Abstract

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. PCOS produces symptoms in approximately 5 to 10% of women of reproductive age (12–45 years old) and is thought to be one of the leading causes of the female subfertility.

Aims: The aim of this work is to study the effect of metformin use for reducing early pregnancy loss in pregnant patients with PCOS.

Methodology: Type of study: Randomized controlled trial study; Site of study: Maternity hospital of Ain Shams University. Duration of study: Six months from August 2015 – February 2016. Study population: One hundred and eighty six patients were assessed for eligibility. Twenty patients were excluded during the duration of the study. One hundred and sixty six patients with PCOS who got pregnant after the administration of Metformin divided on 2 groups, each group included 83 patients.

Results: One hundred and sixty six pregnant women with criteria of PCO and receiving preconception Metformin were divided randomly on 2 sub groups as follows: Group (A): 83 patients stopped metformin at diagnosis of pregnancy (5-6 weeks gestation calculated from 1st day of a reliable LMP). Group (B): 83 patients continued metformin until end of 1st trimester (14 weeks gestation calculated from 1st day of a reliable LMP)

Conclusion: In conclusion, the continued use of metformin in pregnant women with PCOS during 1st trimester was associated with a significant reduction in the rates of early pregnancy loss. It was well tolerated by patients with a minimum of side effects. However, extended studies are required to evaluate its effect on further pregnancy complications and fetal outcomes.

Recommendations: Based on this study, Metformin is recommended to be used in PCO patients during induction of ovulation and continued during 1st trimester of pregnancy. Further studies are recommended to study the effect of metformin all through pregnancy and notice its effect on other complications during 2nd and 3rd trimester.

Keywords: Metformin, Early pregnancy loss, pregnant women, polycystic ovary syndrome, PCOS.

Chapter I

POLYCYSTIC OVARY SYNDROME (PCOS)

Polycystic ovary syndrome (PCOS) was first reported in modern medical literature by two American scientists Stein and Leventhal who, in 1935, described seven women suffering from amenorrhea, hirsutism, and enlarged ovaries with multiple cysts "two to four times the normal size, sometimes distinctly globular", "tunica thickened, though, and fibrotic", "follicle cysts near the cortex and almost entirely confined to the cortex". "The color of the ovary was oyster gray with bluish areas where the cysts were superficial and appeared on the surface as sago-like bodies" ***(Stein IF, Leventhal ML, et al. 1935)***

Clinical Presentation and diagnosis criteria

The clinical presentation of PCOS varies widely. Women with PCOS often seek care for menstrual disturbances, clinical manifestations of hyperandrogenism, and infertility.

Menstrual disturbances:

Menstrual disturbances commonly observed in PCOS include oligomenorrhea, amenorrhea, and prolonged erratic menstrual bleeding ***(Farquhar C., et al. 2007)***.

Approximately 85%–90% of women with oligomenorrhea have PCOS while 30%–40% of women with amenorrhea will have PCOS ***(Hart R, et al. 2007).***

Hyperandrogenism:

More than 80% of women presenting with symptoms of androgen excess have PCOS. Hirsutism is a common clinical presentation of hyperandrogenism occurring in up to 70% of women with PCOS**.** Hirsutism is evaluated using a modified Ferriman–Gallwey scoring system**.** ***(Azziz R, et al. 2004) (Fauser B, et al. 2012) (Ferriman D, Gallwey J. 1961)***

This tool is used to evaluate hair growth at seven sites: upper lip, chin/face, chest, back, abdomen, arms, and thighs. A score of 0 is given in the absence of terminal hair growth and a score of 4 is given for extensive growth. A total score of 8 (2 sites with extensive hair growth) or more is indicative of hirsutism. ***(Unluhizarci K, et al. 2012)***.

In addition, PCOS occurs in 50% of women with less severe distribution of unwanted hair growth. ***(Souter I, et al. 2004).***

Acne can also be a marker of hyperandrogenism but is less prevalent in PCOS and less specific than hirsutism. Approximately 15%–30% of adult women with PCOS present with acne ***(Wijeyaratne C, et al. 2002).***

The difference in prevalence of hirsutism and acne may be attributed to the difference in expression of 5α-reductase in the sebaceous gland and the hair follicle, and resulting higher dihydrotestosterone in the hair follicle. ***(Lowenstein E. 2006).***

Some experts recommend that women presenting with acne be asked about their menstrual history and be evaluated for other signs of hyperandrogenism. ***(Lowenstein E. 2006).***

Infertility:

Infertility affects 40% of women with PCOS. ***(Teede H, et al 2010).***

PCOS is the most common cause of anovulatory infertility. Approximately 90%–95% of anovulatory women presenting to infertility clinics have PCOS. Women with PCOS have a normal number of primordial follicles and primary and secondary follicles are significantly increased. However, due to derangements in factors involved in normal follicular development, follicular growth becomes arrested as follicles

reach a diameter of 4–8 mm. Because a dominant follicle does not develop, ovulation does not ensue***. (Brassard M, et al. 2008)***

In addition, spontaneous abortion occurs more frequently in PCOS with incidences ranging from 42%–73%. ***(Glueck C, et al. 2001)***

Diagnosis of PCOS:

Diagnostic criteria for PCOS have been offered by three groups: the National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD); ***(Zawadski JK, et al. 1992)*** the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM***); (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group.2004)*** and the Androgen Excess and PCOS Society***. (Azziz R, et al. 2006)*** These criteria are summarized in Table 1.

Table (1): Criteria for the diagnosis of polycystic ovary syndrome.

NIH/NICHD 1992	ESHRE/ASRM (Rotterdam criteria) 2004	Androgen Excess Society 2006
Exclusion of other androgen excess or related disorders	Exclusion of other androgen excess or related disorders	Exclusion of other androgen excess or related disorders
Includes all of the following:	Includes two of the following:	Includes all of the following:
• Clinical and/or biochemical hyperandrogenism	• Clinical and/or biochemical hyperandrogenism	• Clinical and/or biochemical hyperandrogenism
• Menstrual dysfunction	• Oligo-ovulation or anovulation	• Ovarian dysfunction and/or polycystic ovaries
	• Polycystic ovaries	

While there are certain consistencies between the criteria offered by the different groups, important differences exist. Each issuing group considers PCOS a diagnosis of exclusion, and other diagnoses, such as congenital adrenal hyperplasia, nonclassic adrenal hyperplasia, Cushing syndrome, androgen-secreting tumor, idiopathic hyperandrogenism, idiopathic hirsutism, hyperprolactinemia, and thyroid disorders must be excluded. Because 20%–30% of otherwise normal women have evidence of multiple cysts on their ovaries**,** the presence of polycystic ovaries (PCO) alone was not considered sufficient by any group. The NIH/NICHD and the Androgen Excess Society require that patients have signs or symptoms of hyperandrogenism such as hirsutism, or hyperandrogenemia, defined as elevated free testosterone, reduced SHBG (sex hormone-binding globulin), elevated free testosterone index, or elevated

dehydroepiandrosterone sulfate**.** ***(Zawadski JK, et al. 1992. Azziz R, et al 2006)***

However, ESHRE/ASRM (Rotterdam) criteria allows for the diagnosis of PCOS without the presence of hyper-androgenemia or clinical hyperandrogenism. Women with ovulatory dysfunction and the presence of polycystic ovaries are considered to have PCOS by the Rotterdam criteria. Another key difference between the criteria is how oligomenorrhea or amenorrhea are viewed. The Rotterdam criteria did not require irregular menses or ovulatory dysfunction for diagnosis citing that women with regular menstrual cycles could be considered to have PCOS in the presence of PCO and hyperandrogenemia or hyperandrogenism Subclinical ovulatory dysfunction can occur in women with regular menstrual bleeding**.** However, NIH/NICHD excludes the diagnosis of PCOS in women with regular menses and subclinical ovulatory dysfunction**..** ***(Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group.2004) (Azziz R, et al 2006)***

The diagnosis of PCOS using the Rotterdam and AES criteria depends on the use of a reliable method to describe polycystic ovarian morphology. The criteria for polycystic ovarian morphology proposed by the Rotterdam consensus group includes the presence of 12 or more follicles measuring between 2 and 9 mm in diameter and/or an increased ovarian

volume of greater than 10 cm^3. This presentation in one ovary sufficiently defines the polycystic ovary**.** ***(Rotterdam ESHRE/ ASRM-Sponsored PCOS Consensus Workshop Group.2004)***

However, since that time, significant advancements in ultrasound image technology have been made, improving resolution and allowing for the detection of smaller follicles**.** ***(Lujan ME, et al. 2013)***

This has prompted calls for revising the criteria used to define polycystic ovarian morphology. Allemand et al used three-dimensional transvaginal ultrasound to measure the mean follicle number per ovary (FNPO) and the maximum number of follicles in a single sonographic plane in ten patients with diagnosed PCOS and 29 normoandrogenic ovulatory controls**.** ***(Allemand MC, et al. 2006)***

Using two-dimensional transvaginal ultrasound, Dewailly et al measured the total number of all follicles that were less than 10 mm in diameter throughout the ovary and also measured the ovarian volume**.** A mean FNPO of ≥20.1 identified PCO with 100% specificity and 70% sensitivity. A maximum number of follicles in a single sonographic plane of ten identified PCO with 100% specificity and 90% sensitivity. Ovarian volume, measured by two-dimensional transvaginal ultrasound, of ≥13.0

cm^3 predicted PCO with a specificity of 100% and a sensitivity of 50%. ***(Dewailly D, et al. 2011)***

A threshold follicle number of 19 had a sensitivity for predicting PCO of 81% and a specificity of 92%. Ovarian volume of 7 cm^3 predicted PCO with a sensitivity of 87% and a specificity of 89%. Lujan et al measured FNPO, follicle counts in a single cross section, and ovarian volume in images that were digitally archived for offline analysis. In their analysis, a FNPO threshold of 26 follicles had a sensitivity of 85% and specificity of 94% in discriminating between subjects with PCOS and controls. A threshold of nine follicles for follicle counts in a single cross section had a sensitivity of 69% and specificity of 90%. The threshold for ovarian volume of 10 cm^3 yielded a sensitivity of 81% and a specificity of 84%. ***(Lujan ME, et al. 2013)***

Epidemiology:

Prevalence estimates for PCOS, as defined by the NIH/NICHD criteria, indicate that PCOS is a common endocrinopathy affecting 10.48% women of reproductive age in Egypt ***(Saleh H, et al. 2014)***

Recently, several groups have demonstrated that the prevalence of PCOS varies depending on the diagnostic criteria used (see Table 2). ***(Yildiz BO, et al. 2012)***

These studies consistently report that the prevalence estimates using the Rotterdam criteria are two to three times greater than those obtained using the NIH/NICHD criteria.

Table (2): Prevalence of polycystic ovary syndrome (PCOS) using different diagnostic criteria.

Source	Population	NIH/NICHD criteria	ESHRE/ASRM (Rotterdam) criteria	Androgen excess and PCOS society criteria
March et al	728 Australian women	8.7%	17.8%	12.0%
Mehrabian et al	820 Iranian women	7%	15.2%	7.92%
Tehrani et al	929 Iranian women	7.1%	14.6%	11.7%
Yildiz et al	392 Turkish women	6.1%	19.9%	15.3%

Risk Factors:

Genetic Predisposition:

Family history of PCOS is a risk factor for PCOS. Based on the clustering of cases in families, PCOS is considered to be a heritable disorder. ***(Legro RS, et al. 1998)***

A high prevalence of PCOS or its features among first-degree relatives is suggestive of genetic influences. In addition, greater concordance has been reported in monozygotic twins versus dizygotic twins. However, the mode of inheritance remains elusive. Issues that hamper progress in this area include the heterogeneity of PCOS phenotypes, difficulty in assigning a phenotype to men, postmenopausal women, and prepubertal girls, and difficulties in obtaining large enough sample sizes to allow for adequate statistical power. ***(Amato P, et al. 2004) (Vink JM, et al. 2006) (Goodarzi MO, et al. 2001)***

A genome wide association study conducted amongst Han Chinese has identified loci on chromosomes 2p16.3, 2p21, and 9q33.3. ***(Chen ZJ, et al. 2011)***

Obesity:

A history of weight gain often precedes the development of the clinical features of PCOS, and following a healthy lifestyle has been shown to reduce body weight, abdominal fat, reduce testosterone, improve insulin resistance, and decrease hirsutism in women with PCOS. ***(Isikoglu M, et al. 2007) (Moran LJ, et al. 2011)***

Obese women referred for assistance with weight loss had a prevalence of PCOS of 28.3***%.*** However, in an unselected population, prevalence of PCOS did not vary significantly based on obesity class***. (Alvarez-Blasco F, et al. 2006)***

PCOS prevalence rates for underweight, normal-weight, overweight, mildly obese, moderately obese, and severely obese women were 8.2%, 9.8%, 9.9%, 5.2%, 12.4%, and 11.5%, respectively. The authors concluded that obesity may increase the risk of PCOS but that the effect was modest. ***(Yildiz B, et al. 2008)***

Medical Disorders:

Epilepsy:

An increased frequency of reproductive disorders, including PCOS, has been reported in women with epilepsy**.** ***(Herzog AG. 2006)***

Using NIH criteria for diagnosis, Bilo et al identified PCOS in 13 of 50 women (26%) with epilepsy. Among the 16 patients who were not treated for epilepsy at presentation, five (31%) were diagnosed with PCOS, supporting the contention that epilepsy, independent of antiepileptic drugs, increases the risk of PCOS. Valproic acid, an antiepileptic drug widely used to treat epilepsy, bipolar disorder, and migraine, is associated with

features of polycystic ovary syndrome when used to treat women with epilepsy. ***(Bilo L, et al 2001)***

These features include menstrual disturbances, polycystic ovarian morphology, and elevated serum testosterone**.** ***(Betts T, et al. 2003)***

Substitution of lamotrigine for valproic acid in women with epilepsy resulted in reductions in body mass index, fasting serum insulin, and testosterone concentrations. Thus, the confounding effects of medication must be considered when evaluating the literature that probes the relationship between epilepsy, bipolar disorder, and PCOS. ***(Isojarvi JI, et al. 1998)***

Diabetes Mellitus:

The link between PCOS and Type2 DM stems from the association of each condition with obesity and insulin resistance. Type2 DM develops in the context of insulin resistance combined with β-cell dysfunction, insulin deficiency and hyperglycemia. By contrast, PCOS develops in the context of insulin resistance and compensatory hyperinsulinemia. Insulin has pleiotropic actions including co-gonadotrophic effects on tissues, such as the ovaries, that remain insulin sensitive, thus augmenting ovarian theca cell steroidogenesis. By contrast, the link between Type1 DM and PCOS does not result from obesity and insulin resistance, but rather from adverse effects of hyperinsulinemia that in turn result from exogenous

administration of insulin with supraphysiological concentrations within the systemic circulation ***(Thomas M, et al. 2012).***

Type 1, Type 2, and gestational diabetes have been associated with an increased prevalence of PCOS. A study screened 85 Caucasian women with type 1 diabetes mellitus for PCOS using the NIH/NICHD criteria. PCOS was diagnosed in 16 of these women (18.8%). ***(Escobar-Morreale HF, et al. 2000)***

Subsequently, A more recent study screened 38 women with type 1 diabetes mellitus matched controls for PCOS using the ESHRE/ASRM criteria**.** The prevalence of PCOS was 40.5% . ***(Codner E, et al. 2006)***

In type 2 diabetes, PCO are extremely common, occurring in 82% of women. The prevalence of PCOS in type 2 diabetes using the NIH/NICHD criteria has been estimated to be 26.7%. ***(Conn JJ, et al. 2000) (Peppard HR, et al. 2001)***

A diagnosis of PCOS was verified in 15 of 94 women (16%) with gestational diabetes and in six of 94 (6.4%) of those without gestational diabetes. ***(Kashanian M, et al. 2008)***

Prenatal and Childhood Factors:

A number of factors that are associated with an increased risk of PCOS have been identified in children***. (Rosenfield RL. 2007).***

Prenatal factors include high birth weight in girls born to overweight mothers, congenital virilization, and low birth weight. Risk factors apparent later in childhood include premature pubarche, atypical central precocious puberty, obesity syndromes, acanthosis nigricans, and metabolic syndrome. A high index of suspicion for the diagnosis of PCOS is warranted in adolescents with persistently irregular menses and these risk factors. ***(Nicandri KF, et al 2012)***

Association of PCOS with other Comorbidities:

Insulin Resistance:

Although the demonstration of insulin resistance is not required to make the diagnosis of PCOS, it is clear that hyperinsulinemic insulin resistance plays a prominent role in PCOS. The prevalence of insulin resistance in PCOS ranges from 50%–70% and occurs independent of obesity. The effect of obesity on insulin resistance is additive to that of PCOS**.** ***(Schachter M, et al. 2003) (Dunaif A, et al. 1989)***

Consistent with the increased prevalence of insulin resistance, metabolic syndrome is also more common in women