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# Polycyclic Ovarian Syndrome and it Effect on Fertility

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**Annotation:** Polycystic ovary syndrome is the most common endocrinological disorder in women of reproductive age. It is commonly associated with anovulatory subfertility, for which there are a range of treatment options available to help them conceive. These options are given in a step-wise manner with an appropriate selection of patients to maximise success rates with minimal complications. This review discusses the importance and involvement of multidisciplinary care when offering treatment to women with subfertility. Multidisciplinary care gives an excellent opportunity to identify, assess risk, and potentially prevent future morbidities and complications while treating women for fertility issues. We have also summarised the various options available for fertility treatment: pharmacological treatments, nonpharmacological intervention, and assisted reproductive technology.

**Keywords:** PCOS, fertility, ovulation induction, IVF.

## 1_1_Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder that impactsmany women of the reproductive age worldwide , This syndrome is often associated withenlarged and dysfunctional ovaris, excess androgen levels, resistance to insulin, etc. Itis estimated that approximately every 1 in 10 women face PCOS before menopause and struggle with its complications Although the high ratio of luteinizing hormone (LH) to follicle-stimulating hormone(FSH) and increased frequency of gonadotropin-releasing hormone (GnRH) is known as the underlying causes of PCOS the exact etiology and pathology have not beencomprehensively well-known .Evidence suggests the role of different external andinternal factors, including insulin resistance (IR), hyperandrogenism (HA), environmental factors, genetic, and epigenetics. In addition, it is worth mentioning that PCOS increases therisk of further complications like cardiovascular diseases , type 2 diabetes mellitus ,metabolic syndrome . depression, and anxiety . (Barr, Hart, Reeves, Sharp, & Jeanes, 2011)

To manage this condition, the most crucial step is to lose at least 5% of the weight;therefore, having a regular exercise plan and fat and sugar-free diets are also recommendedto every woman with PCOS.

Furthermore, in some cases, taking complementary and alternative medicine strategies with or without other treatments is preferable due to theirprior beliefs, lower costs, etc. (Pau et al., 2013)

Physicians tend to use (combined) oral contraceptives, antiandrogen agents, insulinsensitizers, and ovulation inducers , Up until today, there is no United States Foodand Drug Administration (USFDA) approved medication specifically for PCOS, and allmentioned medications are used off-label Apart from the essential need for improve- ment in the research and development of new drug molecules and new drug discovery,novel medications could be found with drug repurposing methods ,On this very spot,there are plenty of medications, previously approved by USFDA for indications rather thanPCOS; and, today, there is a desire to implement them as the therapeutic options in themanagement of PCOS. (Barr, Hart, Reeves, Sharp, & Jeanes, 2011)

### Aim of the research

1. To know the reasons for and symptoms of ovarian cysts.
2. To know how to prevent ovarian cyst disease.
3. To know how it occurs and how can be treated and prevented.

### 1-Polycystic ovary syndrome

Polycystic ovary syndrome, or PCOS, is the most common endocrine disorder in women of reproductive age.( Kollmann M, Martins WP, Raine-Fenning N (2014)) The syndrome is named after cysts which form on the ovaries of some people with this condition, though this is not a universal symptom, and not the underlying cause of the disorder. Legro RS (2017)

Women with PCOS may experience irregular menstrual periods, heavy periods, excess hair, acne, pelvic pain, difficulty getting pregnant, and patches of thick, darker, velvety skin. The primary characteristics of this syndrome include: hyperandrogenism, anovulation, insulin resistance, and neuroendocrine disruption.

A review of international evidence found that the prevalence of PCOS could be as high as 26% among some populations, though ranges between 4% and 18% are reported for general populations. Mortada R, Williams T (August 2015)

The exact cause of PCOS remains uncertain, and treatment involves management of symptoms using medication. Pal L, ed. (2013)

**Definition**

Two definitions are commonly used:

- NIH

In 1990 a consensus workshop sponsored by the NIH/NICHD suggested that a person has PCOS if they have all of the following: Dumont A, Robin G, Catteau- Jonard S, Dewailly D (December 2015)

1. oligoovulation
2. signs of androgen excess (clinical or biochemical)
3. exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism

**2.1. Rotterdam**

In 2003 a consensus workshop sponsored by ESHRE/ASRM in Rotterdam indicated PCOS to be present if any two out of three criteria are met, in the absence of other entities that might cause these findings: (Pau et al., 2013). Glintborg et al. (2012)

1. oligoovulation and/or anovulation
2. excess androgen activity
3. polycystic ovaries (by gynecologic ultrasound)

The Rotterdam definition is wider, including many more women, the most notable ones being women without androgen excess. Critics say that findings obtained from the study of women with androgen excess cannot necessarily be extrapolated to women without androgen excess(Shahedur et al., 2012).

**2.2. Androgen Excess PCOS Society**

In 2006, the Androgen Excess PCOS Society suggested a tightening of the diagnostic criteria to all of the following:

1. excess androgen activity
2. oligoovulation/anovulation and/or polycystic ovaries
3. exclusion of other entities that would cause excess androgen activity

**2.3. Signs and symptoms**

Signs and symptoms of PCOS include irregular or no menstrual periods, heavy periods, excess body and facial hair, acne, pelvic pain, difficulty getting pregnant, and patches of thick, darker, velvety skin, ovarian cysts, enlarged ovaries, excess androgen, weight gain and hirsutism(Shahedur et al., 2012).

Associated conditions include type 2 diabetes, obesity, obstructive sleep apnea, heart disease, mood disorders, and endometrial cancer.

Common signs and symptoms of PCOS include the following:

- Menstrual disorders: PCOS mostly produces oligomenorrhea (fewer than nine menstrual periods in a year) or amenorrhea (no menstrual periods for three or more consecutive months), but other types of menstrual disorders may also occur.
- Infertility: This generally results directly from chronic anovulation (lack of ovulation).
- High levels of masculinizing hormones: Known as hyperandrogenism, the most common signs are acne and hirsutism (male pattern of hair growth, such as on the chin or chest), but it may produce hypermenorrhea (heavy and prolonged menstrual periods), androgenic alopecia (increased hair thinning or diffuse hair loss), or other symptoms. Approximately three-quarters

of women with PCOS (by the diagnostic criteria of NIH/NICHD 1990) have evidence of hyperandrogenemia. (Moran, Brink worth, & Norman, 2008)

- Metabolic syndrome: This appears as a tendency towards central obesity and other symptoms associated with insulin resistance, including low energy levels and food cravings. Serum insulin, insulin resistance, and homocysteine levels are higher in women with PCOS.
- Polycystic ovaries: Ovaries might get enlarged and comprise follicles surrounding the eggs. As result, ovaries might fail to function regularly. This disease is related to the number of follicles per ovary each month growing from the average range of 6-8 to double, triple or more

Women with PCOS tend to have central obesity, but studies are conflicting as to whether visceral and subcutaneous abdominal fat is increased, unchanged, or decreased in women with PCOS relative to non-PCOS women with the same body mass index. In any case, androgens, such as testosterone, androstanolone (dihydrotestosterone), and nandrolone decanoate have been found to increase visceral fat deposition in both female animals and women (Shahedur et al., 2012).

Although 80% of PCOS presents in women with obesity, 20% of women diagnosed with the disease are non-obese or "lean" women. However, obese women that have PCOS have a higher risk of adverse outcomes, such as hypertension, insulin resistance, metabolic syndrome, and endometrial hyperplasia.

Even though most women with PCOS are overweight or obese, it is important to acknowledge that non-overweight women can also be diagnosed with PCOS. Up to 30% of women diagnosed with PCOS maintain a normal weight before and after diagnosis. "Lean" women still face the various symptoms of PCOS with the added challenges of having their symptoms properly addressed and recognized. Lean women often go undiagnosed for years, and usually are diagnosed after struggles to conceive. Lean women are likely to have a missed diagnosis of diabetes and cardiovascular disease. These women also have an increased risk of developing insulin resistance, despite not being overweight. Lean women are often taken less seriously with their diagnosis of PCOS, and also face challenges finding appropriate treatment options. This is because most treatment options are limited to approaches of losing weight and healthy dieting(Shahedur et al., 2012).

### 2.4. Hormone levels

Testosterone levels are usually elevated in women with PCOS. In asystematic review and meta-analysis of sexual dysfunction related to PCOS which included 5,366 women with PCOS from 21 studies, testosterone levels were analyzed and were found to be 2.34 nmol/L (67 ng/dL) in women with PCOS and 1.57 nmol/L (45 ng/dL) in women without PCOS. In a 1995 study of 1,741 women with PCOS, mean testosterone levels were 2.6 (1.1–4.8) nmol/L (75 (32–140) ng/dL). In a 1998 study which reviewed many studies and subjected them to meta-analysis, testosterone levels in women with PCOS were 62 to 71 ng/dL (2.2–2.5 nmol/L) and testosterone levels in women without PCOS were about 32 ng/dL (1.1 nmol/L). In a 2010 study of 596 women with PCOS which used liquid chromatography–mass spectrometry (LC–MS) to quantify testosterone, median levels of testosterone were 41 and 47 ng/dL (with 25th–75th percentiles of 34– 65 ng/dL and 27–58 ng/dL and ranges of 12–184 ng/dL and 1–205 ng/dL) via two different labs. If testosterone levels are above 100 to 200 ng/dL, per different sources, other possible causes of hyperandrogenism, such as congenital adrenal hyperplasia or an androgen-secreting tumor, may be present and should be excluded(Shahedur et al., 2012).

### 2.5. Associated conditions

Warning signs may include a change in appearance. But there are also manifestations of mental health problems, such as anxiety, depression, and eating disorders. (Moran, Brink worth, & Norman, 2008)

A diagnosis of PCOS suggests an increased risk of the following:

- ✓ Endometrial hyperplasia and endometrial cancer (cancer of the uterine lining) are possible, due to overaccumulation of uterine lining, and also lack of progesterone, resulting in prolonged stimulation of uterine cells by estrogen. It is not clear whether this risk is directly due to the syndrome or from the associated obesity, hyperinsulinemia, and hyperandrogenism.
- ✓ Insulin resistance/type 2 diabetes. A review published in 2010 concluded that women with PCOS have an elevated prevalence of insulin resistance and type 2 diabetes, even when controlling for body mass index (BMI). PCOS is also associated with higher risk for diabetes.
- ✓ High blood pressure, in particular if obese or during pregnancy
- ✓ Depression and anxiety
- ✓ Dyslipidemia – disorders of lipid metabolism – cholesterol and triglycerides. Women with PCOS show a decreased removal of atherosclerosis-inducing remnants, seemingly independent of insulin resistance/type 2 diabetes.
- ✓ Cardiovascular disease, with a meta-analysis estimating a 2-fold risk of arterial disease for women with PCOS relative to women without PCOS, independent of BMI.
- ✓ Strokes
- ✓ Weight gain
- ✓ Miscarriage
- ✓ Sleep apnea, particularly if obesity is present
- ✓ Non-alcoholic fatty liver disease, particularly if obesity is present
- ✓ Acanthosis nigricans (patches of darkened skin under the arms, in the groin area, on the back of the neck) (Moran, Brink worth, & Norman, 2008)
- ✓ Autoimmune thyroiditis

The risk of ovarian cancer and breast cancer is not significantly increased overall.

**Cause**

PCOS is a heterogeneous disorder of uncertain cause. There is some evidence that it is a genetic disease. Such evidence includes the familial clustering of cases, greater concordance in monozygotic compared with dizygotic twins and heritability of endocrine and metabolic features of PCOS. There is some evidence that exposure to higher than typical levels of androgens and the anti-Müllerian hormone (AMH) in utero increases the risk of developing PCOS in later life.

It may be caused by a combination of genetic and environmental factors. Risk factors include obesity, a lack of physical exercise, and a family history of someone with the condition. Diagnosis is based on two of the following three findings: anovulation, high androgen levels, and ovarian cysts. Cysts may be detectable by ultrasound. Other conditions that produce similar symptoms include adrenal hyperplasia, hypothyroidism, and high blood levels of prolactin. (Pau et al., 2013). Glintborg et al. (2012)

**2.6. Genetics**

The genetic component appears to be inherited in an autosomal dominant fashion with high genetic penetrance but variable expressivity in females; this means that each child has a 50% chance of inheriting the predisposing genetic variant(s) from a parent, and, if a daughter receives the variant(s), the daughter will have the disease to some extent. The genetic variant(s) can be inherited from either the father or the mother, and can be passed along to both sons (who may be asymptomatic carriers or may have symptoms such as early baldness and/or excessive hair) and daughters, who will show signs of PCOS. The phenotype appears to manifest itself at least partially

via heightened androgen levels secreted by ovarian follicle theca cells from women with the allele. The exact gene affected has not yet been identified. In rare instances, single-gene mutations can give rise to the phenotype of the syndrome. Current understanding of the pathogenesis of the syndrome suggests, however, that it is a complex multigenic disorder.

Due to the scarcity of large-scale screening studies, the prevalence of endometrial abnormalities in PCOS remains unknown, though women with the condition may be at increased risk for endometrial hyperplasia and carcinoma as well as menstrual dysfunction and infertility. (Moran, Brink worth, & Norman, 2008)

The severity of PCOS symptoms appears to be largely determined by factors such as obesity. PCOS has some aspects of a metabolic disorder, since its symptoms are partly reversible. Even though considered as a gynecological problem, PCOS consists of 28 clinical symptoms(Pau et al., 2013). Glintborg et al. (2012).

Even though the name suggests that the ovaries are central to disease pathology, cysts are a symptom instead of the cause of the disease. Some symptoms of PCOS will persist even if both ovaries are removed; the disease can appear even if cysts are absent. Since its first description by Stein and Leventhal in 1935, the criteria of diagnosis, symptoms, and causative factors are subject to debate. Gynecologists often see it as a gynecological problem, with the ovaries being the primary organ affected. However, recent insights show a multisystem disorder, with the primary problem lies in hormonal regulation in the hypothalamus, with the involvement of many organs. The term PCOS is used due to the fact that there is a wide spectrum of symptoms possible. It is common to have polycystic ovaries without having PCOS; approximately 20% of European women have polycystic ovaries, but most of those women do not have PCOS. (Moran, Brink worth, & Norman, 2008)

### 2.6. Environment

PCOS may be related to or worsened by exposures during the prenatal period, epigenetic factors, environmental impacts (especially industrial endocrine disruptors, such as bisphenol A and certain drugs) and the increasing rates of obesity. (Pau et al., 2013). Glintborg et al. (2012)

Endocrine disruptors are defined as chemicals that can interfere with the endocrine system by mimicking hormones such as estrogen. According to the NIH (National Institute of Health), examples of endocrine disruptors can include dioxins and triclosan. Endocrine disruptors can cause adverse health impacts in animals. Additional research is needed to assess the role that endocrine disruptors may play in disrupting reproductive health in women and possibly triggering or exacerbating PCOS and its related symptoms.

### 2.7. Pathogenesis

Polycystic ovaries develop when the ovaries are stimulated to produce excessive amounts of androgenic hormones, in particular testosterone, by either one or a combination of the following (almost certainly combined with genetic susceptibility):

- ✓ the release of excessive luteinizing hormone (LH) by the anterior pituitary gland
- ✓ through high levels of insulin in the blood (hyperinsulinaemia) in women whose ovaries are sensitive to this stimulus

A majority of women with PCOS have insulin resistance and/or are obese, which is a strong risk factor for insulin resistance, although insulin resistance is a common finding among women with PCOS in normal-weight women as well. Elevated insulin levels contribute to or cause the abnormalities seen in the hypothalamic–pituitary–ovarian axis that lead to PCOS. Hyperinsulinemia increases GnRH pulse frequency, which in turn results in an increase in the LH/FSH ratio increased ovarian androgen production; decreased follicular maturation; and decreased SHBG binding. Furthermore, excessive insulin increases the activity of 17α-hydroxylase, which catalyzes the conversion of progesterone to androstenedione, which is in turn

converted to testosterone. The combined effects of hyperinsulinemia contribute to an increased risk of PCOS. (Moran, Brink worth, & Norman, 2008)

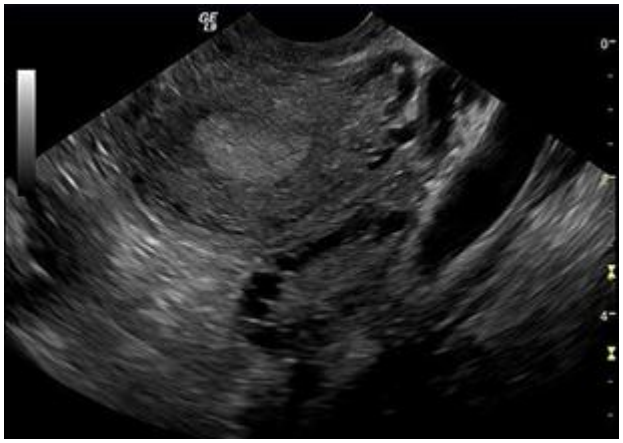
Adipose (fat) tissue possesses aromatase, an enzyme that converts androstenedione to estrone and testosterone to estradiol. The excess of adipose tissue in obese women creates the paradox of having both excess androgens (which are responsible for hirsutism and virilization) and excess estrogens (which inhibit FSH via negative feedback).

The syndrome acquired its most widely used name due to the common sign on ultrasound examination of multiple (poly) ovarian cysts. These "cysts" are in fact immature ovarian follicles. The follicles have developed from primordial follicles, but this development has stopped ("arrested") at an early stage, due to the disturbed ovarian function. The follicles may be oriented along the ovarian periphery, appearing as a 'string of pearls' on ultrasound examination.

PCOS may be associated with chronic inflammation, with several investigators correlating inflammatory mediators with anovulation and other PCOS symptoms. Similarly, there seems to be a relation between PCOS and an increased level of oxidative stress. (Moran, Brink worth, & Norman, 2008)

### 2.8. Diagnosis

Not every person with PCOS has polycystic ovaries (PCO), nor does everyone with ovarian cysts have PCOS; although a pelvic ultrasound is a major diagnostic tool, it is not the only one.[84] The diagnosis is fairly straightforward using the Rotterdam criteria, even when the syndrome is associated with a wide range of symptoms. (Barr, Hart, Reeves, Sharp, & Jeanes, 2011)



Transvaginal ultrasound scan of polycystic ovary

Polycystic ovary as seen on sonography

### 2.9 Differential diagnosis

Other causes of irregular or absent menstruation and hirsutism, such as hypothyroidism, congenital adrenalhyperplasia (21-hydroxylase deficiency), Cushing's syndrome, hyperprolactinemia, androgen-secreting neoplasms, and other pituitary or adrenal disorders, should be investigated.

### 2.10. Assessment and testing Standard assessment

- History-taking, specifically for menstrual pattern, obesity, hirsutism and acne. A clinical prediction rule found that these four questions can diagnose PCOS with a sensitivity of 77.1% (95% confidence interval [CI] 62.7%– 88.0%) and a specificity of 93.8% (95% CI 82.8%–98.7%).(Barr, Hart, Reeves, Sharp, & Jeanes, 2011)
- Gynecologic ultrasonography, specifically looking for small ovarian follicles. These are believed to be the result of disturbed ovarian function with failed ovulation, reflected by the infrequent or absent menstruation that is typical of the condition. In a normal menstrual cycle, one egg is released from a dominant follicle – in essence, a cyst that bursts to release the egg. After ovulation, the follicle remnant is transformed into a progesterone- producing corpus luteum, which shrinks and disappears after approximately 12–14 days. In PCOS, there is a so-called "follicular arrest"; i.e., several follicles develop to a size of 5–7 mm, but not further. No single follicle reaches the preovulatory size (16 mm or more). According to the Rotterdam criteria, which are widely used for diagnosis of PCOS, 12 or more small follicles should be seen in a suspect ovary on ultrasound examination. More recent research suggests that there should be at least 25 follicles in an ovary to designate it as having polycystic ovarian morphology (PCOM) in women aged 18–35 years. The follicles may be oriented in the periphery, giving the appearance of a 'string of pearls'. If a high-resolution transvaginal ultrasonography machine is not available, an ovarian volume of at least 10 ml is regarded as an acceptable definition of having polycystic ovarian morphology. rather than follicle count. (Pau et al., 2013). Glintborg et al. (2012)
- Laparoscopic examination may reveal a thickened, smooth, pearl-white outer surface of the ovary. (This would usually be an incidental finding if laparoscopy were performed for some other reason, as it would not be routine to examine the ovaries in this way to confirm a diagnosis of PCOS.)
- Serum (blood) levels of androgens, including androstenedione and testosterone may be elevated. Dehydroepiandrosterone sulfate (DHEA-S) levels above 700–800 µg/dL are highly suggestive of adrenal dysfunction because DHEA-S is made exclusively by the adrenal glands. The free testosterone level is thought to be the best measure, with approximately 60 per cent of PCOS patients demonstrating supranormal levels. (Barr, Hart, Reeves, Sharp, & Jeanes, 2011)

Some other blood tests are suggestive but not diagnostic. The ratio of LH (luteinizing hormone) to FSH (follicle-stimulating hormone), when measured in international units, is elevated in women with PCOS. Common cut-offs to designate abnormally high LH/FSH ratios are 2:1 or 3:1 as tested on day 3 of the menstrual cycle. The pattern is not very sensitive; a ratio of 2:1 or higher was present in less than 50% of women with PCOS in one study. There are often low levels of sex hormone-binding globulin, in particular among obese or overweight women. Anti-Müllerian hormone (AMH) is increased in PCOS, and may become part of its diagnostic criteria. (Barr, Hart, Reeves, Sharp, & Jeanes, 2011)

### 2.11. Glucose tolerance testing

- Two-hour oral glucose tolerance test (GTT) in women with risk factors (obesity, family history, history of gestational diabetes) may indicate impaired glucose tolerance (insulin resistance) in 15–33% of women with PCOS. Frank diabetes can be seen in 65–68% of women with this condition. Insulin resistance can be observed in both normal weight and overweight

people, although it is more common in the latter (and in those matching the stricter NIH criteria for diagnosis); 50–80% of people with PCOS may have insulin resistance at some level. (Moran, Brink worth, & Norman, 2008)

- Fasting insulin level or GTT with insulin levels (also called IGTT). Elevated insulin levels have been helpful to predict response to medication and may indicate women needing higher doses of metformin or the use of a second medication to significantly lower insulin levels. Elevated blood sugar and insulin values do not predict who responds to an insulin-lowering medication, low-glycemic diet, and exercise. Many women with normal levels may benefit from combination therapy. A hypoglycemic response in which the two-hour insulin level is higher and the blood sugar lower than fasting is consistent with insulin resistance. A mathematical derivation known as the HOMAI, calculated from the fasting values in glucose and insulin concentrations, allows a direct and moderately accurate measure of insulin sensitivity (glucose-level x insulin-level/22.5).

### 2.12. Management

The primary treatments for PCOS include lifestyle changes and use of medications. Goals of treatment may be considered under four categories:

- Lowering of insulin resistance
- Restoration of fertility
- Treatment of hirsutism or acne
- Restoration of regular menstruation, and prevention of endometrial hyperplasia and endometrial cancer

In each of these areas, there is considerable debate as to the optimal treatment. One of the major factors underlying the debate is the lack of large-scale clinical trials comparing different treatments. Smaller trials tend to be less reliable and hence may produce conflicting results. General interventions that help to reduce weight or insulin resistance can be beneficial for all these aims, because they address what is believed to be the underlying cause. As PCOS appears to cause significant emotional distress, appropriate support may be useful. (Shahedur et al., 2012)

### 2.13. Diet

Where PCOS is associated with overweight or obesity, successful weight loss is the most effective method of restoring normal ovulation/menstruation. The American Association of Clinical Endocrinologists guidelines recommend a goal of achieving 10–15% weight loss or more, which improves insulin resistance and all hormonal disorders. Still, many women find it very difficult to achieve and sustain significant weight loss. Insulin resistance itself can cause increased food cravings and lower energy levels, which can make it difficult to lose weight on a regular weight-loss diet. A scientific review in 2013 found similar improvements in weight, body composition and pregnancy rate, menstrual regularity, ovulation, hyperandrogenism, insulin resistance, lipids, and quality of life to occur with weight loss, independent of diet composition.[104] Still, a low GI diet, in which a significant portion of total carbohydrates is obtained from fruit, vegetables, and whole-grain sources, has resulted in greater menstrual regularity than a macronutrient-matched healthy diet. (Pau et al., 2013). Glintborg et al. (2012)

Vitamin D deficiency may play some role in the development of the metabolic syndrome, and treatment of any such deficiency is indicated. However, a systematic review of 2015 found no evidence that vitamin D supplementation reduced or mitigated metabolic and hormonal dysregulations in PCOS. As of 2012, interventions using dietary supplements to correct metabolic deficiencies in people with PCOS had been tested in small, uncontrolled and nonrandomized clinical trials; the resulting data are insufficient to recommend their use.

### 2.14. Medications

Medications for PCOS include oral contraceptives and metformin. The oral contraceptives increase sex hormone binding globulin production, which increases binding of free testosterone. This reduces the symptoms of hirsutism caused by high testosterone and regulates return to normal menstrual periods. Metformin is a medication commonly used in type 2 diabetes mellitus to reduce insulin resistance, and is used off label (in the UK, US, AU and EU) to treat insulin resistance seen in PCOS. In many cases, metformin also supports ovarian function and return to normal ovulation. Spironolactone can be used for its antiandrogenic effects, and the topical cream eflornithine can be used to reduce facial hair. A newer insulin resistance medication class, the thiazolidinediones (glitazones), have shown equivalent efficacy to metformin, but metformin has a more favorable side effect profile. The United Kingdom's National Institute for Health and Clinical Excellence recommended in 2004 that women with PCOS and a body mass index above 25 be given metformin when other therapy has failed to produce results. Metformin may not be effective in every type of PCOS, and therefore there is some disagreement about whether it should be used as a general first line therapy. In addition to this, metformin is associated with several unpleasant side effects: including abdominal pain, metallic taste in the mouth, diarrhoea and vomiting. The use of statins in the management of underlying metabolic syndrome remains unclear. (Pau et al., 2013). Glintborg et al. (2012) It can be difficult to become pregnant with PCOS because it causes irregular ovulation. Medications to induce fertility when trying to conceive include the ovulation inducer clomiphene or pulsatile leuprorelin. Evidence from randomised controlled trials suggests that in terms of live birth, metformin may be better than placebo, and metform plus clomiphene may be better than clomiphene alone, but that in both cases women may be more likely to experience gastrointestinal side effects with metformin.

Metformin is thought to be safe to use during pregnancy (pregnancy category B in the US). A review in 2014 concluded that the use of metformin does not increase the risk of major birth defects in women treated with metformin during the first trimester. Liraglutide may reduce weight and waist circumference in people with PCOS more than other medications.

### 2.15. Infertility

Not all women with PCOS have difficulty becoming pregnant. But some women with PCOS may have difficulty getting pregnant since their body does not produce the hormones necessary for regular ovulation. PCOS might also increase the risk of miscarriage or premature delivery. However, it is possible to have a normal pregnancy. Including medical care and a healthy lifestyle to follow. For those that do, anovulation or infrequent ovulation is a common cause and PCOS is the main cause of anovulatory infertility. Other factors include changed levels of gonadotropins, hyperandrogenemia, and hyperinsulinemia. Like women without PCOS, women with PCOS that are ovulating may be infertile due to other causes, such as tubal blockages due to a history of sexually transmitted diseases. (Shahedur et al., 2012) For overweight anovulatory women with PCOS, weight loss and diet adjustments, especially to reduce the intake of simple carbohydrates, are associated with resumption of natural ovulation. Digital health interventions have been shown to be particularly effective in providing combined therapy to manage PCOS through both lifestyle changes and medication. (Barr, Hart, Reeves, Sharp, & Jeanes, 2011) For those women that after weight loss still are anovulatory or for anovulatory lean women, then ovulation induction using the medications letrozole or clomiphene citrate are the principal treatments used to promote ovulation. Previously, the anti- diabetes medication metformin was recommended treatment for anovulation, but it appears less effective than letrozole or clomiphene. (Pau et al., 2013). Glintborg et al. (2012) For women not responsive to letrozole or clomiphene and diet and lifestyle modification, there are options available including assisted reproductive technology procedures such as controlled ovarian hyperstimulation with follicle- stimulating hormone (FSH) injections followed by in vitro fertilisation (IVF).

Though surgery is not commonly performed, the polycystic ovaries can be treated with a

laparoscopic procedure called "ovarian drilling" (puncture of 4–10 small follicles with electrocautery, laser, or biopsy needles), which often results in either resumption of spontaneous ovulations or ovulations after adjuvant treatment with clomiphene or FSH. (Ovarian wedge resection is no longer used as much due to complications such as adhesions and the presence of frequently effective medications.) There are, however, concerns about the long-term effects of ovarian drilling on ovarian function.

### 2.16. Mental Health

Although women with PCOS are far more likely to have depression than women without, the evidence for anti-depressant use in women with PCOS remains inconclusive. However, the pathophysiology of depression and mental stress during PCOS is linked to various changes including psychological changes such as high activity of pro-inflammatory markers and immune system during stress (Pau et al., 2013). Glintborg et al. (2012)

PCOS is associated with other mental health related conditions besides depression such as anxiety, bipolar disorder, and obsessive–compulsive disorder.

### 2.17. Hirsutism and acne

When appropriate (e.g., in women of child-bearing age who require contraception), a standard contraceptive pill is frequently effective in reducing hirsutism. Progestogens such as norgestrel and levonorgestrel should be avoided due to their androgenic effects. Metformin combined with an oral contraceptive may be more effective than either metformin or the oral contraceptive on its own.

Other medications with anti-androgen effects include flutamide, and spironolactone, which can give some improvement in hirsutism. Metformin can reduce hirsutism, perhaps by reducing insulin resistance, and is often used if there are other features such as insulin resistance, diabetes, or obesity that should also benefit from metformin. Eflornithine (Vaniqa) is a medication that is applied to the skin in cream form, and acts directly on the hair follicles to inhibit hair growth. It is usually applied to the face. 5-alpha reductase inhibitors (such as finasteride and dutasteride) may also be used; they work by blocking the conversion of testosterone to dihydrotestosterone (the latter of which responsible for most hair growth alterations and androgenic acne). (Barr, Hart, Reeves, Sharp, & Jeanes, 2011)

Although these agents have shown significant efficacy in clinical trials (for oral contraceptives, in 60–100% of individuals), the reduction in hair growth may not be enough to eliminate the social embarrassment of hirsutism, or the inconvenience of plucking or shaving. Individuals vary in their response to different therapies. It is usually worth trying other medications if one does not work, but medications do not work well for all individuals. (Shahedur et al., 2012)

## 3. Materials and Methods

### 3.1. Study Design

Inclusion criteria are: age between 18 and 45 years old, Iranian and Persian speaking, ability to read and write, no known medical conditions according to self- report or using patients' records including diabetes, hypertension, thyroid disorders, hyperprolactinemia, Cushing's syndrome, adrenal hyperplasia, no antidepressant medication, no hormone therapy, no oral contraceptive, no glucocorticoids, no anti-obesity medication, no special diet, and not being a professional athlete. Women were selected based on Rotterdam criteria (at least two out of three criteria) including amenorrhea, oligomenorrhea, clinical or lab evidence of hyperandrogenism including hirsutism, alopecia, acne or increased serum levels of androgens, ultrasound evidence of PCOS including more than 12 follicles in each ovary with a diameter of 2-9 mm or increased volume of ovary to more than 10 cm3, and confirmation of the gynecologist in the center. Healthy women were selected from women visiting the same Kirkuk Diagnostic Center, Dr. Sherine Haider Hakim's. , but without signs of the disease according to Rotterdam criteria. Sample size was determined using

the below formula with CI 95% as 10people in each group.

### 3.2. Measurement Instrument

Data collection tools were demographics, diet, IPAQ1 and unhealthy behavior questionnaires, tape measure and scale. Demographics questionnaire included age, height, weight, BMI, education level, marital status, if married: husband's education, monthly income, menstruation history such as menarche, interval between menses, obstetrics history like parity, number of miscarriages, number of preterm births, and use of assisted fertility methods. The researcher-made diet questionnaire comprised 28 items with 0 to 112 points, where higher score showed more appropriate diet. There were 16 items for positive diet and 12 items for negative diet. Total score was measured by considering from 4 points for daily to 0 for never regarding the positive items and vice versa for the negative items. The total score was converted to 0 to 100 for statistical analysis, and 0-33, 34-66 and 67-100 were considered for inappropriate, quite appropriate and appropriate diet, respectively. Content validity was used to validate the questionnaire. Its reliability was measured as 0.80 using Cronbach's alpha. IPAQ was developed in 1998 in Geneva by WHO and CDC for age groups of 15-69. It has 27 items that report physical activity based on MET-min.week. One MET equals the amount of energy consumed in one minute of rest. IPAQ classifies people based on MET into 3 groups of low activity (<600 MET), average activity (600-3000 MET) and high activity (>3000 MET). This questionnaire is standard and its validity has been confirmed using content validity in previous studies (Dinger, Behrens, & Han, 2006; Hazavehei, Asadi, Hassanzadeh, & Shekarchizadeh, 2008). Its reliability was reported as 0.80 in 12 countries by Craig et al. in 2003 (Craig et al., 2003). Unhealthy behavior questionnaire was researcher-made with 8 items and 22 points. The scores were converted to 0-100, where 0-33, 34-66 and 67-100 respectively showed the lowest, moderate and the highest high risk behaviors. Content validity was used to validate this questionnaire, and retest was used to determine its reliability. A non-flexible metal tape measure (Laika, Italy) and a scale (Secca, Germany) were used to measure height and weight, respectively. The scale was validated using a standard 1-kg weight, and calibrated with the same weight after every 10 times of weighing, according to manufacturer's recommendation. The reliability of the tape measure was measured using a standard non-flexible tape measure that was not affected by climatic conditions. The data were analyzed in the SPSS v 17 software and an alpha level of 0.05 for all statistical tests. Independent t test was used to compare pairs of data in groups if the data had normal distribution, Man-Whitney test was used if the data did not have normal distribution, and Chi-square test was used for qualitative data. Finally, logistic regression was used for the whole set of data.

### 3.3. Data Collection and Interventions

After obtaining the permission from authorities of Kirkuk Diagnostic Center, Dr. Sherine Haider Hakim's the women with PCOS and healthy women were identified using multi stage random sampling, and were invited to participate with respect to ethical considerations. After they were briefed about the objectives and methods of the study, and were reassured about the confidentiality of the information, they signed written consent form and were enrolled. The questionnaires were filled out by the researcher in about 10 minutes. Sampling continued until enough samples were selected. The subjects were matched for age, and body mass index (BMI).

## 4. Results

In this study, 01 women with PCOS and 01 healthy women participated. The mean age was 28.85±6.525 and 29.57±7.794 years in the PCOS group and the healthy groups, respectively. The mean BMI was 24.02±3.48 and 23.47±3.281 kg.m2 in the PCOS and the healthy groups, respectively. There was no significant difference between the two groups. There was no difference between the two groups in terms of subjects' education, their husbands' education, subjects' occupation, their husbands' occupation, monthly income and marital status. (Table 1 demonstrates demographics of the subjects).

**Table 1 .The absolute and relative frequency distribution of demographics in the two groups**

| Variable | PCOS (01) number | Non-PCOS)01) number | P-value |
|---|---|---|---|
| Education | 37 high school | 29 high school | 0.260* |
| Husbands' education | 15 high school | 12 high school | 0.410* |
| Occupation | 44 housewife | 55 housewife | 0.170** |
| Husbands''- occupation | 20 self-employed | 19 self- employed | 0.841** |
| Monthly income <600 thousand Rials | 28 | 25 | 0.775* |
| Marital status | 35 married | 34 married | 0.860** |

There was no significant difference between the two groups in terms of infertility, history of assisted fertility methods, age at menarche (p=0.172), and the number of miscarriages (p=0.142). Nonetheless, there was a significant difference between the two groups in terms of parity (p=0.004) and the number of preterm births (p=0.049).

Table 2 demonstrates the comparison of the two groups in terms of diet, physical activity and unhealthy behaviors. there was a significant difference between the two groups in terms of diet and physical activity (p<0.001). The mean score of unhealthy behaviors was 6.43 and 5.94 in the PCOS group and the healthy group, respectively, but the difference was not significant (p=0.7).

**Table 2. Comparison of mean scores of different dimensions of lifestyle in the two groups**

| Variable | PCOS (01) | Non-PCOS01 | P- value |
|---|---|---|---|
| Diet | 58.34±7.55 | 68.50 ±8.87 | <0.001* |
| Physical activity (MET) | 809.85±629.19 | 1916.8±1708.88 | <0.001** |
| Unhealthy behaviors | 6.43±11.19 | 5.94±11.36 | 0.7* |

**Table 3. Calculating regression coefficients of lifestyle and demographics in the two groups***

| Variable | OR | P- value | CI (95%) |
|---|---|---|---|
| Age (years) | 0.875 | 0.109 | 0.743-1.030 |
| BMI (kg.m2) | 0.971 | 0.827 | 0.742-1.270 |
| Education | 0.895 | 0.810 | 0.364-2.203 |
| Occupation | 1.188 | 0.660 | 0.551-2.562 |
| Age at menarche (years) | 0.643 | 0.050 | 0.413-0.999 |
| Menarche interval (day) | 0.243 | 0.023 | 0.072-0.824 |
| Diet | 0.925 | 0.009 | 1.019-1.147 |
| Physical activity(MET) | 0.930 | 0.009 | 1.019-1.135 |
| Unhealthy behaviors | 0.992 | 0.837 | 0.963-1.054 |

As can be seen in Table 3, bivariate logistic regression model shows that diet, and physical activity significantly affect affliction with PCOS.

## 5. Discussion

The analysis of the data showed a significant relationship between PCOS and inappropriate diet (p=0.009), low physical activity (p=0.009). In recent years, researchers have attended to factors involved in incidence or severity of PCOS. Nutritional habits are one dimension of lifestyle which affects people's physical health (Shahedur et al., 2012). Based on the results of our study, the two

groups were significantly different in terms of the mean consumption of different food groups in food pyramid. Few studies have been conducted on lifestyle and nutritional habits of people with PCOS (Barr, Hart, Reeves, Sharp, & Jeanes, 2011). Appropriate diet is an important factor in initiating and maintaining normal function of puberty and fertility (Altieri et al., 2013). Nowadays, correcting lifestyle through adjusting diet and exercising aim to normalize androgen levels and set ovulation is considered as the first line of treatment for these patients (Novak et al., 2012). Some studies have reported a strong relationship between increased risk of infertility due to failure to ovulate and high consumption of animal proteins, complete carbohydrates, foods with high glycemic index, low fat dairy and sodas (Altieri et al., 2013). Insulin resistance causes hyperandrogenemia and disrupts normal ovary function, but dairy products reduce insulin resistance, and low fat dairy is related to hyperandrogenemia (Pourghassem Gargari, Houjeghani, Mahboob, Farzadi, & Safaeian, 2011). Pourghassem Gargari et al. (2011) assessed the pattern of receiving nutrients in women with PCOS and healthy women, and reported that mean intake of energy, carbohydrates, fat and protein was higher in control group. Furthermore, the frequency of consuming milk and dairy, fruits and nuts was less in women with PCOS ($p<0.05$). The results of this study were inconsistent with those of the present study in terms of intake of carbohydrate, fat and protein, but consistent in terms of consuming milk, dairy, fruits and nuts. Eman et al. (2012) reported higher calorie intake ($p=0.001$) and fat intake ($p=0.019$) in women with PCOS, which is in line with the present study. Altieri et al. (2013) studied food habits of obese women with PCOS and its relationship with hormones and metabolism, and observed that the mean consumption of cookies ($p=0.013$), cheese ($p=0.049$) and greasy foods ($p=0.048$) was higher in the PCOS group than in the control. The results of this study are consistent with ours regarding consuming cookies and greasy food, and inconsistent regarding consuming cheese. Given the fact that in most studies, people's hormonal, metabolic and clinical status improved after changing their diet, and the role of obesity and inappropriate nutrition has been recognized effective in this disease, it is necessary to provide them with consultation and educational services regarding appropriate nutrition. We observed that women with PCOS had less activity than healthy women regarding average and high intensity activity. Nowadays, correcting lifestyle through diet and exercising which normalized androgen levels and improves ovulation is the first line of treatment in these patients (Hoeger, 2006). Exercises that involve larger muscles can reduce insulin resistance and comprise an important part of non- medical treatment (Moran, Brink worth, & Norman, 2008). Exercise and physical activity reduces body fat, which is the storage for estrogens and steroid hormones (Alijani & Hiatgheibi, 2002). Although increased physical activity causes better glucose metabolism, increases sensitivity of cells to insulin and reduces abdominal fat regardless of weight loss, studies show that physical activity of people with PCOS is really low (Barr et al., 2011). The results of the study by Eleftheriadou et al. (2012), titled 'exercise and low activity in people with PCOS' showed that girls with PCOS are less inclined to do physical activity ($p<0.001$), and when they attended, its frequency and intensity were lower than those of the control group. These results were true for thin people with PCOS as compared with the control.

The results of this study are in line with ours. However, the number of sitting hours was not significantly different in the two groups in this study, which is against our findings. Moran et al. (2013) conducted a study on the effect of diet, physical activity and sedentary lifestyle on BMI in women with PCOS and healthy women for 13 years (1996-2009) in Australian women born between 1973 and 1978. They did not report a significant difference between the two groups in terms of physical activity, which is inconsistent with our results. They reported a significant difference between the sitting hours of the two groups, which is in line with our findings. Haqq et al. (2014) conducted a meta-analysis titled lifestyle interventions and endocrine presentation in PCOS, and concluded that physical activity improved SHBG, FSH, testosterone and androstenedione in those with PCOS. Our results in this regard show that low physical activity was low in both groups, which is in line with previous studies. Given the role of exercising in preventing the incidence or progress of many diseases and its positive effect on improving hormonal status and insulin resistance in these people, it is recommended to provide them with

consultation and educational services. There was no significant relationship between the mean score of unhealthy behaviors between the two groups. Several studies have proved that smoking reduces estrogen levels and increase androgen levels in women at reproductive age. Therefore, smoking increases metabolic syndrome and hyperandrogenism in women with PCOS (Pau et al., 2013). Glintborg et al. (2012) studied 650 white women with PCOS that comprised 390 smoking and 260 non-smoking women. Smoking was found related to increased adrenal response, reduced prolactin level, and aggravated fat profile, but multiple regression showed that PCOS was more prevalent in non-smoking women. In our study, we did not observe a high level of unhealthy behavior and average unhealthy behavior was observed only in 4 people in the PCOS group and 3 people in the healthy group. It seems that sample size was not enough for this test. The researcher recommends a more extensive study in this regard. These data are referring to Iran population because among the items studying there are also nutrition and lifestyle that vary from country to country, and this was a limitation of this study.

## Conclusion

PCOS is a complex reproductive, metabolic, and psychological disorder characterized by a variety of clinical manifestations and a major cause of infertility.

Lifestyle changes should be considered first-line treatment recommendation for PCOS related infertility, before resorting to pharmacological options. Ovulation induction is the next step, being letrozole the first choice, followed by CC. In women who have failed first line oral ovulation induction therapy, gonadotropins are the next line. For women who do not become pregnant with ovulation induction drugs or have additional infertility factors, ART or LOD can be used (Fig. )

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