

A Review on Polycystic Ovarian Syndrome in Relation to Insulin Resistance Pathogenesis

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Abstract: Polycystic ovary syndrome PCOS is considered a multifactorial disorder with various genetic, metabolic, endocrine and environmental abnormalities. In women with PCOS, insulin resistance (IR) is very common which is also related to obesity and weight gain. A literature survey was done using different search engines and databases such as and Google Scholar, PUBMED, NCBI to prepare a narrative review on this topic. PCOS is a most common endocrine disorder prevailing in reproductive age women across the world. The current review has highlighted the role of insulin resistance in the development and the pathogenesis of the disease. Hyperinsulinemia and hyperandrogenemia are two principle factors of PCOS and their cause and effect is still vague. Based on the various data, a positive correlation was also observed between oxidative stress and insulin resistance.

Key words: Insulin Resistance • Hyperinsulinemia • HOMA • BMI • Hyperandrogenemia

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a heterogeneous endocrine disorder differentiated by the expression of ovarian cysts, anovulation and endocrine variation that impact the life of a woman severely. According to data provided by the World Health Organization (WHO), over 116 million women (3.4%) are affected by PCOS all over the world. Hyperandrogenism, oligo-anovulation and polycystic morphology of at least one ovary lead to PCOS. A significant role is played by Insulin resistance (IR), hyperinsulinemia and associated metabolic abnormalities including metabolic syndrome in the development of PCOS. Increased insulin resistance (IR) is an important feature in PCOS and may play a pathogenesis role [1]. Elevated levels of insulin secretion result in weight gain, inflammation and may lead to chronic heart diseases and Type 2 Diabetes [2]. The manifestations of PCOS are not confined only to the gynecological pattern, but women suffering from this syndrome show an increased rate of various co-morbidities such as obesity, hypertension, metabolic

syndrome (MS), dyslipidemia and type 2 diabetes mellitus (DM2) compared compared to women without PCOS. These characteristics, along with other alterations such as endothelial dysfunction and a chronic low-grade inflammatory state, may possibly trigger the risk of developing cardiovascular disease and increased mortality rate [3].

Although the etiology of PCOS is not completely understood yet, the disease is considered a diversified disorder through various genetic, metabolic and endocrine aspects [4]. There is increasing evidence suggesting that the lifestyle of a person also goes hand in hand as it also has a major impact on the etiology of the disease [5]. Hence the current review is focused on the role of insulin resistance (IR), variability of IR in PCOS and also to investigate the association between IR and the different clinical and para-clinical characteristics comprised in the diagnostic criteria for PCOS.

Insulin Resistance and Genetic Elements in PCOS: Insulin resistance (IR) is defined as a decrease in insulin-mediated glucose utilization, commonly (10-25%)

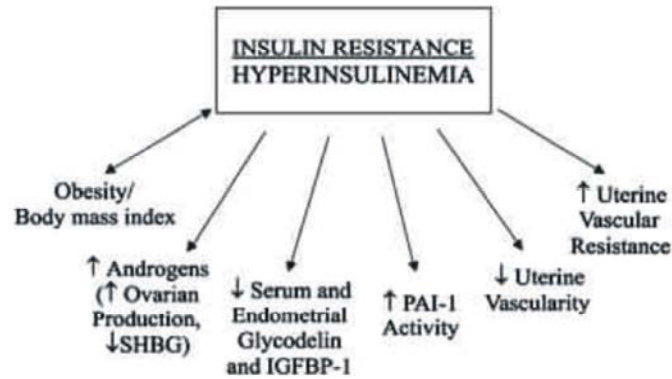


Fig. 1: Effects of hyperinsulinemia

found in the normal population. In both obese as well as lean women affected with PCOS, IR appears even more common up to 50%. The major pathogenic role in androgen production is played by hyperinsulinemia because of the stimulatory effect of insulin on ovarian steroid production [6]. High insulin is a major driver of the condition which leads to impairment of ovulation to produce excess testosterone. It is noticed that the elevation in the rate of PCOS correlates with an increase in obesity and weight gain over the last ten years [4].

In PCOS patients, the frequency of IR and Type 2 Diabetes suggests that impaired glucose tolerance (IGT) is present in 31-35% of women. According to the Third National Health and Nutrition Examination Survey in US, women of similar age without PCOS had a prevalence of IR at 1.6% and diabetes mellitus at 2.2%. In patients with PCOS, imbalance of sex hormone levels leads to hyperinsulinemia, hirsutism and acne problems and this case is more common in obese women with PCOS. It is important to know that non-obese PCOS patients may also have IR, which advocates that insulin plays a major role in the pathogenesis of this disease [7]. Several shreds of evidence suggest that hyperinsulinemia is the primary factor contributing to ovarian hyper-androgenemia as shown in Figure 1 [8].

The most probable risk factor for the development of Type 2 diabetes in women with PCOS is IR in skeletal muscles. In these patients, various abnormalities are associated with IR such as insulin signaling, fatty acid metabolism and mitochondrial oxidative phosphorylation. IR relation with PCOS was further studied based on gene expression studies. Skov *et al.* [6], in their study using two different approaches of global pathway analysis like gene set enrichment analysis (GSEA 1.0), map annotator and pathway profiler (GenMAPP 2.0) which helps to identify the expression of genes in the skeletal muscles.

These resulted in the decreased levels of peroxisome-proliferator-activated receptor gamma. Co-activator alpha (PGC-1alpha) plays a role in the down-regulation of OXPHOS genes in PCOS. Further, it was concluded that obesity and diabetes cannot show reciprocity based on a decrease in OXPHOS gene expression in skeletal muscles. Therefore, the hypothesis of an early association between IR and impaired mitochondrial oxidative metabolism; which is in part mediated by reduced PGC-1alpha levels was confirmed. Moreover, the data indicated that transcriptional alterations in the insulin signaling pathway, fatty acid metabolism and calcium homeostasis may contribute to the potentially unique phenotype of IR in women with PCOS [6].

Effect of diet on PCOS was monitored and showed that intake of macronutrients (proteins, carbohydrates and total fat) and omega-3 PUFA's was higher in the PCOS group as compared to the control group.

The PCOS group had significantly high resolvin D1 (Resolvin D1 is involved in insulin sensitivity by affecting insulin signaling and inflammatory pathways.), fasting insulin, glucose levels and HOMA (Homeostatic model assessment) as compared to control group. Thus IR associated with omega-3 PUFA's can increase the synthesis of resolvin D1. Therefore it can be a contributing factor in reducing IR in PCOS patients [7]. Research conducted by Fatima *et al.* [9] on PCOS patients who had poor antioxidant status as reflected by low levels of glutathione, vitamin C and E and considerably higher activities of antioxidant enzymes like glutathione peroxidase, glutathione reductase and glutathione-s-transferase as compared with control; with showing with showing a positive correlation between oxidative stress and insulin levels in patients. Low levels of antioxidants and increased oxidative stress with IR along with the observed correlation between these parameters propose

that oxidative stress is involved in the pathophysiology of PCOS. Thus, oxidative stress could be a contributory factor to future cardiovascular disease in women in addition to known features like dyslipidemia or central obesity [10, 11].

The nitrotyrosine expression in VAT (visceral adipose tissue) was stronger in PCOS patients. In adipose tissue, a strong correlation of insulin resistance with oxidative stress at the VAT level was established, local oxidative stress and abnormalities of insulin signaling play critical roles in the PCOS pathogenesis [12]. Insulin variable number tandem repeat (VNTR) polymorphism does not increase the risk of PCOS. However, insulin VNTR class III allele is associated with an increase in body mass index (BMI) and homeostatic model assessment- insulin resistance (HOMA-IR) suggesting its function in the pathogenesis of IR and obesity in women with PCOS [13]. There is a higher tendency of occurrence of hyperhomocysteinemia, hyperinsulinemia and also higher BMI in PCOS patients. These factors are critical predictors of PCOS; however, BMI and IR are independent risk factors to increase plasma Hcy (homocysteine) levels in PCOS women [14].

In women with PCOS, angiotensin-converting enzyme (ACE) insertion (I) or deletion (D) gene polymorphism occurs frequently and an attempt was made to determine the association of this polymorphism with IR. The ACE DD genotype was appreciably associated with serum

insulin concentration and measurement of HOMA-IR. ACE DD genotype was found to be associated with increased IR in women with PCOS [15].

On variable logistic regression analysis, increased HOMA-IR was found to be associated with a 2.3-fold increased odd of depression. This association continued to stay significant after controlling for age, BMI and in a model including additional potential confounders. This suggests that IR has a strong independent association with mental depression and may serve as a physiologic mediator. Findings corroborate a piece of sufficient evidence linking IR to depressed mood. The association between IR and depressed mood warrants further investigation to elucidate mechanisms and identify potential therapeutic targets [16].

Obesity, BMR, Mood Swings and IR: PCOS and obesity boast a high concern issue. It has to be noted that insulin resistance (IR) is the fundamental link associating these conditions even though IR may be present in non-obese PCOS women also [2] as body fat percentage seems to be a good indication for IR in patients with normal BMI and without endocrine co-morbidities [16, 17]. For example, in a study on obese adolescent females, it was noticed that obese girls with Hepatic steatosis have suffered multi-tissue IR, visceral adiposity, inflammation and metabolic syndrome multiple components as shown in Figure 2.

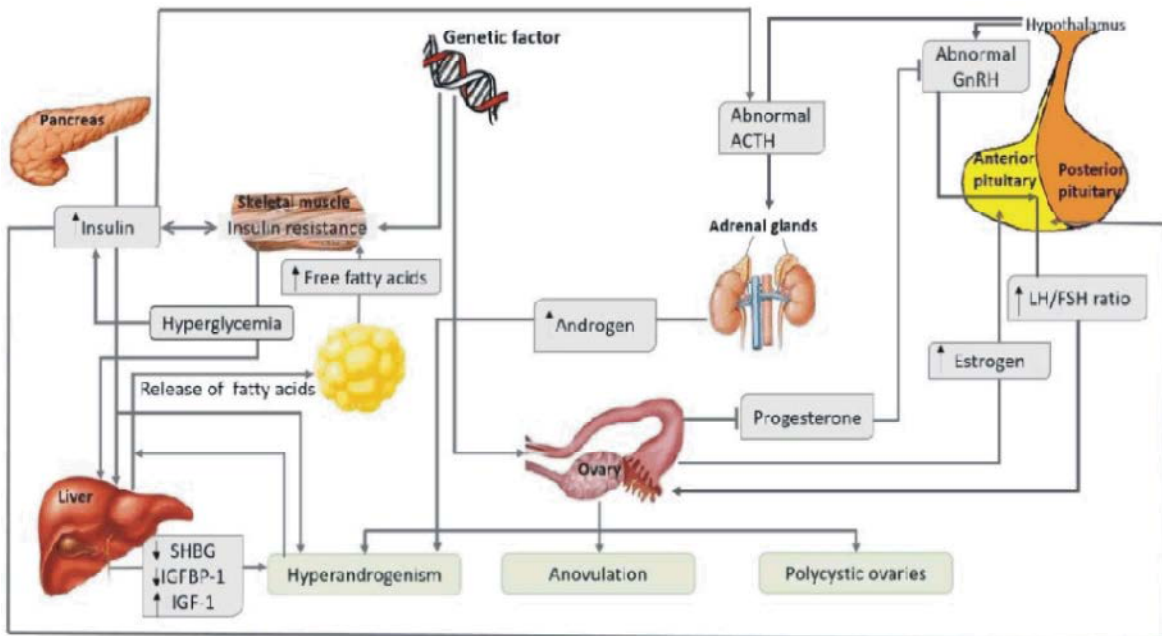


Fig. 2: Organ level effects of insulin resistance in pcos

There are defects in insulin secretion that are independent of obesity. They are more pronounced in women with PCOS who have a first-degree relative with type 2 diabetes. In PCOS, basal insulin secretion is increased, but insulin responses to glucose are inappropriately low [18]. There is a relationship between insulin secretion and glucose tolerance known as disposition index and under normal circumstances, the relation between insulin secretion and sensitivity is constant so that changes in insulin sensitivity are accompanied by reciprocal changes in insulin secretion that maintain normal glucose tolerance. The disposition index in both obese and non-obese women with PCOS is lower compared to eight-matched reproductively normal women [19].

In the non-obese PCOS patients, insulin resistance is not correlated with a more prominent response to stimulation by adrenocorticotropic hormone (ACTH). The pathogenesis and management of PCOS in non-obese patients may be different from those in obese patients [20, 21]. One more finding by Gandevani *et al.* [22] and Cupisti *et al.* [23] suggested that WHtR (waist to height ratio) was a good predictor of IR and MS (metabolic syndrome) among PCOS and healthy women than ABSI. WHtR can be recommended as a screening tool for IR and MS risk assessment among PCOS women as it is considered an inexpensive, non-invasive, simple to assess and easy to calculate measurement tool. A comparative study in obese and lean women with PCOS by Ardawi and Rouzi [21] concluded that hypoadiponectinemia and varying degrees of IR or other metabolic abnormalities of PCOS are involved in the regulation of adiponectin concentration in women with PCOS.

IR is primarily seen in PCOS which marks the importance of dyslipidemia, a decrease in antioxidant vitamins and oxidative stress may be a cause for progressive polycystic ovary syndrome [23]. Women with PCOS, mainly those with IR, contain a significantly decreased BMR [24]. IR has been detected in 80% of women with PCOS and 95% of obese women. The detection of IR is better using the calculated indices HOMA and QUICKI (quantitative insulin-sensitivity check index) [25, 26]. Young lean women with PCOS and IR do not have evidence of NAFLD (non-alcoholic fatty liver disease). But due to the presence of IR, follow-up is required to determine whether these women with PCOS are at the risk of developing NAFLD [27]. The young women with PCOS had a prominent increase in the rate of IR without clinical findings of metabolic disorders or obesity. The HMW (high molecular weight) adiponectin levels were negatively related with IR [26].

Teens who are at a higher risk of developing PCOS showed elevated levels of adiposity and 17-hydroxy progesterone (17-OHP) respectively, but are mainly specified by global IR and resistance to insulin-induced suppression of lipolysis that was independent of adiposity and 17-OHP levels. Therefore, genetic predisposition to PCOS may be related with early IR and adipocyte dysfunction [28].

Obese but not normal-weight PCOS women have lower adiponectin levels whereas resistin concentration did not differ in normal weight and obese PCOS compared to control subjects. It can be hypothesized that the changes are in the relative proportion of adiponectin to resistin, but not circulating adiponectin and resistin levels themselves may have a say in hormonal disturbances but not in insulin resistance in PCOS [29]. Obese and non-obese PCOS women when compared with their age- and BMI-matched controls were metabolically worse and had more visceral adiposity. Non-obese PCOS women pose similar risk to obese PCOS women in having a similar amount of VAT (corrected for body weight) with the risk of development of metabolic complications. Non-obese PCOS should be managed on similar lines as that of obese PCOS for the prevention of metabolic complications in the future [30]. Amongst different abdominal fat compartments, subcutaneous abdominal fat had the strongest association with IR in Indian women with PCOS. Studies to confirm these findings and elucidate the role of subcutaneous fat in IR in PCOS are warranted [31].

Obesity Treatment Effect on PCOS: Obesity is associated with adverse pregnancy outcomes in the larger population, pregnancy complications within PCOS. According to the study performed by Boomsma *et al.* [19], one meta-analysis that looked at pregnancy in women with PCOS and adjusted for differences in obesity in women with PCOS did note increased rates of gestational hypertension, gestational diabetes, preterm labor and infant mortality among women with PCOS.

There are multiple methods in the treatment of obesity in PCOS conditions. A lifestyle change, alterations in diet and increases in physical activity; pharmaceutical treatments that may have some mitigating effects on weight, such as metformin; antiobesity drugs; and finally bariatric surgery. But there are limitations for most of these methods in terms of long-term conformity and maintenance of weight with perhaps the exception of bariatric surgery [32].

Hormones and Proteins Affecting IR in PCOS: Leptin: adiponectin (L:A) ratio may be one of the potential

biomarkers for metabolic syndrome and insulin resistance which is independent of the presence of PCOS disease [20]. Adolescent girls with PCOS and IR are more hirsute and have more acanthosisnigricans (AN) and lower sex hormone-binding globulin (SHBG) and higher fasting insulin levels compared to non-insulin resistant girls [25]. In an experiment, PCOS patients had significantly higher fasting, 1-hour and 2-hour insulin levels and a significantly lower insulin sensitivity index compared with FtMs (female-to-male transsexuals) before and after their T (testosterone) treatment. Higher triglyceride levels and lower HDL cholesterol levels were noted upon T treatment in FtMs compared with the PCOS women. Women suffering from PCOS had increased BMI values. Positive correlations were observed between IR indices and BMI only in women with PCOS. Testosterone administration by itself resulted in little detrimental effects on insulin resistance indices but had a significant influence on lipid profiles. Compared with T, BMI had a greater impact on IR in women with PCOS [24]. Higher concentrations of Luteinizing Hormone (LH) in the phenotypes of PCOS could be ascribed to the higher androgen levels, which stop the hypothalamus from negative feedback regulation by progesterone. Also, the lower LH levels in obese and overweight women of various groups could be ascribed to the increased peripheral aromatization of androgens to estrogens in adipose tissue leading to suppression of secretion of LH [33].

Women with PCOS have greater genomic instability (higher micronuclei and chromosome mis-segregation) as compared to women without PCOS and this increase may be related to the insulin resistance phenotype [34].

Boons to the Effects of IR in PCOS: According to Wu *et al.* [12], acupuncture may improve HOMA-IR, ISI (insulin sensitivity index), FBG (fasting blood glucose) and FINS (fasting insulin) with fewer adverse effects than other treatments, making it bearable for IR.

Short-term exenatide treatment carries a greater efficiency in terms of weight loss, improvement in insulin resistance and reducing inflammation than metformin. However, long-term clinical trials based on large samples are needed to assess exenatide's efficacy and safety in overweight women with PCOS [19].

In females with PCOS and IR, the reduction of hyperinsulinemia which is produced by troglitazone; improves the hyperandrogenism that is one of the features of PCOS, restoring ovulation [31].

Despite several common conditions such as diabetes, IR and MetS have been seen in non-PCOS obese women, the treatment options available for them did not necessarily work effectively in PCOS women because of the complexity of the disease. Moreover, women's age is taken into consideration as one of the factors in predicting pregnancy rate [35]. Typical insulin-sensitizing drugs such as metformin, have been tried to curtail IR and hyperinsulinemia in pregnant PCOS women, with varying results indicating the complexity of the disease and the need for better-controlled studies and additional efforts for PCOS specific drug discovery [36].

Women with type 2 diabetes mellitus (T2DM) were as metabolically inflexible as women with PCOS. When stratifying women with PCOS into those who are metabolically flexible and inflexible, the women who are inflexible display greater amounts of visceral fat and excess androgen. The inability to alter substrate use given the physiological stimulus may lead to subsequent increases in adiposity in women with PCOS thereby further worsening insulin resistance [37].

Women with PCOS and normal glucose tolerance showed higher IR than controls matched for age, BMI and α -cell function. The β -cell function was increased in women with PCOS when compared to the matched controls but not when the lean subjects were compared to the matched controls separately. Therefore, early evaluation of IR in women with PCOS and normal glucose tolerance may be needed [38]. In a research study conducted by Montazerifar *et al* [39], on PCOS women, showed that leptin and adiponectin association with BMI and waist circumference. The studies concluded that there is significantly high levels of leptin and reduction in adiponectin levels of PCOS women compared to controls

CONCLUSION

The overall aim of this review was to highlight the relationship of insulin resistance with the pathogenesis of polycystic ovarian syndrome. It is very clear from the review that PCOS is a multifactorial disorder and alone targeting the insulin resistance mechanism is not going to work feasibly. Further studies in PCOS could possibly develop a personalized therapy or medicine for PCOS women with type 2-diabetes and insulin resistance mechanism. Improving the lifestyle, regulating the hormonal imbalance in women and developing specific site targeted drugs probably may help to understand and cure the disease in future.

REFERENCES

1. Jayagopal, V., E.S. Kilpatrick, S. Holding, P.E. Jennings and S.L. Atkin, 2002. The Biological Variation of Insulin Resistance in Polycystic Ovarian Syndrome. *The Journal of Clinical Endocrinology and Metabolism*, 87: 1560-1562.
2. Toprak, S., A. Yöner, B. Çakır, S. Güler, O. Azal, M. Özata and A. Çorakçı, 2001. Insulin resistance in nonobese patients with polycystic ovary syndrome. *Hormone Research in Paediatrics*, 55: 65-70.
3. Vaidya Atreya, E. Smith. (n.d.). Retrieved from <http://www.atreya.com/ayurveda/Polycystic-Ovary-Syndrome-An.html>.
4. The link between PCOS and insulin resistance. (2018, September 3). Retrieved from <https://helloclue.com/articles/cycle-a-z/the-link-between-pcos-and-insulin-resistance>.
5. Steven, R.L. and L. Whigham, 2012. Polycystic ovary syndrome: How are obesity and insulin resistance involved?, 24(10): OBG Management.
6. Vibe, Skov, D. Glinborg, S. Knudsen, T. Jensen, T.A. Kruse, Q. Tan, K. Brusgaard, H. Beck-Nielsen and K. Højlund, 2007. *Diabetes*, 56: 2349-2355.
7. Mukherjee, S. and A. Maitra, 2010. Molecular & genetic factors contributing to insulin resistance in polycystic ovary syndrome. *Indian Journal of Medical Research*, 131: 743-60.
8. Morshedzadeh, N., A. Saedisomeolia, M. Djalali, M.R. Eshraghian, S. Hantoushzadeh and M. Mahmoudi, 2019. Resolvin D1 impacts on insulin resistance in women with polycystic ovary syndrome and healthy women. *Diabetes & Metabolic Syndrome: Clinical Research and Reviews*, 13: 660-664.
9. Fatima, Q., S. Amin, I.A. Kawa, H. Jeelani, S. Manzoor, S.M. Rizvi and F. Rashid, 2019. Evaluation of antioxidant defense markers in relation to hormonal and insulin parameters in women with polycystic ovary syndrome (PCOS): A case-control study, *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, 13: 1957-1961.
10. Chen, L., W.M. Xu and D. Zhang, 2014. Association of abdominal obesity, insulin resistance and oxidative stress in adipose tissue in women with polycystic ovary syndrome, *Fertility and Sterility*, 102: 1167-1174.
11. Braga, L.D.C., F. Amelio, Godoy-Matos, P.O. Siciliano, J.O.A. Corrêa and D.P. Carvalho, 2018. Is DPP4 activity increased in PCOS?, *Diabetes & Metabolic Syndrome: Clinical Research and Reviews*, 12: 673-675.
12. Liqun, Wu., X. Chen, Y. Liu, J.L.C. Wu, Z. Li, L. Lu and W. Yi, 2019. Role of acupuncture in the treatment of insulin resistance: A systematic review and meta-analysis, *Complementary Therapies in Clinical Practice*, 37: 11-22.
13. Rasool, S.U.A., S. Ashraf, M. Nabi, F. Rashid, S.R. Masoodi, K.M. Fazili and S. Amin, 2019. Insulin gene VNTR class III allele is a risk factor for insulin resistance in Kashmiri women with polycystic ovary syndrome. *Meta Gene*, 21: 2214-5400.
14. Esmaeilzadeh, S., E. Tahmasbpour and M. Gholinezhad-Chari, 2017. Hyperhomocysteinemia, insulin resistance and body mass index in Iranian young women with polycystic ovary syndrome. *Middle East Fertility Society Journal*, 22: 149-155.
15. Celik, O., E. Yesilada, S. Hascalik, N. Celik, I. Sahin, L. Keskin and E. Ozerol, 2010. Angiotensin-converting enzyme gene polymorphism and risk of insulin resistance in PCOS. *Reproductive Bio Medicine Online*, 20: 492-498.
16. Greenwood, E.A., A.L. Pasch, M.I. Cedars, R.S. Legro, E. Eisenberg and H.G. Huddleston, 2018. Insulin resistance is associated with depression risk in polycystic ovary syndrome. *Fertility and Sterility*, 110: 27-34.
17. Giovanna, Muscogiuri, Caterina Policola, Annamaria Prioletta, Gian Pio Sorice, Teresa Mezza, Annapia Lassandro, Silvia Della Casa, Alfredo Pontecorvi and Andrea Giaccari, 2012. Low levels of 25(OH)D and insulin-resistance: 2 unrelated features or a cause-effect in PCOS?. *Clinical Nutrition*, 31: 476-480.
18. Dunaif, A., 1999. Insulin action in the polycystic ovary syndrome. *Endocrinology Metabolic Clinical North*, 28: 341-359.
19. Boomsma, C.M., M.J. Eijkemans, E.G. Hughes, G.H. Visser, B.C. Fauser and N.S. Macklon, 2006. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Human Reproduction Update*, 12: 673-683.
20. Naderpoor, N., S. Shorakae, S.K. Abell, A. Mousa, A.E. Joham, L.J. Moran, N.K. Stepto, P.M. Spritzer, H.J. Teede and B. De Courten, 2018. Bioavailable and free 25-hydroxyvitamin D and vitamin D binding protein in polycystic ovary syndrome: Relationships with obesity and insulin resistance. *The Journal of Steroid Biochemistry and Molecular Biology*, 177: 209-215.
21. Ardawi, M.S.M. and A.A.A. Rouzi, 2005. Plasma adiponectin and insulin resistance in women with polycystic ovary syndrome. *Fertility and Sterility*, 83: 1708-1716.

22. Behboudi-Gandevani, S., F. Ramezani Tehrani, L. Cheraghi and F. Azizi, 2016. Could “a body shape index” and “waist to height ratio” predict insulin resistance and metabolic syndrome in polycystic ovary syndrome? *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 205: 110-114.
23. Cupisti, S., E.J. Giltay, L.J. Gooren, D. Kronawitter, P.G. Oppelt, M.W. Beckmann, R. Dittrich and A. Mueller, 2010. The impact of testosterone administration to female-to-male transsexuals on insulin resistance and lipid parameters compared with women with polycystic ovary syndrome, *Fertility and Sterility*, 94: 2647-53.
24. Gupta, V.S. Mishra, S. Mishra and V. Gupta, 2017. L:A ratio, Insulin resistance and metabolic risk in women with polycystic ovarian syndrome. *Diabetes & Metabolic Syndrome: Clinical Research and Reviews*, 11: S697-S701.
25. Neoklis, A. Georgopoulos, Alexandros D. Saltamavros, Vasiliki Vervita, Kyriakos Karkoulis, George Adonakis, George Decavalas, George Kourounis, Kostas B. Markou and Venetsana Kyriazopoulou, 2009, Basal metabolic rate is decreased in women with polycystic ovary syndrome and biochemical hyperandrogenemia and is associated with insulin resistance, *Fertility and Sterility*, 92: 25-5.
26. Carmina, E. and R.A. Lobo, 2004. Use of fasting blood to assess the prevalence of insulin resistance in women with polycystic ovary syndrome, *Fertility and Sterility*, pp: 661-5.
27. Cankaya, S., B. Demir, S.E. Aksakal, B. Dilbaz, C. Demirtas and U. Goktolga, 2014. Insulin resistance and its relationship with high molecular weight adiponectin in adolescents with polycystic ovary syndrome and a maternal history of polycystic ovary syndrome, *Fertility and Sterility*, 102: 826-830.
28. Magdalena Olszanecka-Glinianowicz, Dorota Kuglin, Anna Dąbkowska-Huć and Piotr Skalba, 2011, Serum adiponectin and resistin in relation to insulin resistance and markers of hyperandrogenism in lean and obese women with polycystic ovary syndrome, *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 154: 57.
29. Ilias Katsikis, Artemis Karkanaki, Georgios Misichronis, Dimitrios Delkos, Eleni A. Kandaraki, Dimitrios Panidis, 2011. Phenotypic expression, body mass index and insulin resistance in relation to LH levels in women with polycystic ovary syndrome, *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 156: 181-185.
30. Magdalena Olszanecka-Glinianowicz, Dorota Kuglin, Anna Dąbkowska-Huć, Piotr Skalba, 2011. Serum adiponectin and resistin in relation to insulin resistance and markers of hyperandrogenism in lean and obese women with polycystic ovary syndrome, *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 154: 57.
31. Isao Hasegawa, Haruo Murakawa, Mina Suzuki, Yasuaki Yamamoto, Takumi Kurabayashi and Kenichi Tanaka, 2006. Effect of troglitazone on endocrine and ovulatory performance in women with insulin resistance-related polycystic ovary syndrome. *Fertility and Sterility*, 71: 323-327.
32. Samira Behboudi-Gandevani, Fahimeh Ramezani Tehrani, Leila Cheraghi and Fereidoun Azizi, 2016. Could “a body shape index” and “waist to height ratio” predict insulin resistance and metabolic syndrome in polycystic ovary syndrome? *European Journal of Obstetrics and Gynecology and Reproductive Biology*, 205: 110-114.
33. Susanne Cupisti, Erik J. Giltay, Louis J. Gooren, Desiree Kronawitter, Patricia G. Oppelt, Matthias W. Beckmann, Ralf Dittrich and Andreas Mueller, 2010. The impact of testosterone administration to female-to-male transsexuals on insulin resistance and lipid parameters compared with women with polycystic ovary syndrome. *Fertility and Sterility*, 94: 2647-2653.
34. Bhattacharya, S.M. and M. Ghosh, 2010. Insulin Resistance and Adolescent Girls with Polycystic Ovary Syndrome, *Journal of Pediatric and Adolescent Gynecology* 23: 158-161.
35. Jami, N.W. and S.A.A. Kadir, 2017. Prediction of pregnancy for assisted reproductive technology: A case study on intracytoplasmic sperm injection. *World Journal of Medical Sciences*, 14: 17-21.
36. Dunaif, A., K.R. Segal, W. Futterweit and A. Dobrjansky, 1989. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes*, 38: 1165-1174.
37. Lisa J. Moran, Manny Noakes, Peter M. Clifton, Robert J. Norman and Michael F. Fenech, 2007. Genome instability is increased in lymphocytes of women with polycystic ovary syndrome and is correlated with insulin resistance. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 639: 55-63.

38. Melanie Cree-Green, Sonalee Ravi, Anne-Marie Carreau, Rachel Sewell, Amy Baumgartner, Gregory Coe, Bryan C. Bergman, Ann Scherzinger, Thomas Jensen, Laura Pyle and Kristen J. Nadeau, 2019. Nonalcoholic fatty liver disease in obese adolescent females is associated with multi-tissue insulin resistance and visceral adiposity markers. *Metabolism Open*, 2: 100011, ISSN 2589-9368.
39. Montazerifar, F., M. Karajibani, M. Ghasemi, F.K. Rouz, F.A. Hosseini and N. Bagheri, 2016. Evaluation of association between serum leptin and adiponectin levels with obesity markers, Lipid profile and hormonal parameters in women with polycystic ovary syndrome, *Middle-East Journal of Scientific Research*, 24: 484-490.