IJPSR (2019), Volume 10, Issue 3 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 12 July 2018; received in revised form, 22 September 2018; accepted, 05 October 2018; published 01 March 2019

POLYCYSTIC OVARIAN SYNDROME- A MULTIFACETED DISEASE: A REVIEW

Mudasir Maqbool, Imran Gani and Mohammad Ishaq Geer *

Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal Srinagar - 190006, Jammu and Kashmir, India.

Keywords:

PCOS, Insulin resistance, Hyperandrogenism, Menstrual irregularity

Correspondence to Author:
Dr. Mohammad Ishaq Geer

Senior Assistant Professor, Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal Srinagar - 190006, Jammu and Kashmir, India.

E-mail: ishaqgeer@gmail.com

ABSTRACT: Polycystic ovarian syndrome (PCOS) is one of the most prevalent endocrine disorders in females of reproductive age. Globally, it has been found that PCOS affects 10% of reproductive-age women when using the NIH criteria for diagnosis, and up to 18% of reproductive-age women are diagnosed with PCOS as per the Rotterdam criteria. Mostly symptoms of PCOS include irregular menstrual cycles, signs of hyperandrogenism and insulin resistance. Women with PCOS are at increased risk for developing reproductive, metabolic and cardiovascular disorders. The measures for management of PCOS targets the symptoms which are present in a patient such as lowering body weight and insulin levels, restoring fertility, treating hirsutism or acne, restoring regular menstruation and preventing complications. Early detection of long-term morbidities through appropriate screening tests constitutes an essential part of the management of this condition. Future research has to focus on the missing blocks in our growing knowledge about this condition, following that physicians will be able to provide the finest care for patients.

INTRODUCTION: Polycystic ovarian syndrome is one of the most prevalent female endocrine disorders. It is a complex heterogeneous disease of unusual etiology, but there is enough evidence that it can, to a large extent, be classified as a genetic disease [1, 2]. As per various studies, PCOS affects 10% of reproductive-age women when using the NIH criteria for diagnosis, and up to 18% of reproductive-age women as per the Rotterdam criteria [3]. However, about 70% of PCOS cases remain undiagnosed in primary care [4]. PCOS is a metabolic disease, and mainly life style changes predispose it.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(3).1072-79

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(3).1072-79

The percent of PCOS affected persons are mostly from diabetic family background, and genetically it has proved that if a mother or sister has PCOS then mostly that women can be affected. In the case of diabetics, the person develops resistance towards insulin which in turn hampers the LH and FSH hormones which causes alterations in menstrual cycle [5-20]. Polycystic Ovarian Syndrome presents with menstrual irregularities, infertility, high levels of masculinizing hormones manifested by acne and hirsutism and metabolic syndrome and other symptoms associated with insulin resistance.

It has been found that serum insulin, insulin resistance, and homocysteine levels are higher in females with PCOS than in the normal females [21]. PCOS leads to a significantly huge economic burden. About 4 billion dollars are spent every year in the United States on screening for the disease and treating its various morbidities, including hirsutism, infertility, and diabetes mellitus [22].

Various predisposing factors for PCOS include [23]: genetic factors; high maternal androgen; endocrinal factors and drugs: such as anti-epileptic drugs (*e.g.*, Valproate). Women with PCOS are at increased risk of presenting with insulin resistance (IR), impaired glucose tolerance (IGT), Type 2 Diabetes mellitus (DM2), obesity, and dyslipidemia [24-26].

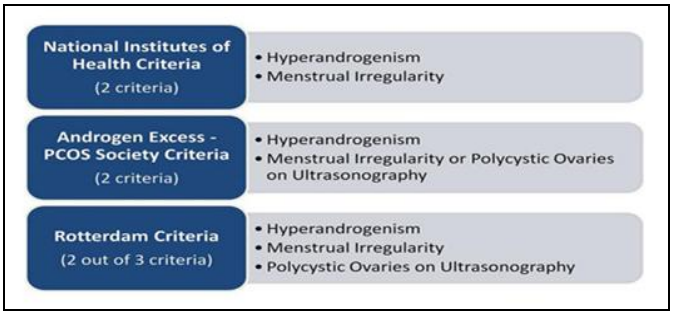
Pathophysiology: The pathophysiology of PCOS as a multifaceted disease shows the involvement of uncontrolled ovarian steroidogenesis, aberrant insulin signaling, excessive oxidative stress, and genetic/environmental factors. In PCOS, ovaries are incited to produce increased amounts of male hormones (androgens), such as testosterone, by either the release of excessive luteinizing hormone, higher levels of insulin in the blood (hyperinsulinaemia) in females whose ovaries are sensitive to this stimulus or decreased levels of sex-hormone binding globulin (SHBG) resulting in excessive free androgens [27]. Females with PCOS have increased gonadotrophin-releasing hormone (GnRH), which leads to an increase in LH/FSH ratio. Majority of patients with PCOS show insulin resistance and central obesity [27, 28].

Hyperinsulinaemia contributes to abnormalities in the hypothalamic-pituitary-ovarian axis leading to PCOS. The sequence various events that precede in PCOS pathogenesis include; increased insulin levels increase GnRH pulse frequency, LH over FSH dominance, excessive ovarian androgen production, diminished follicular maturation and reduced SHBG binding. All these factors lead to the development of PCOS [27, 28]. Various other factors such as exposure to environmental toxins, like endocrine-disrupting chemicals that mimic endogenous hormones and advanced glycation end products, might programme reproductive and metabolic function, leading to PCOS and its associated metabolic dysfunctions, especially if such exposure is persistent and occurs during developmental periods such as fetal life, infancy or childhood [29].

Similar consequences might result from exposure to certain pharmaceutical drugs during critical developmental windows, especially the anti-epileptic and mood stabilizer valproate [30], which is frequently associated with a PCOS-like phenotype in premenopausal women and induces a genomic and molecular signature in theca cell cultures that is similar to that of PCOS [31, 32]. PCOS is indicated by complex positive feedback of insulin resistance and hyperandrogenism [33]. In humans, adipose tissue contains aromatase enzyme, which converts androstenedione to estrone and testosterone to estradiol. Since obese patients possess excessive adipose tissue, it leads them to have both increased androgens and estrogens. The androgens are responsible for hirsutism and virilization whereas estrogens inhibit FSH *via* negative feedback [34]. The ovaries at the time of production have tiny fluid-filled sacs called cysts [35-37].

As the egg grows, the follicle builds up fluid, and once the egg matures, the follicle breaks open, and the egg is released, and this egg travels through the fallopian tube to the uterus (womb) for fertilization that is called ovulation, but in case of women with PCOS, the ovary is unable to produce all the essential hormones which are needed for an egg to fully mature. The follicles may start to grow and build up fluid; however, ovulation does not develop. Rather, a few follicles may remain as cysts [35-37]. Thus, ovulation does not happen, and the hormone progesterone is not made. Without progesterone, a woman's menstrual cycle is sporadic or missing. Furthermore, the ovaries make male hormones, which additionally counteract ovulation [38-53].

Diagnosis of PCOS: [54] Although, pelvic ultrasound is a major diagnostic tool, however, is not the only one. Certain definitions are used for diagnosis of PCOS such as National Institutes of Health (NIH) criteria, Rotterdam Criteria, and Androgen Excess PCOS Society Criteria.



Hyperandrogenism: It is a major patho-physiological feature of PCOS showing the prevalence of 60-80% [55]. Excessive ovarian androgen production by theca cells is the main

culprit to androgen excess in women of reproductive age with PCOS [56], whereas about 20-60% of women with classic anovulatory PCOS have adrenal androgen excess, as determined by elevated dehydroepiandrosterone sulphate (DHEAS) levels [57]. The latter originates mainly from the zona reticularis of the adrenal cortex [58]. Adrenal androgen hypersecretion in PCOS women of reproductive age is also observed after adrenal stimulation [59-61]. Hyperandrogenism is the main criterion in the diagnostic work-up of PCOS. According to the current criteria, it can be indistinctly defined by either hirsutism and excess of blood testosterone (T) levels. However, most but not all PCOS women are hirsute, and no more than 50% have increased T levels measured by commonly used immunoassay methods. This implies that the population of PCOS is rather heterogeneous in displaying its hyperandrogenic phenotype, which may be related to the relative unreliability of the diagnostic criteria used to define hyperandrogenism [62].

The current definition of hirsutism by the modified Ferriman-Gallwey (mF-G) score is largely Unsatisfactory due to a poor interobserver agreement and the intrinsic variability of the scoring system. Also, although most women with hirsutism have high T levels, and some correlation is found between hirsutism scores and T levels in women with PCOS, this relationship becomes only marginally significant when T is measured by more appropriate techniques. According to one hypothesis for the pathogenesis of PCOS, increased peripheral aromatization of androstenedione to estrone leads to excessive secretion of Luteinizing Hormone which leads to a further increase in ovarian androgen production [62].

Menstrual Irregularity: Menstrual disorders and physical manifestations of excessive androgen production is the leading cause of consultation in the adolescent group. Other than metabolic syndrome and primary infertility they are also at high risk for insulin resistance and impaired glucose tolerance. Therefore it is important to identify adolescent at risk, early because diabetes mellitus is asymptomatic at the early stage of insulin resistance and impaired glucose tolerance. Modification in life style can avert the development of metabolic syndrome and diabetes mellitus in these adolescents [63, 64]. The menstruation patterns that follow menarche, especially during the first 2 years, are usually anovulatory, irregular, and occasionally abundant, due to the immaturity of the hypothalamus-pituitary-ovary axis in adolescents [65-67]. After two years of menarche, the hypothalamus-pituitary-ovary axis usually acquires normal functioning. The persistence of anovulatory cycles for more than 24 months after menarche, especially in association with other characteristics of hormonal disorders, suggests ovulatory dysfunction of pathologic origin [68, 69].

As such, menstrual irregularity can sometimes be an unreliable criterion for the diagnosis of PCOS in adolescents [70]. Clinicians monitor the menstrual cycle patterns closely to differentiate physiological anovulation associated with adults from pathological anovulation as an abnormality identified in PCOS [71, 72]. It has been suggested to postpone diagnosis at least 2 years after menarche to establish a persistent menstrual irregularity [73]. However, this may delay the initiation of appropriate treatment [74].

Polycystic Ovaries on Ultrasonography: During puberty, ultrasonography findings are controversial for the diagnosis, as the ovaries show normal physiological changes and variations in the volume and size of the ovaries [75]. Researchers noted that the diagnosis of polycystic ovaries requires strict criteria [76, 77] and should not be assigned based solely on a polycystic or multicystic appearance of the ovary. The diagnosis of polycystic ovaries has been recently reviewed [79]. For diagnostic purposes, normal ovarian volume in female adolescents is considered equal to or less than 10 ml [80].

Management of PCOS: Management of PCOS is based on the aspect of correcting the symptoms present in patients usually such as anovulation, infertility, hirsutism, *etc*. Treatment of PCOS acts to reduce hyperinsulinemia, restore fertility, treat hirsutism or acne, correct menstrual irregularity and prevent endometrial hyperplasia and endometrial cancer [81]. A lifestyle program that addresses healthy diet with caloric restriction, exercises to aid in weight loss and prevention of future weight gain and behavior change support is the best first-line treatment for PCOS [82]. Weight loss reduces hyperinsulinemia and subsequently

hyperandrogenism. Even a small amount of weight loss (5%) can help to restore ovulation and menstrual cycle regularity, assist in mental well-being, decrease the risk of diabetes in high-risk groups and help prevent future cardio-metabolic risk [83-86]. Those who smoke should be offered support to help them quit. Pharmacotherapies are based on whether the patient's main complaint is an irregularity in menstrual cycles, infertility, acne or hirsutism, *etc*. The most common prescribing drugs and therapeutic options used in the management of PCOS include hormonal contraceptives/oral contraceptives, insulin sensitizers, ovulation-inducing agents and anti-androgens [87].

Typically, oral contraceptive pills (OCP's) are first-line agents for Pharmacological management of hirsutism in premenopausal women [87]. Combined OCPs are a good treatment option to regularize menstruation in those not desiring pregnancy, and they are often considered the first line for the treatment of PCOS related hirsutism and acne. Apart from these positive effects on PCOS, OCPs are believed to slightly worsen insulin sensitivity [88-90,] and for this reason, their use may aggravate the already impaired glucose metabolism of women with PCOS. However, studies estimating the role of OCPs on glucose tolerance [91] or insulin sensitivity [92-98] in women with PCOS have obtained conflicting results, and either no effect or a negative modification [91, 94, 96, 97] was reported. There may be some negative influence on lipids also, and a low dose COCP may be preferable [99, 100].

Antiandrogens such as Spironolactone, cyproterone acetate (CPA) or Flutamide work by competitive inhibition of androgen-binding receptors or by decreasing androgen production [101]. Spironolactone shows moderate antiandrogenic action when administered in large doses; however, it has promising effects on hirsutism [102]. It is generally well tolerated, but it occasionally causes fatigue, postural hypotension, and dizziness. CPA is a progestational antiandrogen. CPA is generally well tolerated, though it may cause headaches, nausea, breast tenderness and weight gain. A combination of ethinyl estradiol and CPA is very effective in treating hirsutism and acne. CPA has a marked progestational property apart from its antiandrogenic effect, thus preventing ovulation [103]. Flutamide is a non-steroidal, selective anti-androgenic agent without any progestogenic effect. It is very effective in treating hirsutism. However, it is rarely used alone due to its high cost and the risk of hepatocellular toxicity. Finasteride is a type 2(5-α-reductase) activity inhibitor that inhibits the production of dihydrotestosterone. Hirsutism scores were lower in studies of Finasteride [104]. In comparison to Finasteride, Spironolactone has shown equal or lesser efficacy than Finasteride. It has also been used in combination with a CPA containing OCP. Finasteride as such has a low side effect profile, but its feminizing effects on a male fetus preclude its use in most patients [87].

Insulin sensitizers such as Metformin and thiazolidinediones have insulin-lowering effects by improving insulin sensitivity, and thus, in turn, can decrease circulating androgen levels [87]. Additionally, these agents have a role in the treatment of PCOS because women with PCOS are at an increased risk of insulin resistance, development of metabolic disorders and cardiovascular disease [105]. The US Food and Drug Administration has not approved any antidiabetic agents for the treatment of PCO, but Metformin is preferred at this time because it appears to have the safest risk-benefit ratio, and it can cause weight loss, while as thiazolidinediones can increase weight as a result of fluid retention [105]. The other insulin-sensitizing agents, such as D-chiro-inositol in PCOS treatment is currently under investigation. Inositolglycans have been described as interfering insulin action on thecal steroidogenesis [106].

Clomiphene citrate (CC) is the drug of the first choice for ovulation induction in women with PCOS [107]. CC is a partially selective estrogen receptor modulator. It is the first-step therapy for anovulation; no consistent evidence suggests that Metformin is better than CC regarding cumulative ovulation, pregnancy or live birth rates [108, 109]. Selective aromatase inhibitors like Anastrozole and Letrozole are new ovulation-inducing drugs. They are reversible and highly potent. The mean half-life of Anastrozole and Letrozole is ≈ 45 h only unlike CC, which has a half-life of 5-7 days. To date, Letrozole has been studied much more extensively than Anastrozole [110]. Letrozole was introduced as an assisted reproduction treatment following the appearance of multiple adverse effects of CC, the

complexity of gonadotropin treatment and CC's scant therapeutic success. As per American Society for Reproductive Medicine and the European Society of Human Reproduction and Embryology [107], ovulation induction with gonadotropins and laparoscopic ovarian drilling (LOD) are considered to be second-line therapies for ovulation induction. The gonadotropin approach is less invasive and is best-preferred treatment in women who do not desire surgery. LOD is preferred only when the patient has other indications for surgery or when the patient is not able to comply with the frequent follow-up visits required with gonadotropin therapy [111]. Bromocriptine, a dopaminergic agonist, may also be a useful treatment in women with PCOS associated with hyperprolactinemia [107]. Eflornithine is a topical cream that has been approved by the US Food and Drug Administration for removal of unwanted facial hair in females [87, 105].

CONCLUSION: PCOS is an important endocrine disease that affects women of reproductive age and may cause serious complications. Further, research is needed to determine the exact etiology of PCOS, methods of prevention and proper management. Patients suffering from PCOS are at risk for the development of reproductive, metabolic and cardiovascular disorders, *etc*. Moreover, it may affect daily physical activities. Treatment of PCOS acts to reduce hyperinsulinemia, restore fertility, treat hirsutism or acne, and correct menstrual irregularity. A lifestyle program that addresses healthy diet with caloric restriction, exercise to aid in weight loss and prevention of future weight gain and behavior change support is the best first-line treatment for PCOS Early detection of long-term morbidities through appropriate screening tests constitutes an essential part of the management of this condition. Future research has to focus on the missing blocks in our growing knowledge about this condition. Following those physicians will be able to provide the finest care for patients.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: None

REFERENCES:

1. El-Sharkawy AA, Abdelmotaleb GS, Aly MK and Kabel AM: Effect of metformin on sleep disorders in adolescent girls with the polycystic ovarian syndrome. J Pediatr Adolesc Gynecol 2014; 27(6): 347-52.
2. Nafiye Y, Sevtap K and Muammer D: The effect of serum and intrafollicular insulin resistance parameters and homocysteine levels of nonobese, nonhyperandrogenemic polycystic ovary syndrome patients on *in-vitro* fertilization outcome. Fertil Steril 2010; 93(6): 1864-9.
3. March WA, Moore VM, Willson KJ, Phillips DIW, Norman RJ and Davies MJ: The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Human Reproduction 2010; 25(2): 544-551.
4. Tomlinson JA, Pinkney JH, Evans P, Millward A and Stenhouse E: Screening for diabetes and cardiometabolic disease in women with polycystic ovary syndrome," British Journal of Diabetes and Vascular Disease 2013; 13(3): 115-123.
5. Iljazovic E: Polycystic Ovarian Syndrome in Perimenopausal Women: A Pilot Study-Observation Regarding Study Approach. Reprod Syst Sex Disord 2016; 5: 177.
6. Abiad F: Bariatric surgery in the management of adolescent and adult obese patients with polycystic ovarian syndrome. J Obes Weight Loss Ther 2016; 6: 303.
7. Kabel AM: Polycystic ovarian syndrome: insights into pathogenesis, diagnosis, prognosis, pharmacological and non-pharmacological treatment. J Pharma Reports 2016; 1: 103.
8. Mahendru R and Bansal S: Lifestyle modifications as the first line therapy in polycystic ovary syndrome. J Preg Child Health 2016; 3: e128.
9. Coker E: Polycystic ovarian syndrome and eating disorder quality of life: a pilot study. JFIV Reprod Med Genet 2016; 4: 171.
10. Chhabra S and Taori A: a polycystic ovarian syndrome in perimenopausal women: a pilot study. Reprod Syst Sex Disord 2016; 5: 157.
11. Mbamara SU: Successful pregnancy in a woman with chronic kidney disease due to autosomal polycystic disease- a case report. Gyn Obs (Sunnyvale) 2015; 5: 338.
12. Sharma TR: Polycystic ovarian syndrome and borderline personality disorder: 3 case reports and scientific review of the literature. J Psychiatry 2015; 18: 336.
13. Qu X: Natural approach to coexisting non-alcoholic fatty liver disease and polycystic ovarian syndrome. Endocrinol Metab Syndr 2015; 4: 182.
14. Frossing S: The LIPT-study: on risk markers of vascular thrombosis in polycystic ovary syndrome. A randomized, double-blind, placebo-controlled study of the effect of liraglutide. J Obes Weight Loss Ther 2015; 5: 254.
15. Abdelmeged A: A Comparative study between GnRH antagonist and long agonist protocols in patients with the polycystic ovarian syndrome (PCOS) Undergoing *in-vitro* Fertilization. JFIV Reprod Med Genet. 2015; 3: 137.
16. Asma E and Elmahaishi MS: Does the use of Highly Purified Human Menopausal Gonadotrophin (HP-HMG) avoid Ovarian Hyperstimulation Syndrome (OHSS) in Polycystic Ovary (PCO) Patients in Assisted Reproduction (IVF/ICSI)? Gynecol Obstet (Sunnyvale) 2015; 5: 273.
17. Tan M and Kim SH: Does polycystic ovarian syndrome increase insulin resistance above and beyond obesity? Endocrinol Metab Synd 2014; 3: 142.
18. Orakpo N and Swan JH: Zumba: An antidote for uncontrolled weight gain associated with polycystic ovarian syndrome with subclinical hypothyroidism? J Gerontol Geriat Res 2013; 2: 132.
19. Elsayed MA: Agnucaston and clomiphen citrate in infertile patients with polycystic ovaries. J IVF Reprod Med Genet 2013; 1: 108.

20. El-Hafez HAA: Thyroid function and volume are associated with anthropometric measurements and insulin resistance in Egyptian women with polycystic ovary syndrome. J Diabetes Metab 2013; 4: 288.
21. Pasquali R and Gambineri A: Insulin-sensitizing agents in polycystic ovary syndrome. Eur J Endocrinol 2006; 154(6): 763-75.
22. Azziz R, Marin C, Hoq L, Badamgarav E and Song P: Healthcare-related economic burden of the polycystic ovary syndrome during the reproductive life span. J Clin Endocrino. Metab 2005; 90: 4650-58.
23. Hernandez MI and Mericq V: Polycystic ovarian syndrome. In: Brook C, Clayton P, Brown R, eds. Brook's clinical paediatric endocrinology. Blackwell 2015; 559-70.
24. Diamanti-Kandarakis E and Dunaif A: Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocrine Reviews 2012; 33(6): 981-30.
25. Moran LJ, Misso ML, Wild RA and Norman RJ: Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Human Reproduction Update 2010; 16(4): 347-63.
26. Randeva HS, Tan BK and Weickert MO: Cardiometa-bolic aspects of the polycystic ovary syndrome. Endocrine Reviews 2012; 33(5): 812-41.
27. Strauss JF: Some new thoughts on the pathophysiology and genetics of polycystic ovary syndrome. Ann. N Y Acad. Sci 2003; 997: 42-48.
28. Sharquie KE, Al-Bayatti AA, Al-Ajeel AI, Al-Bahar AJ and Al-Nuaimy AA: Free testosterone, luteinizing hormone/follicle stimulating hormone ratio and pelvic sonography in relation to skin manifestations in patients with polycystic ovary syndrome. Saudi Med J 2007; 28(7): 1039-43.
29. Rutkowska AZ and Diamanti-Kandarakis E: Polycystic ovary syndrome and environmental toxins. Fertil Steril 2016; 106: 948-58.
30. Isojarvi JI, Laatikainen TJ, Pakarinen AJ, Juntunen KT and Myllyla VV: Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. N Engl J Med 1993; 329: 1383-88.
31. Nelson-DeGrave VL: Valproate potentiates androgen biosynthesis in human ovarian theca cells. Endocrinology 2004: 145: 799-08.
32. Wood JR: Valproate-induced alterations in human theca cell gene expression: clues to the association between valproate use and metabolic side effects. Physiol Genom 2005; 20: 233-43.
33. Pasquali R and Gambineri A: Insulin-sensitizing agents in polycystic ovary syndrome. Eur J Endocrinol 2006; 154(6): 763-75.
34. Sathyapalan T and Atkin SL: Mediators of inflammation in polycystic ovary syndrome in relation to adiposity. Mediators Inflamm 2010; 758656.
35. Liu J: Bone Morphogenetic proteins are significantly reduced in the follicular fluid of Han Chinese polycystic ovary syndrome patients. Reprod Syst Sex Disord 2016; 5: 160.
36. Sandhu H and Kuburas R: Insulin resistance in women with polycystic ovary syndrome: optimising treatment by implementing an *in-vitro* insulin resistance organ culture model. Clinics Mother Child Health 2015; 12: e107.
37. Neves EM: Polycystic ovary syndrome: correlation between phenotypes and metabolic syndrome. J Steroids Hormon Sci 2014; 5: 132.
38. Karaca I: Treatment of premenstrual syndrome with progesterone in women with polycystic ovary syndrome. Gynecol Obstet 2013; 3: 151.
39. Denaday F: Polycystic Ovary Syndrome (PCOS). J Fert *In-vitro* 2012; 2: 117.
40. Mahdi WKM: Association of polycystic ovary syndrome and adiponectin gene polymorphisms. Arch Clin Microbiol 2016; 7: 3.
41. Hollinrake E: Increased risk of depressive disorders in women with polycystic ovary syndrome. Fertil Steril. 2007; 87: 1369-76.
42. Herbert DL: Depression: an emotional obstacle to seeking medical advice for infertility. Fertil Steril 2010; 94: 1817-21.
43. Cedars MI: PCOS: key issues and remaining Questions. Fertil Steril 2012; 97: 1.
44. Franks S and Berga SL: Does PCOS have developmental origins? Fertil Steril 2012; 97: 2-6.
45. Fauser BC: Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril 2012; 97: 28-38.
46. Li Y: Polycystic ovary syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from a meta-analysis. Fertil Steril. 2011; 96: 452-458.
47. Hassan MA and Killick SR: Ultrasound diagnosis of polycystic ovaries in women who have no symptoms of polycystic ovary syndrome is not associated with subfecundity or subfertility. Fertil Steril 2003; 80: 966-75.
48. Palomba S: Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril 2009; 92: 1646-58.
49. Eyvazzadeh AD: The role of the endogenous opioid system in polycystic ovary syndrome. Fertil Steril 2009; 92: 1-12.
50. Farrell K and Antoni MH: Insulin resistance, obesity, in?ammation, and depression in polycystic ovary syndrome: biobehavioral mechanisms and interventions. Fertil Steril 2010; 94: 1565-74.
51. Cardinali DP and Rosner JM: Retinal localization of the hydroxyindole-O-methyl transferase (HIOMT) in the rat. Endocrinology 1971; 89: 301-03.
52. Reichlin S: The pineal gland. In: Wilson JD & Foster D (Editors), Williams Textbook of Endocrinology. (8th edn), WB Saunders Company, Philadelphia, USA 1992; 240-53.
53. Djeridane Y: Evidence for melatonin in rodent Harderian gland: a dynamic *in-vitro* study. J Pineal Res 1998; 25: 54-64.
54. Broder-Fingert S, Shah B, Kessler M, Pawelczak M and David R: Evaluation of adolescents for polycystic ovary syndrome in an urban population. J Clin Res Pediatr Endocrinol 2009; 1(4): 188-93.
55. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE and Witchel SF: Criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an androgen excess society guideline. J Clin Endocrinol Metab 2006; 91: 4237-45.
56. Gilling-Smith C, Story H, Rogers V and Franks S: Evidence for a primary abnormality of thecal cell steroidogenesis in the polycystic ovary syndrome. Clin Endocrinol (Oxf) 1997; 47: 93-99.
57. Kumar A, Woods KS, Bartolucci AA and Azziz R: Prevalence of adrenal androgen excess in patients with the

polycystic ovary syndrome (PCOS). Clin Endocrinol (Oxf) 2005; 62: 644-49.
58. Endoh A, Kristiansen SB, Casson PR, Buster JE and Hornsby PJ: The zona reticularis is the site of biosynthesis of dehydroepiandrosterone and dehydroepiandrosterone sulfate in the adult human adrenal cortex resulting from its slow expression of 3β-hydroxysteroid dehydrogenase. J Clin Endocrinol Metab 1996; 81: 3558-65.
59. Carmina E and Lobo RA: Pituitary-adrenal responses to ovine corticotropin-releasing factor in polycystic ovary syndrome and in other hyperandrogenic patients. Gynecol Endocrinol 1990; 4: 225-32.
60. Azziz R, Black V, Hines GA, Fox LM and Boots LR: Adrenal androgen excess in the polycystic ovary syndrome: sensitivity and responsivity of the hypothalamic-pituitary-adrenal axis. J Clin Endocrinol Metab 1998; 83: 2317-23.
61. Moran C, Reyna R, Boots LS and Azziz R: Adrenocortical hyperresponsiveness to corticotropin in polycystic ovary syndrome patients with adrenal androgen excess. Fertil Steril 2004; 81: 126-31.
62. Rodin A, Thakkar H, Taylor N and Clayton R: Hyperandrogenism in Polycystic ovary syndrome. N Engl J Med 1994; 330: 460-5.
63. March WA, Mooe VM, Willson KJ, Phillips DI, Norman RJ and Davies MJ: The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod 2010; 25: 544-51.
64. Franks S: Polycystic ovary syndrome in adolescents; Int J Obesity. 2008; 32: 1035-41.
65. Rosenfield RL: Clinical review: Adolescent anovulation: maturational mechanisms and implication. J Cin Endocrinol Metab 2013; 98(9): 3572-83.
66. Bonny AE, Appelbam H and Connor EL: Clinical variability in approach to polycystic ovary syndrome. J Pediatr Adolesc Gynecol 2012; 25: 259-61.
67. Robinson S, Kiddy D and Gelding SV: The relationship of insulin insensitivity to the menstrual pattern in women with hyperandrogenism and polycystic ovaries. Clin endocrinol. 1993; 39(3): 351-5.
68. Avvad CK, Holeuwerger R and Silva VCG: Menstrual irregularity in the first postmenarchal years: an early clinical sign of polycystic ovary syndrome in adolescence. Gynecol Endocrinol 2001; 15: 170.
69. Nestler JE: Insulin regulation of human ovarian androgens. Hum reprod 1997; 12(S1): 53-62.
70. Kamangar F, Okhovat JP, Schmidt T, Beshay A, Pasch L and Cedars MI: Polycystic ovary syndrome: special diagnostic and therapeutic considerations for children. Pediatr. Dermatol 2015; 32: 571-578.
71. Franks S: Adult polycystic ovary syndrome begins in childhood. Best Pract. Res. Clin. Endocrinol Metab 2002; 16: 263-72.
72. Wiksten-Almstromer M, Hirschberg AL and Hagenfeldt K: Prospective follow-up of menstrual disorders in adolescence and prognostic factors. Acta Obstet Gynecol Scand 2008; 87: 1162-68.
73. Hardy TS and Norman RJ: Diagnosis of adolescent polycystic ovary syndrome. Steroids 2013; 78: 751-54.
74. Powers SE, Uliassi NW, Sullivan SD, Tuchman LK, Mehra R and Gomez-Lobo V: Trends in standard workup performed by pediatric subspecialists for the diagnosis of adolescent polycystic ovary syndrome. J Pediatr Adolesc Gynecol 2015; 28: 43-46.
75. Dewailly D, Lujan ME, Carmina E, Cedars MI, Laven J and Norman RJ: Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society Hum Reprod Update 2014; 20: 334-52.
76. Jonard S, Robert Y, Cortet-Rudelli C, Pigny P, Decanter C and Dewailly D: Ultrasound examination of polycystic ovaries: is it worth counting the follicles? Hum Reprod 2003; 18: 598-03.
77. Carmina E, Orio F, Palomba S, Longo RA, Lombardi G and Lobo RA: Ovarian size and blood flow in women with polycystic ovary syndrome and their correlations with endocrine parameters. Fertil Steril 2005; 84: 413-19.
78. Jonard S, Robert Y and Dewailly D: Revisiting the ovarian volume as a diagnostic criterion for polycystic ovaries. Hum Reprod 2005; 20: 2893-98.
79. Balen AH, Laven JS, Tan SL and Dewailly D: Ultrasound assessment of the polycystic ovary: International consensus definitions. Hum Rep Update 2003; 9: 505-14.
80. Carmina E, Oberfield SE and Lobo RA: The diagnosis of polycystic ovary syndrome in adolescents. Am J Obstet Gynecol 2010; 203: 201.e201-e05.
81. Teede H, Deeks A and Moran L: Polycystic ovary syndrome: A complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med 2010; 8: 41.
82. Teede HJ, Misso ML and Deeks AA: Assessment and management of Polycystic ovary syndrome: summary of an evidence-based guideline. Med J Aust 2011; 195: 65-112.
83. Pasquali R, Gambineri A and Pagotto U: The impact of obesity on reproduction in women with polycystic ovary syndrome. BJOG 2006; 113: 1148-59.
84. Knowler W, Barrett-Connor E, Fowler S, Hamman RF, Lachin JM and Walker EA: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393-03.
85. Norman RJ, Davies MJ, Lord JM and Moran LJ: The role of lifestyle modifications in polycystic ovary syndrome. Trends Endocrinol Metab 2002; 13: 235-7.
86. Clark AM, Thornley B, Tomlinson L, Galletley C and Norman RJ: Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. Hum Reprod 1998; 13: 1502-5.
87. Badawy A and Elnashar A: Treatment options for polycystic ovary syndrome. Int J Womens Health 2011; 3: 25-35.
88. Kasdorf G and Kalkhoff RK: Prospective studies of insulin sensitivity in normal women receiving oral contraceptive agents. J Clin Endocrinol Metab 1988; 66: 846-52.
89. Skouby SO, Andersen O, Saurberey N and Kuhl C: Oral contraception and insulin sensitivity: *in-vivo* assessment in normal women and women with previous gestational diabetes. J Clin Endocrinol Metab 1987; 64: 519-23.
90. Godsland IF, Walton C, Felton C, Proudler A, Patel A and Wynn V: Insulin resistance, secretion, and metabolism in users of oral contraceptives. J Clin Endocrinol Metab 1992; 74: 64-70.
91. Nader S, Riad-Gabriel MG and Saad MF: The effect of a desogestrel-containing oral contraceptive on glucose tolerance and leptin concentrations in hyperandrogenic women. J Clin Endocrinol Metab 1997; 82: 3074-77.
92. Pasquali R, Fabbri R, Venturoli S, Paradisi S, Antenucci D and Melchionda N: Effect of weight loss and antiandrogenic therapy on sex hormone blood levels and insulin resistance in obese patients with polycystic ovaries. Am J Obstet Gynecol 1986; 154: 114-39.
93. Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen K and Tapanainen JS:

Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. J Clin Endocrinol Metab 2000; 85: 3161-68.
94. Cibula D, Fanta M, Hill M, Sindelka G, Skrha J and Zivny J: Insulin sensitivity in non-obese women with polycystic ovary syndrome during treatment with oral contraceptives containing low-androgenic progestin. Hum Reprod 2002; 17: 76-82.
95. Dahlgren E, Landin K, Krotkiewski M, Holm G and Janson PO: Effects of two antiandrogen treatments on hirsutism and insulin sensitivity in women with polycystic ovary syndrome. Hum Reprod 1998; 13: 2706-11.
96. Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen K and Tapanainen JS: Metformin versus ethinyl estradiol cyproterone acetate in the treatment of nonobese women with polycystic ovary syndrome: a randomized study. J Clin Endocrinol Metab 2003; 88: 148-56.
97. Korytkowski M, Mokan M, Horwitz M and Berga S: Metabolic effects of oral contraceptives in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1995; 80: 3327-34.
98. Armstrong VL, Wiggan MI, Ennis CN, Sheridan B, Traub AI and Atkinson AB: Insulin action and insulin secretion in polycystic ovary syndrome treated with ethinyloestradiol/cyproterone acetate. QJM 2001; 94: 31-37.
99. Halperin IJ, Kumar SS, Stroup DF and Laredo SE: The association between the combined oral contraceptive pill and insulin resistance, dysglycemia and dyslipidemia in women with polycystic ovary syndrome: a systematic review and meta-analysis of observational studies. Hum Reprod 2011; 26: 191-01.
100. Meyer C, McGrath BP and Teede HJ: Effects of medical therapy on insulin resistance and the cardiovascular system in polycystic ovary syndrome. Diabetes Care 2007; 30: 471-8.
101. Falsetti L, Gambera A, Platto C and Legrenzi L: Management of hirsutism. Am J Cli Der 2000; 1(2): 89-99.
102. Lobo RA, Shoupe D, Serafini P, Brinton D and Horton R: The effects of two doses of spironolactone on serum androgens and anagen hair in hirsute women. Fertil Steril 1985; 43(2): 200-5.
103. Rosenfield RL: Clinical practice. Hirsutism. N Engl J Med 2005; 353(24): 2578-88.
104. Lumachi F and Rondinone R: Use of cyproterone acetate, finasteride, and spironolactone to treat idiopathic hirsutism. Fertil Steril 2003; 79(4): 942-6.
105. ACOG Committee on Practice Bulletins-Gynecology. ACOG Practice Bulletin No 108: Polycystic ovary syndrome. Obstet Gynecol 2009; 114(4): 936-49.
106. Poretsky L, Bhargava G, Kalin MF and Wolf SA: Regulation of insulin receptors in the human ovary: *in-vitro* studies. J Clin Endocrinol Metab 1988; 67: 774-8.
107. The Thessaloniki ESHRE/ASRM-Sponsored PCOS consensus workshop group. Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril 2008; 89(3): 505-52.
108. Diamanti-Kandarakis E, Christakou C. D, Kandaraki E and Economou FN: Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. Eur J Endocrinol 2010; 162: 193-12.
109. Palomba, S, Falbo A, Zullo F and Orio FJr: Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. Endocr Rev 2009; 30: 1-50.
110. Badawy A, Abdel AI and Abulatta M: Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertil Steril 2009; 92(3): 849-52.
111. Perales-Puchalt A and Legro RS: Ovulation induction in women with polycystic ovary syndrome. Steroids 2013; 78: 767-72.

How to cite this article:
Maqbool M, Gani I and Geer MI: Polycystic ovarian syndrome- a multifaceted disease: a review. Int J Pharm Sci & Res 2019; 10(3): 1072-79. doi: 10.13040/IJPSR.0975-8232.10(3).1072-79.