The Egyptian Journal of Hospital Medicine (July 2018) Vol. 72 (2), Page 4005-4011

Role Of Insulin Like Growth Factor in Polycystic Ovary Syndrome

Magdi A. Laban[1], Tarek A. Shemais[2], Ehab Mohamed Elhelw[3] and Ahmed R. El-Hassanin[2]

[1]Department of Medical Biochemistry, Faculty of Medicine, Cairo, [2]Department of Medical Biochemistry, Faculty of Medicine, Damietta, [3]Department of Obstetrics and Gynecology, Faculty of Medicine, Damietta, Al-Azhar university, Egypt.

Corresponding author: Ahmed Ramadan el-Hassanin, **Tel:** 00201001574914, **E-mail address:** Medodoc2017@ azhar.edu.eg.

ABSTRACT

Objectives: The polycystic ovary syndrome (PCOS) is conventionally defined as a combination of hyperandrogenism and anovulation with polycystic ovaries. Insulin-like growth factor I (IGF-I) is a 70 aa polypeptide hormone with endocrine, paracrine, and autocrine effects. it is now established that the ovary is a site of IGF-I gene expression and reception. However, this huge amount of data could be somehow distractive since different species may produce distinct IGFs (or their relative binding proteins and receptors) at different stages of follicular development.

Objective: The aim of this work was to determine the serum level of IGF-I to evaluate its role in PCOS.

Subjects and Methods: Twenty-five infertile women with PCOS diagnosed by ultrasound examination and a history of oligomenorrhea, hirsutism and obesity were studied. Serum levels of insulin-like growth factor-1 (IGF-1) and hormonal profile were measured. Fifteen healthy and fertile women with regular menstrual cycles served as a comparison group.

Results: The serum levels of IGF-I were significantly elevated in women with PCOS compared with control and there was positive correlation between IGF-I from one side and each of BMI, W/H ratio, LH, LH/FSH ratio, TSN, T/SHBG ratio, right and left ovarian volumes. On the other side, IGF-I was inversely correlated with SHBG, right and left uterine artery PI and RI.

Conclusion: The significant finding of this study is that PCOS patients have increased circulating IGF-I levels than healthy controls and it can be used as a biochemical marker for PCOS.

Keywords: Insulin-like growth factor; Polycystic ovary syndrome, Hormonal profile.

INTRODUCTION

PCOS is a diagnosis of exclusion and the conditions which are similar to PCOS either biochemically or clinically should be excluded such as thyroid dysfunction, hyperprolactinemia, Cushing's syndrome and virializing tumors. Until now insulin resistance and cardiometabolic features are not actually part of PCOS diagnostic criteria and this is due to deficiency of the accurate methods for measurement of insulin resistance [1]. PCOS is the most common endocrinopathy in women of the reproductive age and it can be detected in early adolescence. The prevalence of PCOS ranging from 4% to 8% previously [2] but later the prevalence increased due to the use of different diagnostic criteria and might reach to 18% [3]. Insulin resistance represents about 50% to 80% in the pathophysiology in women with PCOS especially in those with severe PCOS who are overweight [4]. Insulin-like growth factor I (IGF-I) is a 70 aa polypeptide hormone with endocrine, paracrine and autocrine effects. It shares >60% homology with IGF-II and by 50% homology with proinsulin structures [5]. Most of IGF-I actions are mediated through the union of IGF-I to its putative receptor, IGF-IR, a tyrosine kinase that is one of the most potent natural activators of Akt pathway [6]. However, IGF-I can also bind to the insulin receptor (with a lower affinity), as a secondary effect through which this hormone mediates some of its metabolic functions [7] due to their high homology. Complementarily, insulin can also bind to IGF-IR with a lower specificity than insulin receptor. The involvement of the IGF system as intraovarian regulators of folliculogenesis has been intensively studied in a variety of mammalian species, and it is now established that the ovary is a site of IGF-I gene expression and reception [8]. In brief, GH enhances the development of small antral follicles to the gonadotrophin-dependent stages and stimulates oocyte maturation, whereas IGFs increase granulose cell proliferation, steroidogenesis and oocyte growth in most mammalian species [9].

The aim of this work was to determine the serum level of IGF-I to evaluate its role in PCOS.

SUBJECTS AND METHODS

This study included a total of 25 women with polycystic ovary and 15 women as a control with normal ovaries, attending at Obstetrics and Gynecology Department, New Damietta Faculty of Medicine -Al Azhar University. Approval of the ethical committee and a written informed consent from all the subjects were obtained. This study was conducted between July 2017 to January 2018.

The study subjects were divided into two groups:

Group I: Twenty-five women with PCOS, having PCO on ultrasound examination and a history of anovulatory menstrual cycles and/or oligomenorrhea, with or without hirsutism, acne and obesity and/or elevated serum LH and/or elevated serum androgen concentrations, who did not receive any treatment for at least 3 months.

Received:28/4/2018
Accepted:7/5/2018

Group II: Fifteen women with normal ovary and had regular ovulatory menstrual cycles and normal ovaries as demonstrated on base line ultrasound examination.

Exclusion criteria: Subjects suffering from any systemic disease like diabetes mellitus, hypertension, cardiovascular system diseases, and renal dysfunction. Obese subjects with BMI >35 kg/m^2. Smokers

Both patients and controls were subjected to: Full history taking, full clinical examination and abdominal sonography. **The following investigations:** Serum insulin like growth factor 1 (IGF1) concentration. Hormonal assays which included FSH, LH, basic Estradiol (E2), Total Testosterone and SHBG. Liver function tests: Albumin, alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP). Renal function tests: Blood urea nitrogen (BUN) and serum creatinine. Complete blood picture (CBC)

Statistical analysis:

SPSS (Statistical Package for the Social Sciences; Version 24.0, Chicago, IL) was used for all statistical analyses. Mean value and standard deviation were calculated using descriptive statistics. Comparison between groups was carried out by Student's t-test (for continuous and normally distributed data), and differences were considered statistically significant if $p < 0.05$. The Pearson's correlation test was used for regression analysis to correlate two normally distributed continuous sets of data.

Table (1) shows means and standard deviation of age, weight, height, body mass index (BMI), Waist/hip ratio and parity of studied females and there were significant increase of weight, BMI, Waist/hip ratio and parity in PCOS when compared to control group.

Table (2) shows means, standard deviation and P value of FSH, LH, FSH/LH ratio, TSN, Estradiol, SHBG and T/SHBG ratio of studied females and there was significant increase of LH, LH/FSH ratio, TSN, SHBG and T/SHBG ratio in PCOS when compared to control group.

Table (3) shows means, standard deviation and P value of Ultrasound and Doppler indices in studied females there was statistically significant increase of both right and left ovarian volumes in PCOS when compared to control group. On the other side, there was statistically significant decrease of both right and left pulse index (PI) and resistance index (RI) in PCOS when compared to control group.

Table (4) shows means, standard deviation and P value of IGF-I in studied females and there was statistically significant increase in PCOS when compared to control group.

Table (5) shows Correlation between IGF-I and other parameters in studied females and there was positive (proportional) correlation between IGF-I from one side and each of BMI, W/H ratio, LH, LH/FSH ratio, TSN, T/SHBG ratio, right and left ovarian volumes. On the other side, IGF-I was inversely (negatively) correlated with SHBG, right and left uterine artery PI and RI.

RESULTS

Table (1): Shows age, weight, height, body mass index (BMI), Waist/hip ratio and parity in studied groups.

	Age (years)	**Weight (Kg)**	**Height (M)**	**BMI (kg/m^2)**	**Waist/hip ratio**	**Parity**
PCOS	Mean 24.92 ±SD 3.12	Mean71.60 ±SD 7.59	Mean 1.59 ±SD 0.0577	Mean28.23 ±SD 2.48	Mean 1.00 ±SD 0.038	Mean0.76 ±SD 0.66
Control	Mean 25.73 ±SD 2.68	Mean61.20 ±SD 10.07	Mean1.584 ± 0.0618	Mean24.26 ±SD 2.76	Mean 0.89 ±SD 0.024	Mean2.33 ±SD 0.72
P value	0.41(ns)	<0.001*	0.70(ns)	<0.001*	<0.001*	<0.001*

NS: Non-significant.

Table (2): Shows FSH, LH, FSH/LH ratio, TSN, Estradiol, SHBG and T/SHBG ratio in studied groups

	PCOS Mean±SD	Control Mean±SD	P value
FSH (mIU/ml)	4.98±1.49	5.50±1.55	0.29(ns)
LH (mIU/ml)	12.32±3.77	6.00±1.93	<0.001*
FSH/LH ratio	2.52±0.52	1.08±0.13	<0.001*
TSN (ng/dl)	109.52±19.36	59.06±13.23	<0.001*
Estradiol (pg/ml)	26.40±6.69	28.66±6.12	0.29(ns)
SHBG (nmol/l)	18.68±3.08	26.40±6.10	<0.001*
T/SHBG ratio	0.062±0.021	0.023±0.005	<0.001*

Table (3): Shows Ultrasound and Doppler indices in studied groups

	PCOS Mean±SD	Control Mean±SD	P value
Right ovarian volume (mm^3)	13.28±1.03	9.56±0.90	<0.001*
Left ovarian volume (mm^3)	13.59±1.21	9.80±0.95	<0.001*
Right uterine artery pulse index (PI)	4.44±0.27	4.81±0.30	<0.001*
Left uterine artery PI	4.26±0.34	4.84±0.42	<0.001*
Right uterine artery resistance index (RI)	0.92±0.03	0.98±0.07	<0.001*
Left uterine artery RI	0.91±0.04	1.02±0.14	<0.001*

Table (4): Shows means, standard deviation and P value of IGF-I in studied groups.

IGF-I (µg/L)	Mean±SD	P
PCOS	26.02±9.41	*0.014**
Control	19.22±5.21	
Total	23.47±8.68	

Table (5): Shows Correlation between IGF-I and other parameters in studied groups

	IGF-I	
	R	**P**
Age	-0.25	0.11
BMI	**0.26**	**0.10**
W/H ratio	**0.71**	**<0.001***
LH	**0.86**	**<0.001***
FSH	0.14	0.35
LH/FSH ratio	**0.74**	**0.001***
TSN	**0.86**	**0.001***
Estradiol	-0.13	0.40
SHBG	**-0.62**	**<0.001***
T/SHBG ratio	**0.86**	**<0.001***
Right uterine artery PI	**-0.80**	**<0.001***
Left uterine artery PI	**-0.76**	**<0.001***
Right uterine artery RI	**-0.69**	**<0.001***
Left uterine artery RI	**-0.63**	**<0.001***
Right ovarian volume	**0.74**	**<0.001***
Left ovarian volume	**0.71**	**<0.001***

Figures:

Figure (1): LH and FSH in studied females.
Figure (2): LH/FSH ratio in studied females
Figure (3): TSN, estradiol and SHBG in studied females.
Figure (4): IGF-I in studied females.
Figure (5): correlation between IGF-I and LH.
Figure (6): Correlation between IGF-I and LH/FSH ratio.
Figure (7): ROC characteristics curve for IGF-I for prediction of PCOS.

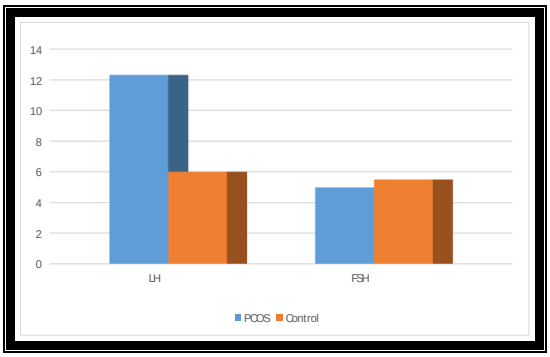

Figure (1)

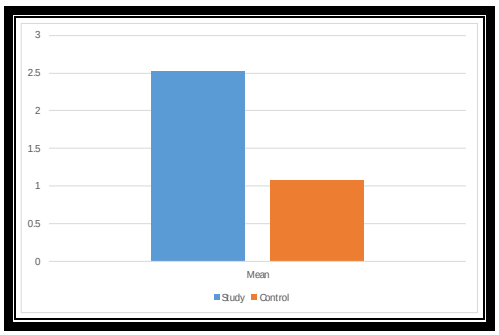

Figure (2)

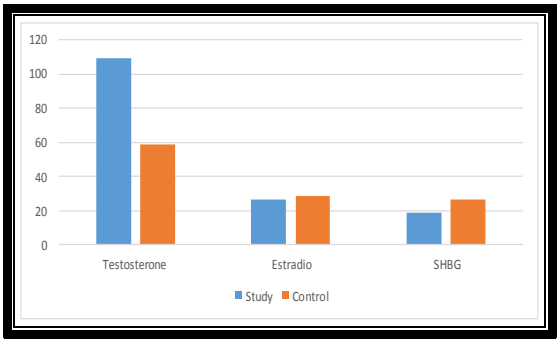

Figure (3)

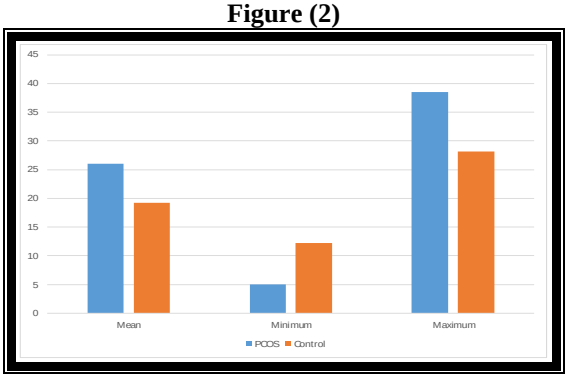

Figure (4)

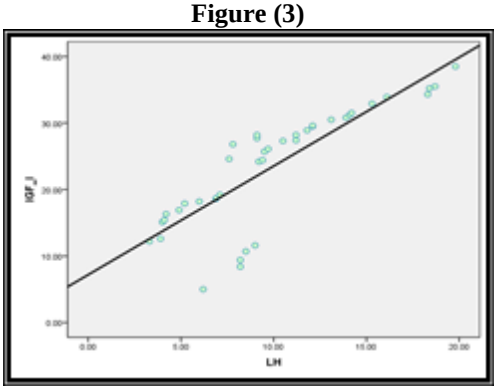

Figure (5)

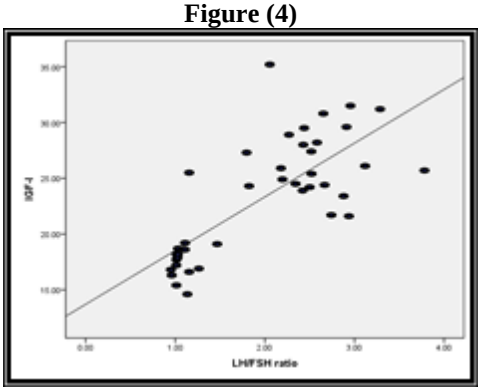

Figure (6)

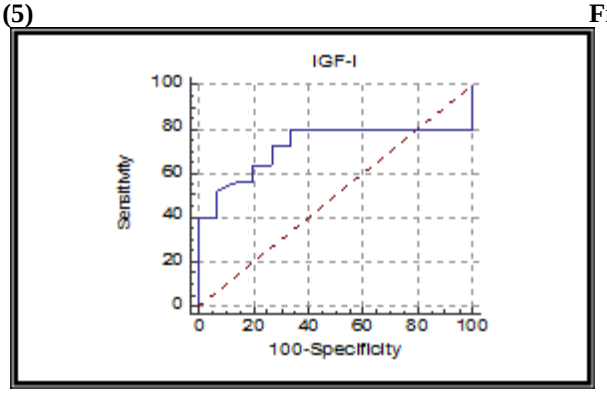

Figure (7)

DISCUSSION

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder that is defined by a combination of signs and symptoms of androgen excess (hirsutism and/or hyperandrogenemia) and ovarian dysfunction (oligo-ovulation and/or polycystic ovarian morphology (PCOM), provided that other specific diagnoses, such as hyperprolactinemia and non-classic congenital adrenal hyperplasia, have been excluded. The prevalence of PCOS in premenopausal women ranges from ~6% (using the older, more restrictive

criteria) to ~20% (when applying current, more inclusive definitions), possibly making this syndrome the most common endocrine and metabolic disorder in women of reproductive age [10]. The pathophysiology and intrinsic mechanisms underlying PCOS are complex because etiologies vary, and the different features are considerably intertwined. The interplay between these mechanisms results in and perpetuates the clinical features of PCOS, including hyperandrogenism, PCOM and ovulatory dysfunction, in addition to the associated mood disturbances, psychosexual dysfunction and long-term morbidities. In addition, the development of PCOS has a strong genetic component [11]. There are currently three main diagnostic criteria for defining PCOS. The evaluation of PCOS entails determining the presence or absence of: hyper-androgenism, ovulatory dysfunction and PCOM. Hyperandrogenism is clinically determined based on the presence of hirsutism using a visual scoring system, such as the Modified Ferriman–Gallwey (mFG) method, and biochemically measuring the levels of circulating androgens. The clinical detection of ovulatory dysfunction is generally based on a history of polymenorrhea or oligo-amenorrhea, or by assessing ovulatory function using luteal phase progesterone levels in hirsute women who are otherwise eumenorrheic. Ovarian ultrasonography is used to identify PCOM [12]. The involvement of the IGF system as intraovarian regulators of folliculogenesis has been intensively studied in a variety of mammalian species, and it is now established that the ovary is a site of IGF-I gene expression and reception [8]. IGF-I may play a role at various stages of follicular development: a) initiation of growth of the primordial follicle; b) at a secondary follicle stage, IGF-I may be involved on induction of FSH receptor (FSH-R) expression on granulosa cell and their differentiation, theca cell survival and cortical granules formation in oocytes and c) at antral follicular stage, IGF-I may increase follicle sensitivity to gonadotrophin, oocyte maturation and LH receptor (LH-R) expression in granulosa and theca cells enhancing their proliferation and steroidogenic activity. In humans, IGF-I also stimulates vascular endothelial growth factor production by granulose cells [13].

The present study was aimed to assess the role of IGF-1 in serum of cases of polycystic ovary syndrome. This study started from July 2017 to January 2018 at Obstetrics and Gynecology Department, Faculty of Medicine, New Damietta, Al Azhar University. The study comprised 25 PCOS patients and 15 matched healthy controls. The diagnosis of PCOS was made by the presence of any 2 of the following 3 criteria: (1) clinical and/or biochemical evidence of hyperandrogenism; (2) chronic oligo-/anovulation; and/or (3) polycystic ovaries on ultrasound. PCO was defined as the presence of 12 or more follicles in each ovary, each measuring 2-9 mm in diameter, and/or increased ovarian volume > 10 ml [14]. Patients suffering from Cushing's syndrome, thyroid dysfunctions, androgen- secreting tumor, enzyme deficiency (21- hydroxylase in particular), decreased ovarian reserve (primary ovarian insufficiency), or type 1 or type 2 diabetes were excluded. None of the subjects were taking any medication for at least 3 months before the study. All the patients had clinical and/or biochemical hyperandrogenism and chronic anovulation, and 80% of the patients had polycystic ovaries on ultrasound. The control group consisted of healthy women who had regular menstrual cycles (28 ± 2 days, without clinical or biochemical hyperandrogenism or polycystic ovary and with no history of any drug intake for at least 3 months. Additional exclusion criteria for both groups were smoking and alcohol consumption. Informed consent was taken from patients who agreed to participate in the study. Approval of the Ethics Committee was taken before start of the study. All cases underwent: full history taking, full clinical examination, and abdominal sonography and laboratory investigations. The last included liver and kidney function tests, CBC and hormonal studies including LH, FSH, Total Testosterone and SHBG.IGF-1 serum concentration were measured by Elisa technique.

There was significant increase of weight in PCOS when compared to control group. However, there was no significant difference between both groups as regards the height and there was significant increase of BMI in PCOS when compared to control group were compatible with those done by **Chang et al.** [15].

There was significant increase of waist circumference and W/H ratio in PCOS when compared to control group. Tokmak et al., reported similar results as regard waist circumference and W/H ratio in PCOS women [16]. Gupta and Mishra

also found significant high value of W/H ratio in PCOS [17].

There is an increased risk for Gestational Diabetes Mellitus (GDM) in PCOS pregnancies, which is largely explained by obesity, but also partly by the underlying PCOS. Since GDM may be associated with neonatal morbidity, its screening during second-trimester PCOS pregnancies seems reasonable [18].

There was statistically significant decrease of parity in PCOS when compared to control group. These results were consistent with those of **Mikola et al.** [18].

There was significant increase of LH and LH/FSH ratio in PCOS when compared to control group ($p < 0.001$) while there was no significant difference between PCOS and control group regarding FSH (p 0.29). Tokmak et al., also reported the similar results [16]. While Ranjbaran et al., reported that a noticeable decline in FSH and an increase in LH levels together with a significant increase in LH/FSH ratio were found in PCOS patients [19].

There was no significant difference between PCOS and control group regarding estradiol (p 0.29). This agrees with studies made by Bostanci et al., who reported that Estradiol was not significantly different between the PCO group and the controls [20].

There was statistically significant increase of testosterone in PCOS when compared to the controls ($p < 0.001$), while there was statistically significant decrease of SHBG in PCOS when compared to the controls ($p < 0.001$). In addition, there was significant increase of T/SHBG ratio in PCOS when compared to the controls ($p < 0.001$). These results were compatible with those of **Duan et al.** [21].

IGF-I ranged from 14.60 to 35.20 µg/L, the mean value was 23.26±5.31; and there was statistically significant increase in PCOS when compared to control group (26.76±3.28 vs 17.42±1.34 respectively) and ($p < 0.014$). These results coincide with that of the studies done by Kebapcilar et al., who found that there was highly significant increase in IGF-I levels in PCOS subjects in relation to the controls [22].

There was positive (proportional) correlation between IGF-I from one side and each of LH and LH/FSH ratios. IGF-1 seems to have an overall negative effect on normal folliculogenesis and ovulation suggesting that the pathogenesis of PCOS may involve interrelated abnormalities of the IGF-1 and ovarian steroidogenesis systems [23]. It has been proposed that the elevated LH often found in this disorder, may increase IGF-1 production by theca cells within the polycystic ovary and enhance androgen production [24]. In this respect, the last investigators have detected IGF-1 receptors in theca cells. In addition, they also have shown that IGF-1 stimulate granulosa cell for estrogen production. It has been demonstrated that IGF-1 stimulates aromatase activity in the human ovary and suggested that lowering IGF-1 levels could potentially lower androgen and estrogen [25].

REFERENCES

1. **Teede HJ, Hutchison SK, Zoungas S (2007):** The management of insulin resistance in polycystic ovary syndrome. Trends in Endocrinol Metab., 18: 273-279.
2. **Diamanti-Kandarakis E, Kouli CR, Bergiele AT *et al.* (1999):** A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. J Clin Endocrinol Metab., 84: 4006-4011.
3. **March WA, Moore VM, Willson KJ *et al.* (2010):** The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod., 25: 544-551.
4. **Legro RS, Castracane VD, Kauffman RP (2004):** Detecting insulin resistance in polycystic ovary syndrome: purposes and pitfalls. Obstet Gynecol Surv., 59: 141-154.
5. **Le Roith D (1997):** Seminars in medicine of the beth israel deaconess medical center. Insulin-like growth factors. N Engl J Med., 336(9):633–640.
6. **Annenkov A (2009):** The insulin-like growth factor (IGF) receptor type 1 (IGF1R) as an essential component of the signalling network regulating neurogenesis. Mol Neurobiol., 40(3):195–215.
7. **Rinderknecht E, Humbel RE (1978):** Primary structure of human insulin-like growth factor II. FEBS Lett., 89(2): 283–286.
8. **Adashi EY (1998):** The IGF family and folliculogenesis. J Reprod Immunol., 39(1–2):13–19.

9. **Silva JR, Figueiredo JR, van den Hurk R (2009):** Involvement of growth hormone (GH) and insulin-like growth factor (IGF) system in ovarian folliculogenesis. Theriogenology, 71(8):1193–1208.
10. **Escobar-Morreale, Héctor. F (2018):** Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nature Reviews Endocrinology, https:// doi. org/ 10. 1038/nrendo.2018.24.
11. **Azziz R, Carmina E, Chen Z *et al.* (2016):** Polycystic ovary syndrome. Nature Reviews Disease Primers, 2: 16057.
12. **Unfer V, Proietti S, Gullo G *et al.* (2014):** Polycystic Ovary Syndrome: Features, Diagnostic Criteria and Treatments. Endocrinology & Metabolic Syndrome, 3(3): 1000136.
13. **Puche J and Castilla-Cortázar (2012):** Human conditions of insulin-like growth factor-I (IGF-I) deficiency. Journal of Translational Medicine, 10(1): 224.
14. **Rotterdam E (2004):** Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril., 81: 19-25.
15. **Chang C, Huang S, Soong Y et al. (2014):** Circulating irisin and glucose-dependent insulinotropic peptide are associated with the development of polycystic ovary syndrome. Journal of Clinical Endocrinology and Metabolism, 99(12): E2539–E2548.
16. **Tokmak A, Bodur S, Erkilinc S *et al.* (2017):** The Value of Prostate-Specific Antigen in Diagnosis of Polycystic Ovarian Syndrome in Adolescent Girls. Journal of Pediatric and Adolescent Gynecology, https:// doi. org/ 10. 1016/ j.jpag.2017.11.004.
17. **Gupta V and Mishra S (2017):** L:A ratio, Insulin resistance and metabolic risk in women with polycystic ovarian syndrome. Diabetes and Metabolic Syndrome: Clinical Research and Reviews, 11: S697–S701.
18. **Mikola M, Hiilesmaa V, Halttunen M *et al.* (2001):** Obstetric outcome in women with polycystic ovarian syndrome. Human Reproduction (Oxford, England), 16(2): 226–229.
19. **Ranjbaran J, Farimani M, Tavilani H et al. (2016):** Matrix metalloproteinases 2 and 9 and MMP9/NGAL complex activity in women with PCOS. Reproduction, 151(4): 305–311.
20. **Bostanci MS, Akdemir N, Cinemre B, Cevrioglu AS (2015):** Serum irisin levels in patients with polycystic. European Review for Medical and Pharmacological Sciences, 19: 4462–4468.
21. **Duan Y, Feng Z, Deng H *et al.* (2017):** Decreased circulating levels of betatrophin in Chinese women with polycystic ovary syndrome. Int J Clin Exp Med., 10(3): 5196–5202.
22. **Kebapcilar A, Tatar M, Ipekci S *et al.* (2014):** Cornea in PCOS patients as a possible target of IGF-1 action and insulin resistance. Archives of Gynecology and Obstetrics, 290(6): 1255–1263.
23. **van Dessel (1999):** Elevated Serum Levels of Free Insulin-Like Growth Factor I in Polycystic Ovary Syndrome. Journal of Clinical Endocrinology & Metabolism, 84(9): 3030–3035.
24. **Erickson GF, Magoffin DA, Cragun JR, Chang RJ (1990):** The effects of insulin-like growth factors-1 and II on oestradiol production by granulosa cells of polycystic ovaries. J Clin Endocrinol Metab., 70: 894–902.
25. **Abd El Aal M, Mohamed A, Amine F, Meki A (2005):** Vascular endothelial growth factor and insulin-like growth factor-1 in polycystic ovary syndrome and their relation to ovarian blood flow. European Journal of Obstetrics Gynecology and Reproductive Biology, 118(2): 219–224.