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Effects of Metformin Treatment on Pregnancy Outcomes in Women with Polycystic Ovary Syndrome and Insulin Resistance

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Summary

Polycystic Ovarian Syndrome (PCOS) is a clinical entity characterized by chronic anovulation and functional ovarian hyperandrogenism, LH and insulin dependent. Currently, first-line drugs in the treatment of polycystic ovary disease are metformin and glitazones (Thiazolidinediones) , and if necessary, antiandrogenic drugs, estrogens, progestins , or small doses of dexamethasone can be added. This study aimed to assess the Effects of Metformin Treatment on Pregnancy Outcomes in Women with Polycystic Ovary Syndrome and Insulin Resistance in a short term open labeled clinical trial included 30 PCOS patients, treated with metformin 1.7 g daily divided into two doses (850 mg/dose), orally. The patients were followed up monthly and clinically evaluated. We concluded that Metformin was effective treatment in PCOS cases, given its low cost, good tolerance and absence of significant adverse effects, is an excellent drug to use in patients with PCOS associated with insulin resistance, especially those with metabolic disorders and dyslipidemia

Keywords: *Polycystic Ovary Syndrome, Etiology , Hyperinsulinemia, insulin resistance, Metformin*

1 INTRODUCTION

Polycystic ovary syndrome (PCOS) , also known as Stein-Leventhal syndrome) is a polyendocrine syndrome accompanied by impaired ovarian function (absence or irregularity of ovulation , increased secretion of androgens and estrogens), pancreas (hypersecretion of insulin), adrenal cortex (hypersecretion) hypothalamus and pituitary gland(1,2).

Definitions

There are two definitions of polycystic ovary syndrome most commonly used in clinical practice. The first definition was developed in 1990 by consensus of a panel of experts formed by the American National Institutes of Health (NIH). According to this definition, a patient should be diagnosed with polycystic ovary disease if she simultaneously has Symptoms of excess activity or excess secretion of androgens (clinical and / or biochemical); Oligovulation or anovulation and if other causes that can cause polycystic ovaries are excluded(3,4). The second definition was formulated in 2003 by a consensus of European experts formed in Rotterdam. By this definition, a diagnosis is made if a patient has any two of the following three symptoms at the same time; symptoms of excess activity or excess secretion of androgens (clinical or biochemical); oligovulation or anovulation; and polycystic ovaries on abdominal ultrasound. The Rotterdam definition is much broader and includes significantly more patients in the group suffering from this syndrome.(4,5)

Clinical manifestations of PCOS:

Polycystic Ovarian Syndrome (PCOS) is a clinical entity characterized by chronic anovulation and functional ovarian hyperandrogenism, LH and insulin dependent(6). It is the most common endocrine disorder in women of reproductive age, with a prevalence of 3-10% (2). It represents the most common cause of anovulatory infertility and of early pregnancy loss (7,8)

Oligomenorrhea , amenorrhea, irregular and painful menstruation. Infertility, usually the result of chronic anovulation or oligoovulation (9). Increased blood levels of androgens especially free testosterone (10)(11). Obesity (central, apple shape) are common in patients with PCOS (12). Androgenic alopecia (13); Acanthosis; Acrochordons , appearance of stretch marks (14) , long periods of symptoms resembling those of premenstrual syndrome , depression , dysphoria , drowsiness, lethargy, apathy, chronic pain in the lower abdomen or in the lower back, in the

pelvic region, probably due to compression of the pelvic organs by enlarged ovaries or due to hypersecretion of prostaglandins in the ovaries and endometrium; the exact cause of chronic polycystic ovarian pain is unknown (6,15,16)

On ultrasonography, multiple ovarian cysts look like a "strings-of-pearl ", an increase in the size of the ovaries by 1.5-3 times due to the emergence of many small cysts. Ovaries appear thickened, smooth and their outer surface is pearly-white. Thickened, hyperplastic endometrium of the uterus as a result of a prolonged excess of estrogen, not balanced by adequate progesterone effects. Laboratory findings include increased LH level or increased LH / FSH ratio greater than 1: 1 , lower levels of sex steroid-binding globulins (17–19).

Etiology and pathogenesis : the exact reasons for the development of PCOS are unknown, however, great importance is attached to the pathological decrease in insulin sensitivity of peripheral tissues, primarily adipose and muscle tissue while maintaining the insulin sensitivity of ovarian tissue . A situation of pathologically increased insulin sensitivity of ovarian tissue is also possible while maintaining normal insulin sensitivity of peripheral tissues. Pathological tissue insulin resistance, hyperinsulinemia and insulin hypersecretion in polycystic ovary often (but not always) result from obesity or overweight. At the same time, these phenomena themselves can lead to obesity, since the effects of insulin are an increase in appetite, an increase in the deposition of fat and a decrease in its mobilization. In the pathogenesis of polycystic ovaries, importance is also attached to violations of the regulating hypothalamic-pituitary influences: excessive secretion of LH , abnormally increased LH / FSH ratio , increased " opioidergic " and decreased dopaminergic in the hypothalamus-pituitary gland system. The condition may be aggravated and more difficult to treat if there is concomitant hyperprolactinemia , subclinical or clinically significant thyroid insufficiency... Such combinations are found in these women much more often than in the general population, which may indicate the polyendocrine or polyetiological nature of the Stein-Leventhal syndrome (20–22). Some researchers attach importance to the increased level of prostaglandins and other mediators of inflammation in the ovaries tissues and in the follicular fluid in patients with polycystic ovaries and believe that in the pathogenesis of polycystic ovary syndrome, the aseptic inflammation of the ovarian tissue, transferred inflammatory diseases of the female genital area or autoimmune mechanisms (23).

Hyperinsulinemia and insulin resistance in PCOS:

An association of this syndrome with hyperinsulinism and insulin resistance (IR) has been observed in more than 70% of obese PCOS women and 30 to 50% of lean ones and IR playing a key role in pathogenesis of PCOS (24), The origin insulin-resistance is not in a congenital defect of the insulin receptor but, in a post-receptor event. In 2006 Draznin published that the problem is that a phosphorylation of serine occurs, which decreases the activity of tyrosine kinase, altering the post-receptor translation(25). The translation of the insulin signal is not correctly recognized by the target tissues, with the exception of the ovary, which would use a different translation pathway(26). Peripheral insulin resistance induces, in a compensatory way, an overproduction of insulin, which will exacerbate its effects on insulin-sensitive tissues(27,28). At the ovarian level, insulin can act through several pathways 1) in synergism with LH, 2) stimulating its own receptor in thecal cells and the ovarian stroma, 3) by increasing the synthesis of IGF-1 or 4) using IGF-1 receptors (hybrid receptor). Its action causes an increase in the ovarian synthesis of androgens, thanks to the fact that it induces an increase in the activity of the enzyme P450 17 . Likewise, insulin stimulates the enzyme P450 17 of reticular cells of the adrenal gland, increasing the secretion of androgens (DHEAS), enhancing the action of ACTH. On the other hand, hyperinsulinemia blocks the hepatic synthesis of SHBG and IGFBP1, increasing the levels of free androgens (29–33). Currently, the relationship between insulin resistance and PCOS is generally recognized and occurs in this group of patients 2-3 times more often than in the general population. It has been established that in PCOS, insulin resistance can occur both with increased and normal body weight (34–36). Literatures mentioned that Hyperinsulinism is associated with and endometrial hyperplastic processes (37). The effect of insulin on ovarian steroidogenesis is realized both through its own receptors and indirectly through IGF-1 (insulin like growth factor) receptors . insulin stimulates the hormonal activity of all parts of the ovary which leads to an increase in the synthesis of all sex steroids. However, the most significant effect of insulin on increasing the activity of 17α-hydroxylase and 17α-lyase, key enzymes in the biosynthesis of androgens in the ovaries. Activation of steroidogenesis also occurs due to an increase in the number of luteinizing hormone (LH) receptors in granulosis, caused by hyperinsulinism. The growth effects of insulin on the ovary are manifested in the stimulation of theca interstitial cells, which, in addition to

hyperandrogenism, leads to the formation of a polycystic structure and an increase in its volume An excess of androgens inhibits folliculogenesis., Thus, ovarian steroidogenesis in insulin resistance is characterized by excessive formation of androgens, monotonous secretion of estradiol (E 2), which does not reach the level of the middle of the follicular phase of a healthy woman (32,38,39). Central mechanisms of action of insulin consist in sensitizing pituitary cells to the action of gonadotropin-releasing hormone (GnRH). LH secretion is more sensitive to its effects, in addition, the half-life of LH is longer than that of follicle-stimulating hormone (FSH). The consequence of this is an imbalance of gonadotropins due to a predominant increase in LH synthesis. The effect of hyperinsulinism on the gonadotropic activity of the pituitary gland is to increase the level of LH secretion, which leads to an increase in the vicious circle leading to anovulation, oligomenorrhea, hyperandrogenism, polycystic morphology of the ovaries . In addition to the direct effect on ovarian steroidogenesis, insulin has an effect on androgen metabolism, reducing the concentration of sex steroid binding globulins and IGF-1 (39,40).

Treatment

Historically, the very first attempts to treat polycystic ovary syndrome consisted of surgical intervention - decapsulation of the ovaries or their partial resection with the removal of the most affected tissue areas, or excision of the ovarian bed (ovarian wedge resection), or the careful application of diathermy of the ovaries. In some cases, such operations were successful and made it possible to restore the woman's fertility , as well as to achieve a sharp decrease in the secretion of androgens by the ovaries, and the normalization of the menstrual cycle. However, surgical intervention is not always possible, and it did not always lead to success(40–42).

Traditional conservative treatment consisted of prescribing anti- androgens , estrogens , progestins with antiandrogenic activity, or their combination(40).

Metformin in treatment of PCOS

Currently, first-line drugs in the treatment of polycystic ovary disease are metformin and glitazones (Thiazolidinediones). To them, if necessary, antiandrogenic drugs, estrogens, progestins , or small doses of dexamethasone can be added(43,44).

Metformin is a biguanide used in the management of patients with non-insulin dependent diabetes mellitus, capable of increasing insulin sensitivity, normalizing blood glucose levels without the risk of hypoglycemia. Its mechanism of action is multifactorial, mainly exerted at the liver level where it decreases gluconeogenesis or basal glucose production. In the periphery it stimulates glucose uptake by muscle and fat tissue. It is not clear whether its peripheral effect derives from directly improving post-receptor activity or after increasing non-oxidative glucose metabolism. (44–47)

In PCOS, metformin has been used in both obese and thin patients as the first insulin-sensitizing agent (48). However, insulin-sensitizing drugs (ISD) in PCOS act through reduction of levels of circulating insulin. On the other hand, many effects have been documented to be related to metformin in PCOS cases; such as returning ovulation, weight reduction, lowering miscarriage risks, reduction of androgens and lowering the risks of gestational diabetes. Previous relevant studies showed that when ovarian stimulation regime combined with metformin a significant improvement reported in pregnancy outcomes (47,49,50). Earlier studies showed that metformin is effective in induction of ovulation in PCOS cases and it can be used as first line of treatment, but with changes in lifestyle (51). Also these studies showed that 46% of cases treated with metformin were ovulated successfully compared to only 24% of PCOS cases who did not receive metformin. The rate of ovulation was higher when metformin combined with clomiphene (52). conversely, other study found that such combination was not superior to clomiphene alone (53). From other point of view, other studies have shown that pregnancy outcomes improved when metformin added to ovarian stimulating regime (52). Other effects of metformin in PCOS patients include weight loss, steroidogenesis , reduce miscarriage and gestational DM rates . Also metformin has shown to have prophylactic effect in reduction of long term disease risks. Additionally metformin suggested to reduce the risk of endometrial cancer. However, several studies are conflicting about the role and benefit of metformin in PCOS, and conflicting results are published in this regard. Therefore, we aimed in our study to evaluate the short-term clinical, biochemical and reproductive effect of metformin therapy in 30 patients with PCOS and also to know the various predictive parameters of response to treatment in comparison to control group who did not receive Metformin(52).

2 PATIENTS AND METHODS

This short-term open labeled clinical trial conducted at AlForat AlAwsat teaching Hospital during a period of 18 months (January 2020 to July 2021). A total of 30 patients with PCOS who consulted gynecology department of our Hospital and our private clinics were included . All patients who met the inclusion criteria were received metformin in form of 850 mg tablets two times daily. Treatment was according to clinical guidelines , practice and judgment of gynecologists in addition to consultation of an expert specialist endocrinologist. The age of the patients ranged from 20 to 40 years.

Case definition: The criterion used to define PCOS was according to Rotterdam criteria was formulated in 2003 by a consensus of European experts (5) .

Regular cycles were defined as inter-menstrual intervals of 21-35 days. Oligomenorrhea was defined as menstruation with an interval greater than 35 days and less than 8 cycles / year. Amenorrhea as the absence of menstruation for more than 3 months.

The criteria for the diagnosis of insulin resistance corresponded to baseline hyperinsulinism (> 20 mIU / ml) and at 2 hours (> 60 mIU / ml) after an oral glucose load test (75 g), or the index glycemia / insulinemia <4.5.

The study protocol consisted of the administration of metformin 1.7 g daily divided into two doses (850 mg/dose), orally. All patients were evaluated under baseline conditions and after receiving the drug for 6 months. On both occasions, plasma levels of FSH, LH, total and free testosterone, sex hormone binding globulin (SHBG), Prolactin, DHEAS, glycemia and insulinemia, and ovarian volume evaluation with transvaginal ultrasonography were measured. The examinations were carried out in the early follicular phase, or at any time in the case of amenorrhea. For all patients in metformin group, an expert specialist endocrinologist was consulted regularly. The patients were followed up monthly and evaluated for menstrual regularity, weight, blood pressure, and hirsutism score and they were asked to spontaneously report any adverse drug effects. Eleven Patients wanted pregnancy and continued to receive the drug for up to a year, in an open labeled trial. Before including them in the study, ovarian

and adrenal tumor causes of hyperandrogenism, congenital adrenal hyperplasia, thyroid changes and hyperprolactinemia were ruled out.

Diabetic patients and those who were receiving hormonal therapy, anorectics or drugs that affect lipoprotein metabolism in the 3 months prior to the study were excluded from the study.

The study was approved by the Hospital Management office, Najaf Health directorate-Ethical committee and signed informed consents obtained from all patients to participate in the study with full rights to leave the study at any time.

All Statistical analyses and procedures were performed using the statistical package for social sciences (SPSS) version 25 with assistance of expert professional biostatistician. For statistical analysis, paired t test used to compare pre vs. post treatment results at a level of significance of 0.05 or less to be considered as significant difference.

3 RESULTS

The mean age of patients at time of inclusion was 25.8 ± 4.3 (range: 20 – 40) years. Mean body mass index (BMI) was 33.4 ± 3.8(range 28-44) kg/m² and Majority of patients 27/30 (90%) were obese (BMI>30 kg/m²). Out of all PCOS cases, 23 (76.7%) had oligoamenorrhea, 7 (23.3%) Amenorrhea. Hirsutism in 18 cases (60%) and in 16 cases (53.3%) Hirsutism score was 7 or higher. Infertile women were 11 (36.7), 17 patients (56.7%) had elevated total and free testosterone. On ultrasound, 19 patients (63.3%) had polycystic ovaries demonstrated with 8 or more subcapsular follicles of 3 to 8 mm in diameter, with increased stroma and bilateral ovarian volume, (Table 1)

Clinical effects

At the end of the six months of treatment, 20 (66.7%) of 30 patients normalized their menstrual cycle. Among the studied group, 11 infertile patients and wanted pregnancy, in whom progesterone measured in in the mid-luteal phase and the cycles were ovulatory, among those patients, seven out of 11(63.3%) women achieved pregnancy at the 5th to 7th month of treatment. One of them had a spontaneous abortion at 8 weeks and the other 6 patients had physiological pregnancies. There were no changes in the hirsutism score or body mass index at the end of the 6 months of treatments. We did not find significant variations in the average

ovarian volume: 12.6 ml and 11.5 ml, during therapy. No significant changes were observed in the lipid profile of the patients at the end of the treatment , in all comparisons , P>0.05 (Table 2). Hormonal levels of sex steroids, gonadotropins, and insulin showed that 16/30 patients (63.3%) had a significant decrease in baseline insulin level and two hours after glucose overload. A significant decrease in free testosterone reported in 21 (70%) of patients. We also found a significant increase in plasma SHBG levels in 14 patients(46.7%). We observed a downward trend in total testosterone. We did not find significant change in blood glucose levels and in the oral glucose overload test in any of the patients after treatment with metformin (Table 3). In (Figure 1). we divide the patients into two groups, according to menstrual changes during treatment as successful response (n = 19) and unsuccessful response (n = 11). These two subgroups were compare and we observed that no clinical or biochemical parameter was predictive of response to metformin (Table 4). We did not find serious adverse effects to the drug, except for mild gastrointestinal disorders (nausea, diarrhea) that occurred at the beginning of treatment and that were not a reason for its suspension.

Table 1. Baseline characteristics of 30 PCOS women

Variable	No.	%
Mean age ± SD (year)*	25.8 ± 4.3	-
Mean BMI ± SD (kg/m²)	33.4 ± 3.8	-
Obesity	27	90.0
Oligomenorrhea	23	76.7
Amenorrhea	7	23.3
Hirsutism	18	60.0
Hirsutism score ≥ 7	16	53.3
Infertility	11	36.7
Elevated total testosterone	17	56.7
Elevated free testosterone	17	56.7
PCOS on ultrasound	19	63.3

SD: standard deviation of mean

Table 2. Menstrual pattern before and during metformin therapy

Menstrual pattern	Before treatment		After treatment	
	No.	%	No.	%
Oligomenorrhea	22	73.3	9	30.0
Amenorrhea	8	26.7	1	3.3
Eumenorrhea	0	0.0	20	66.7
P. value < 0.001				

Table 3. Comparison of patients characteristics before and after metformin treatment

Variable	Before treatment		After treatment		**P. value**
	Mean	SD	Mean	SD	
BMI (kg/m²)	33.4	3.8	32.1	4.2	0.720 ns
LH	11.7	6.8	10.1	3.4	0.580 ns
FSH	5.6	1.7	5.8	0.9	0.640 ns
Baseline Insulin	39.8	15.2	21.3	8.6	<0.001 sig
Insulin (2 hours)	204.1	82.4	119.2	52.3	<0.001 sig
Total testosterone (ng/dL)	95.6	31.2	47.3	33.1	<0.001 sig
Free testosterone (ng/dL)	8.4	6.7	2.1	0.78	<0.001 sig
DHEAS (µg /dl)	235.9	114	150.9	103.6	<0.001 sig
SHBG (nmol/L)	17.5	3.9	25	11.5	0.003 sig
Ovarian volume (ml)	12.6	7.7	11.5	6.1	0.117 ns

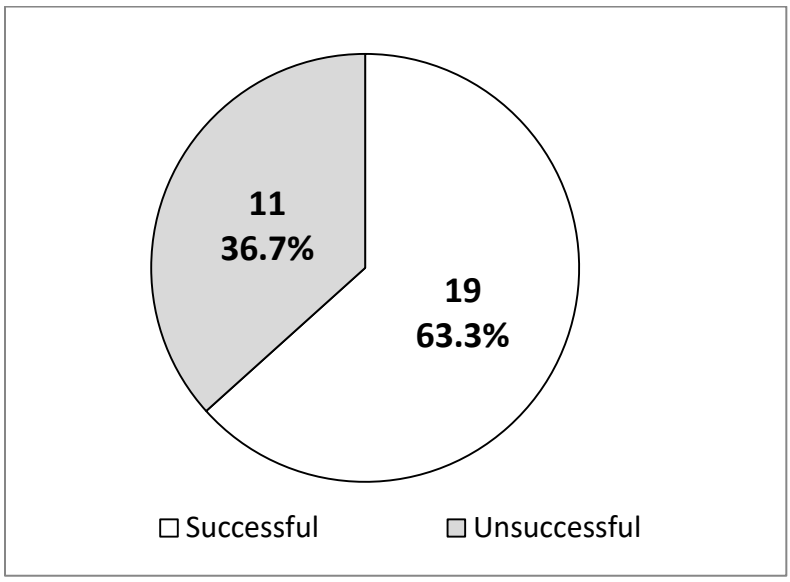

Figure 1. Distribution of the studied group according to the menstrual changes during treatment

Table 4. Basal hormonal levels responding and non-responding to metformin PCOS patients

	Successful response (n= 19)		Unsuccessful response (n = 11)		P. value
	Mean	SD	Mean	SD	
BMI	33.1	3.9	33.9	5.6	0.530 ns
LH	15.2	6.3	7.3	4.3	0.121 sig
Basal insulin	28.3	6.9	51.2	4.9	0.817 ns
Insulin 2 hours	207.7	83.2	198.7	151.8	0.336 ns
Total test	79.5	35.2	117	54.9	0.114 ns
Free test	10.5	6.7	2.35	0.2	0.213 ns
DHEAS	269.8	96.4	192.5	133.5	0.307 ns

4 | DISCUSSION

The findings of this study demonstrate that metformin produces a reduction in the basal plasma concentrations of total and free testosterone and the secretion of DHEAS (adrenal androgen marker) and an increase in circulating SHBG levels, in women with PCOS. These effects are explained by a lowering effect caused by the drug in basal plasma insulin levels as glucose post-overload. Improves insulin resistance, which would cause a decrease in the activity of the cytochrome P450c17 enzyme in both cells and adrenal glands. These effects

cannot be explained by a decrease in weight, as has been described by other authors (48,52) , since BMI did not change significantly in the course of treatment of our patients.

The decrease in insulin level reduces the hepatic arrest of SHBG synthesis by HEP G2 cells which causes an increase in plasma concentrations of SHBG and, in turn, a decrease in free testosterone levels. This would improve the intra-follicular microenvironment (54), allowing better development and growth of the follicle, leading to ovulatory cycles, normalization of menstrual function and pregnancy, as occurred in 11 of our patients.

We did not observe changes in plasma LH levels that found by some authors (55,56), but not by others (57,58) . Our patients were probably not very responsive to this benefit described for metformin because majority had severe obesity (BMI> 35). Our study, in agreement with others, showed that metformin can improve endocrine, metabolic and reproductive abnormalities in PCOS (59,60). Our study, like others, demonstrated that metformin treatment produced a significant decrease in ovarian androgen levels, concomitant with a decrease in insulinemia(46,52,61). We believe that the predominant etiopathogenic factor in our patients was dependent on hyperinsulinism and not on LH .

This work, in the short term, failed to demonstrate improvement in hirsutism in patients with PCOS, while other authors demonstrated a significant effect on hirsuitism (62). This can be explained by the time required to act on the sexual hair growth cycle, therefore, a longer observation time would be needed to obtain any conclusion. We agree with the literature that, with the decrease in insulin and the level of androgens, there is a greater number of ovulatory cycles as the intra-follicular microenvironment improves (33,63). It has been shown that, in patients with PCOS, hyperinsulinemia adversely affects embryo implantation by decreasing glycodelin (placenta factor-14) and the concentration of IGF BP1, proteins produced in the endometrial glands. It also adversely affects endometrial thickness and vascularization, which can be measured by Doppler ultrasonography(64). Metformin would improve implantation rates by increasing these proteins and increasing vascularization of the endometrium. It has been reported that it decreases the resistance index of the spiral arteries by 20% and improves vascular penetration by 19 to 69%, which ultimately results in a decrease in the rates of early abortions (65).

5 | CONCLUSIONS

Metformin was effective treatment in PCOS cases, given its low cost, good tolerance and absence of significant adverse effects, is an excellent drug to use in patients with PCOS associated with insulin resistance, especially those with metabolic disorders and dyslipidemia. It would also be the first-line drug to induce ovulation in infertile patients with this syndrome. However, further studies are still needed for longer duration with larger sample size for better evaluation and assessment.

Ethical Issue:

All ethical issues were approved by the author, in accordance with Ethical Principles of Declaration of Helsinki of the world Medical Association, 2013, for research involving human subjects

6 | BIBLIOGRAPHY

1. Meier R. Polycystic ovary syndrome. Nurs Clin North Am. 2018;53(3):407–20.
2. Wolf WM, Wattick RA, Kinkade ON, Olfert MD. Geographical prevalence of polycystic ovary syndrome as determined by region and race/ethnicity. Int J Environ Res Public Health. 2018;15(11):2589.
3. Azziz R. Diagnostic criteria for polycystic ovary syndrome: A reappraisal. Fertil Steril. 2015;83(5):1343–5.
4. Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol. 2018;14(5):270–84.
5. Wang R, Mol BWJ. The Rotterdam criteria for polycystic ovary syndrome: evidence-based criteria? Hum Reprod. 2017;32(2):261–4.
6. Barbieri RL, Ehrmann DA. Clinical manifestations of polycystic ovary syndrome in adults. JMSP. 2014;17(8):148–62.
7. Mayrhofer D, Hager M, Walch K, Ghobrial S, Rogenhofer N, Marculescu R, et al. The prevalence and impact of polycystic ovary syndrome in recurrent miscarriage: a retrospective cohort study and meta-analysis. J Clin Med. 2020;9(9):2700.
8. Hussein B, Alalaf S. Prevalence and characteristics of polycystic ovarian syndrome in a sample of infertile Kurdish women attending IVF infertility center in maternity teaching hospital of Erbil City. 2013;2013(September):577–85.
9. Joham AE, Teede HJ, Ranasinha S, Zoungas S, Boyle J. Prevalence of infertility and use of fertility treatment in women with polycystic ovary syndrome: data from a large community-based cohort study. J women's Heal. 2015;24(4):299–307.

10. Nadaraja RND, Pavai Sthaneshwar M, Nuguelis Razali MBBS Mo. Establishing the cut off values of androgen markers in the assessment of polycystic ovarian syndrome. Malays J Pathol. 2018;40(1):33–9.
11. Khan A, Karim N, Ainuddin JA, Fahim MF. Polycystic Ovarian Syndrome: Correlation between clinical hyperandrogenism, anthropometric, metabolic and endocrine parameters. Pakistan J Med Sci. 2019;35(5):1227.
12. Boumosleh JM, Grundy SM, Phan J, Neeland IJ, Chang A, Vega GL. Metabolic concomitants of obese and nonobese women with features of polycystic ovarian syndrome. J Endocr Soc. 2017;1(12):1417–27.
13. Akdeniz DD, Yılmaz C. Early onset androgenic alopecia: not a cosmetic problem but a sign of life time risk factors. Male phenotypic equivalent of polycystic ovarian syndrome: Is There a Male Phenotype of PCOS. Med Sci Discov. 2021;8(4):231–6.
14. Mukkamala S, Aruna C, Ramamurthy D, Sridevi K, Senthil AL, Kameti S. Cutaneous manifestations in polycystic ovarian syndrome: a clinico-epidemiological study. J Pakistan Assoc Dermatology. 2019;28(4):410–4.
15. Sulaiman MAH, Al-Farsi YM, Al-Khaduri MM, Waly MI, Saleh J, Al-Adawi S. Psychological burden among women with polycystic ovarian syndrome in Oman: a case–control study. Int J Womens Health. 2017;9:897.
16. Chaudhari AP, Mazumdar K, Mehta PD. Anxiety, depression, and quality of life in women with polycystic ovarian syndrome. Indian J Psychol Med. 2018;40(3):239–46.
17. Ahmed AA, Moselhy SS, Kumosani TA, Huwait EA, Al-Ghamdi MA, Al-Madani KA, et al. Ultrasonographic and biochemical assessments as early prediction of polycystic ovarian syndrome in obese women. Afr Health Sci. 2020;20(2):676–81.
18. Tripathy P, Sahu A, Sahu M, Nagy A. Ultrasonographic evaluation of intra-abdominal fat distribution and study of its influence on subclinical atherosclerosis in women with polycystic ovarian syndrome. Eur J Obstet Gynecol Reprod Biol. 2017;217:18–22.
19. Gupta V, Sharma S, Raina SK, Bedi GK. Clinical, ultrasonographic, and biochemical correlates of polycystic ovarian syndrome: A case–control study from a Tertiary Care Center in North India. J Sci Soc. 2018;45(1):8.
20. Panarina O V, Rashidova MA, Belenkaya L V, Trofimova TA, Sholokhov LF. Modern concepts of the pathogenesis of polycystic ovary syndrome (literature review). Acta Biomed Sci (East Sib Biomed Journal). 2017;2(4):9–14.
21. Ibáñez L, Oberfield SE, Witchel S, Auchus RJ, Chang RJ, Codner E, et al. An international consortium update: pathophysiology, diagnosis, and treatment of polycystic ovarian syndrome in adolescence. Horm Res Paediatr. 2017;88:371–95.
22. Witchel SF, Oberfield SE, Peña AS. Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. J Endocr Soc. 2019;3(8):1545–73.
23. Sathyapalan T, Atkin SL. Mediators of inflammation in polycystic ovary syndrome in relation to adiposity. Mediators Inflamm. 2010;2010.
24. Orbetzova MM. Clinical Impact of Insulin Resistance in Women with Polycystic Ovary Syndrome. In: Polycystic Ovarian Syndrome. IntechOpen; 2020.

25. Draznin B. Molecular mechanisms of insulin resistance: serine phosphorylation of insulin receptor substrate-1 and increased expression of p85α: the two sides of a coin. Diabetes. 2006;55(8):2392–7.
26. Nestler JE, Jakubowicz DJ, Falcon de Vargas A, Brik C, Quintero N, Medina F. Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. J Clin Endocrinol Metab. 2018;83(6):2001–5.
27. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev. 2015;26(2):19.
28. Ferrannini E, Balkau B, Coppack SW, Dekker JM, Mari A, Nolan J, et al. Insulin resistance, insulin response, and obesity as indicators of metabolic risk. J Clin Endocrinol Metab. 2007;92(8):2885–92.
29. Dupont J, Scaramuzzi RJ. Insulin signalling and glucose transport in the ovary and ovarian function during the ovarian cycle. Biochem J. 2016;473(11):1483–501.
30. Marshall JC, Dunaif A. All women with PCOS should be treated for insulin resistance. Fertil Steril. 2012;97(1):18–22.
31. Cree-Green M, Rahat H, Newcomer BR, Bergman BC, Brown MS, Coe G V, et al. Insulin resistance, hyperinsulinemia and mitochondria dysfunction in non-obese girls with polycystic ovarian syndrome. J Endocr Soc. 2017;
32. Sozen I, Arici A. Hyperinsulinism and its interaction with hyperandrogenism in polycystic ovary syndrome. Obstet Gynecol Surv. 2015;55(5):321–8.
33. Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev. 2016;37(5):467–520.
34. Wang J, Wu D, Guo H, Li M. Hyperandrogenemia and insulin resistance: the chief culprit of polycystic ovary syndrome. Life Sci. 2019;236:116940.
35. Shorakae S, Ranasinha S, Abell S, Lambert G, Lambert E, de Courten B, et al. Inter-related effects of insulin resistance, hyperandrogenism, sympathetic dysfunction and chronic inflammation in PCOS. Clin Endocrinol (Oxf). 2018;89(5):628–33.
36. Moghetti P, Tosi F. Insulin resistance and PCOS: chicken or egg? J Endocrinol Invest. 2021;44(2):233–44.
37. Shan W, Ning C, Luo X, Zhou Q, Gu C, Zhang Z, et al. Hyperinsulinemia is associated with endometrial hyperplasia and disordered proliferative endometrium: a prospective cross-sectional study. Gynecol Oncol. 2014;132(3):606–10.
38. Garg D, Merhi Z. Relationship between Advanced Glycation End Products and Steroidogenesis in PCOS. Reprod Biol Endocrinol [Internet]. 2016;14(1):71. Available from: https://doi.org/10.1186/s12958-016-0205-6
39. King SM, Modi DA, Eddie SL, Burdette JE. Insulin and insulin-like growth factor signaling increases proliferation and hyperplasia of the ovarian surface epithelium and decreases follicular integrity through upregulation of the PI3-kinase pathway. J Ovarian Res [Internet]. 2013;6(1):12. Available from: https://doi.org/10.1186/1757-2215-6-12
40. Vázquez-Borregoa MC, Antonio C. Fuentes-Fayosa MDG, Castañoa JP, Kinemane RD, Luque RM. The Pituitary Gland is a Novel Major Site of Action of Metformin in Non-Human Primates: a Potential Path to Expand and Integrate Its Metabolic Actions. Cell Physiol Biochem 2018;491444-1459. 2018;49(9):1444–59.

41. Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. Int J Womens Health. 2011;3:25.
42. Hoeger KM, Dokras A, Piltonen T. Update on PCOS: consequences, challenges, and guiding treatment. J Clin Endocrinol Metab. 2021;106(3):e1071–83.
43. Luque-Ramírez M, Nattero-Chávez L, Ortiz Flores AE, Escobar-Morreale HF. Combined oral contraceptives and/or antiandrogens versus insulin sensitizers for polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2018;24(2):225–41.
44. Vanky E, Kjøtrød SB, Maesel A, Bjerve KS, Carlsen SM. Dexamethasone reduces androgen levels in metformin-treated patients with polycystic ovary syndrome. Fertil Steril. 2004;81(2):459–62.
45. Seli E, Duleba AJ. Treatment of PCOS with metformin and other insulin-sensitizing agents. Curr Diab Rep. 2004;4(1):69–75.
46. La Marca A, Artensio AC, Stabile G, Volpe A. Metformin treatment of PCOS during adolescence and the reproductive period. Eur J Obstet Gynecol Reprod Biol. 2005;121(1):3–7.
47. Haas J, Bentov Y. Should metformin be included in fertility treatment of PCOS patients? Med Hypotheses. 2017;100:54–8.
48. Trolle B, Flyvbjerg A, Kesmodel U, Lauszus FF. Efficacy of metformin in obese and non-obese women with polycystic ovary syndrome: a randomized, double-blinded, placebo-controlled cross-over trial. Hum Reprod. 2007;22(11):2967–73.
49. Awwad J, Ghazeeri G. Role of insulin sensitizing drugs in PCOS management. Polycystic Ovary Syndr Curr Emerg Concepts. 2013;165.
50. Dunaif A. Drug insight: insulin-sensitizing drugs in the treatment of polycystic ovary syndrome—a reappraisal. Nat Clin Pract Endocrinol Metab. 2008;4(5):272–83.
51. Medicine PC of the AS for R. Role of metformin for ovulation induction in infertile patients with polycystic ovary syndrome (PCOS): a guideline. Fertil Steril. 2017;108(3):426–41.
52. Lashen H. Review: Role of metformin in the management of polycystic ovary syndrome. Vol. 1, Therapeutic Advances in Endocrinology and Metabolism. 2010. p. 117–28.
53. Palomba S, Russo T, Orio Jr F, Falbo A, Manguso F, Cascella T, et al. Uterine effects of metformin administration in anovulatory women with polycystic ovary syndrome. Hum Reprod. 2006;21(2):457–65.
54. Qu X, Donnelly R. Sex Hormone-Binding Globulin (SHBG) as an Early Biomarker and Therapeutic Target in Polycystic Ovary Syndrome. Int J Mol Sci [Internet]. 2020 Nov 1;21(21):8191. Available from: https://pubmed.ncbi.nlm.nih.gov/33139661
55. Kurzthaler D, Hadziomerovic-Pekic D, Wildt L, Seeber BE. Metformin induces a prompt decrease in LH-stimulated testosterone response in women with PCOS independent of its insulin-sensitizing effects. Reprod Biol Endocrinol [Internet]. 2014 Oct 11;12:98. Available from: https://pubmed.ncbi.nlm.nih.gov/25304843
56. Mansfield R, Galea R, Brincat M, Hole D, Mason H. Metformin has direct effects on human ovarian steroidogenesis. Fertil Steril. 2003;79(4):956–62.
57. Ulloa-Aguirre A, Portocarrero L, Zariñán T, Olivares A, Carranza-Lira S, Veldhuis JD, et al. Effects of metformin on inappropriate LH release in women with polycystic ovarian

syndrome and insulin resistance. Reprod Biomed Online [Internet]. 2006;12(6):669–83. Available from: https://www.sciencedirect.com/science/article/pii/S1472648310610796

58. Guan Y, Wang D, Bu H, Zhao T, Wang H. The Effect of Metformin on Polycystic Ovary Syndrome in Overweight Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Francomano D, editor. Int J Endocrinol [Internet]. 2020;2020:5150684. Available from: https://doi.org/10.1155/2020/5150684
59. Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, et al. Metformin Effects on Clinical Features, Endocrine and Metabolic Profiles, and Insulin Sensitivity in Polycystic Ovary Syndrome: A Randomized, Double-Blind, Placebo-Controlled 6-Month Trial, followed by Open, Long-Term Clinical Evaluation1. J Clin Endocrinol Metab [Internet]. 2000 Jan 1;85(1):139–46. Available from: https://doi.org/10.1210/jcem.85.1.6293
60. Sam S, Ehrmann DA. Metformin therapy for the reproductive and metabolic consequences of polycystic ovary syndrome. Diabetologia [Internet]. 2017;60(9):1656–61. Available from: https://doi.org/10.1007/s00125-017-4306-3
61. Daneshjou D, Mehranjani MS, Modarres SZ, Shariatzadeh MA. Sitagliptin/Metformin: A New Medical Treatment in Polycystic Ovary Syndrome. Trends Endocrinol Metab. 2020;
62. Kelly CJG, Gordon D. The effect of metformin on hirsutism in polycystic ovary syndrome. Eur J Endocrinol. 2002 Aug;147(2):217–21.
63. Baptiste CG, Battista M-C, Trottier A, Baillargeon J-P. Insulin and hyperandrogenism in women with polycystic ovary syndrome. J Steroid Biochem Mol Biol [Internet]. 2009/12/28. 2010 Oct;122(1–3):42–52. Available from: https://pubmed.ncbi.nlm.nih.gov/20036327
64. Sakumoto T, Tokunaga Y, Tanaka H, Nohara M, Motegi E, Shinkawa T, et al. Insulin resistance/hyperinsulinemia and reproductive disorders in infertile women. Reprod Med Biol. 2010;9(4):185–90.
65. Jakubowicz DJ, Seppälä M, Jakubowicz S, Rodriguez-Armas O, Rivas-Santiago A, Koistinen H, et al. Insulin reduction with metformin increases luteal phase serum glycodelin and insulin-like growth factor-binding protein 1 concentrations and enhances uterine vascularity and blood flow in the polycystic ovary syndrome. J Clin Endocrinol Metab. 2011;86(3):1126–33.

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