulin resistance, fasting glucose level ranged from 18.8 μU/ml to 43.3 μU/ml. Two subjects had fasting glucose level < 20 μU/ml. Five subjects had fasting glucose level of 20 - 25 μU/ml, while four had levels > 25 μU/ml. Mean fasting glucose level for this group was 24.882 μU/ml. There was a significant difference of two groups using Mann-Whitney U test ($p = 0.001$).

In this study, mean of G:I ratio for the group of PCOs patients without insulin resistance was 15.152. In the group of PCOs patients with insulin resistance, mean of G:I ratio was 3.709. Significant differences were found between the two groups ($p = 0.001$).

Legro et al. in their study predicted insulin resistance in PCOs patients based on fasting glucose level of > 20 μU/ml, whereas Acien et al. and Gennarelli et al. in their studies reported that level of fasting glucose level > 30 μU/ml was usually associated with insulin resistance in PCOs patients.[22-24]

Castracane et al. in their study reported that fasting glucose level > 20 μU/ml in Caucasian women and fasting glucose level > 23 μU/ml in Mexican-American women may indicate insulin resistance in women with PCOs.[25]

Setiawan in his study reported that mean fasting glucose level in insulin resistance group was 25.386 μU/ml and G:I ratio was 3.701.[21]

In the group of PCOs patients with insulin resistance, most of subjects were overweight with BMI 25 - 29.9 kg/m^2 (6 patients; 54.5%). Significant differences were found between two groups, using Chi-square test ($p = 0.004$).

BMI of ≥ 25 kg/m^2 is one of the criteria of the American Association of Clinical Endocrinologists to diagnose insulin resistance.

In Medan, Setiawan reported that most of PCOs patients with insulin resistance (42.9%) had BMI of 25 - 29.9 kg/m^2.[21]

Ferrannini et al. obtained data from the European Group for the Study of Insulin Resistance (EGIR) for the prevalence of hyperinsulinemia dan insulin resistance (IR) according based on BMI as the following: From BMI parameters according to WHO, the prevalence of both hyperinsulinemia and insulin resistance of BMI < 25 kg/m^2 was 10%; BMI 25 - 28 kg/m^2, the prevalence of hyperinsulinemia was 30% while the prevalence of insulin resistance was 12%; BMI 29 - 37 kg/m^2 the corresponding prevalence was 48% and 35%; and BMI > 37 kg/m^2 the corresponding prevalence was 80% and 60%.[4,6]

Holte et al. in their study established that insulin resistance was mostly found in PCOs patients of European women with BMI of 28 kg/m^2 or more.[26]

Based on menstrual cycle pattern, oligomenorrhea was the mostly menstrual pattern in both groups, 26 subjects (52.0%) in the group of PCOs patients without insulin resistance whereas 6 subjects (52.5%) in the group of PCOs patients with insulin resistance. Analysis with Chi-square did not produce any significant difference ($p = 0.839$).

Dunaif et al. and Robinsen et al. reported significant differences of insulin sensitivity between PCOs patients with anovulatory cycles and those with ovulatory cycles. PCOs patients with anovulatory cycles showed insulin resistance while PCOs patients with regular menstrual cycles did not.[19,27]

Abbott et al. concluded that there was a strong correlation between menstrual cycle irregularity and insulin resistance in PCOs women.[28]

Setiawan found that oligomenorrhea menstrual cycle pattern was the most menstrual pattern in PCOs patients without insulin resistance (52.9%) also in PCOs patients with insulin resistance, the prevalence was 57.1%.[21]

Ovarian volume in each study group. Chi-square analysis yielded no significant difference in terms of ovarian volume, with $p = 0.792$. Ovarian volume exceeding 30 ml formed the highest frequency.

The number of follicles from each group. Within the group of PCOs patients with insulin resistance were found 11 subjects (100%) with follicles totaling 50 or more. Meanwhile, in the group without insulin resistance, 41 subjects (82.0%) had 50 or more follicles. Chi-square analysis yielded no significant difference ($p = 0.127$) notwithstanding, there existed a tendency for insulin resistance in PCOs patients with ≥ 50 follicles.

From the reproductive hormone profile of both study groups, an increase of LH/FSH could be appreciated, with the ratio > 1. Mean reproductive hormone profile for both groups did not exhibit any significant differences. This was evidenced by the Mann-Whitney test showing $p > 0.05$.

CONCLUSION

In this study of 61 patients with PCOs utilizing the Glucose Ratio/Fasting Insulin (G:I Ratio) test method, it was found that 11 subjects (18.0%) had insulin resistance whereas 50 subjects (82.0%) did not experience insulin resistance. There was a significant relationship between fasting glucose level with the phenomenon of insulin resistance with mean fasting glucose level at 24.882 μU/ml.

The highest frequency of insulin resistance in this study resided in the group categorized as overweight as per WHO criteria (BMI 25 - 29.9 kg/m^2).

RECOMMENDATIONS

All this while, one of the treatment strategies for PCOs sufferers is the administration of Insulin-sensitizing Agents such as Metformin, Rosiglitazone, and Pioglitazone.

This study clearly demonstrated that the prevalence of insulin resistance in PCOs patients was 18.0%. Therefore evidently not all PCOs patients experiences insulin resistance.

In order to provide accurate treatment to PCOs patients, it is best to perform a G:I ratio test to identify insulin resistance prior to instituting therapy comprising Insulin-sensitizing Agents.

REFERENCES

1. Franks S. Polycystic ovary syndrome [published erratum appears in N Engl J Med 1995 23; 333(21): 1435] [see comments]. N Engl J Med. 1995; 333: 853-61
2. Murizah MZ, Ridzuan J, Adibah I. Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction, achievement of pregnancy, and live birth in Asian women with polycystic ovary syndrome: a randomized controlled trial. Fertil Steril 2009; 91(2): 514-21
3. Zhaolian W, Yunxia C, Lin Cong. Effect of metformin pretreatment on pregnancy outcome of in vitro matured oocytes retrieved from women with polycystic ovary syndrome. Fertil Steril 2008; 90(4): 1149-54
4. Batukan C, Baysal B. Metformin improves ovulation and pregnancy rates in patients with polycystic ovary syndrome. Arch Gynecol Obstet 2001; 265: 124-7
5. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol. 1935; 29: 181-6
6. Rosenfield RL. Current concepts of polycystic ovary syndrome. Bailleres Clin Obstet Gynaecol. 1997; 11: 307-33
7. Achard M, Thiers MJ. Le virilisme pilaire et son association à l' insuffisance glycolytique (diabète des femmes à barbe). Bull Acad Natl Med. 1921; 86: 51-64
8. Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM, Roth J. The syndromes of insulin resistance and acanthosis nigricans. Insulin-receptor disorders in man. N Engl J Med. 1976; 294: 739-45
9. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev. 1997; 18: 774-800
10. Burghen GA, Givens JR, Kitabchi AE. Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. J Clin Endocrinol Metab. 1980; 50: 113-16
11. Pasquali R, Venturoli S, Paradisi R, Capelli M, Parenti M, Melchionda N. Insulin and C-peptide levels in obese patients with polycystic ovaries. Horm Metab Res. 1982; 14: 284-87
12. Chang RJ, Nakamura RM, Judd HL, Kaplan SA. Insulin resistance in nonobese patients with polycystic ovarian disease. J Clin Endocrinol Metab. 1983; 57: 356-59
13. Shoupe D, Kumar DD, Lobo RA. Insulin resistance in polycystic ovary syndrome. Am J Obstet Gynecol. 1983; 147: 588-92
14. Dunaif A, Hoffman AR, Scully RE, Flier JS, Longcope C, Levy LJ, Crowley WF Jr. Clinical, biochemical, and ovarian morphologic features in women with acanthosis nigricans and masculinization. Obstet Gynecol. 1985; 66: 545-52
15. Stuart CA, Peters EJ, Prince MJ, Richards G, Cavallo A, Meyer WJD. Insulin resistance with acanthosis nigricans: the roles of obesity and androgen excess. Metab Clin Exp. 1986; 35: 197-205
16. Dunaif A, Graf M, Mandeli J, Laumas V, Dobrjansky A. Characterization of groups of hyperandrogenic women with acanthosis nigricans, impaired glucose tolerance, and/or hyperinsulinemia. J Clin Endocrinol Metab. 1987; 65: 499-507
17. Lundberg PA. Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long-term follow-up focusing on natural history and circulating hormones. Fertil Steril. 1992; 57(3): 505-13
18. Meirow D, Yossepowitch O, Rosler A. Insulin resistant and non-resistant polycystic ovary syndrome represent two clinical and endocrinological subgroups. Hum Reprod 1995; 10: 1951-56 Bibliographic Links
19. 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
20. Legro RS, Castracane VD, Kauffman RP. Detecting insulin resistance in polycystic ovary syndrome: purposes and pitfalls. Obstet Gynecol Surv. 2004; 59: 141-54
21. Setiawan A. Identifikasi Resistensi Insulin Pada Pasien PCOs Dengan Menggunakan Fasting Glucose/Insulin Ratio (G:I Ratio). Tesis. Departemen Obstetri and Ginekologi Fakultas Kedokteran USU, RSHAM-RSPM: Juni, 2008
22. Legro RS, Finegood D, Dunaif A. A Ratio Glucose/Fasting Insulin is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 1998; 83(8): 2694-98
23. Acien P, Querada F, Matallin P, Villanoya E, Lopez-Femadez JA, Acien M, Mauri M, Alfayate R. Insulin, androgens, and obesity in women with and without polycystic ovary syndrome: a heterogeneous group of disorders. Fertil Steril. 1999; 72: 32-40
24. Gennareli G, Holte J, Berglund L, Berne C, Massobrio M, Lithell H. Prediction models for insulin resistance in the polycystic ovary syndrome. Hum Reprod. 2000; 15: 2098-2102
25. Castracane VD, RP Kauffman. (Jan 1, 2003) Controlling SOPK, Part 1: Assessing insulin sensitivity. Contemporary OG/GYN
26. Holte J, Bergh T, Gennarelli G, Wide L. The independent effects of polycystic ovary syndrome and obesity on serum concentrations of gonadotrophins and sex steroids in premenopausal women. Clin Endocrinol. 1994; 41: 473-81
27. Robinson S, Kiddy D, Gelding SV. The relationship of insulin insensitivity to menstrual pattern in women with hyperandrogenism and polycystic ovaries. Clin Endocrinol. 1993; 39: 351-55
28. Abbott DH, Dumesic DA, Franks S. Developmental origin of polycystic ovary syndrome - a hypothesis. J Endocrinol. 2002; 174: 1-5