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# A COMPREHENSIVE REVIEW ON POLYCYSTIC OVARY SYNDROME AND ITS THERAPEUTIC MANAGEMENT FOR OVULATION INDUCTION IN INFERTILE WOMEN- PART-I

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**ABSTRACT**
Polycystic ovarian (PCO) disease or Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects 6-8% of women. It is characterized by infrequent ovulation or anovulation, high androgen levels in the blood, and the presence of multiple persistent ovarian cysts. The objective of this study was to perform a comprehensive review of the literature to determine therapeutic management for ovulation induction in infertile women of polycystic ovary syndrome. Literature search was performed in November 2013 in the following electronic databases: Medline, Ebsco, Pubmed, Dove Press and the Cochrane Library. We performed a search over the period December 1980 to May 2014 and only PCOS were included. Search terms were as follows; Based on Rotterdam Criteria, Insulin resistance, Polycystic ovary syndrome. Further relevant papers were located by hand-searching the reference lists of recent reviews and original articles. Only human studies were included. The results of PCOS has serious health consequences, abnormal glucose tolerance, hypertension, obestiy, ovariantheca cells, type 2 diabetes and dyslipidemia. During pregnancy, these women have an increased risk of spontaneous abortion and gestational diabetes . Hyperinsulinaemia, the consequence of insulin resistance, stimulates both ovarian and adrenal androgen secretion and suppresses sex hormone-binding globulin synthesis from the liver, resulting in an increase in free, biologically active androgens. Based on available data in the literature, authors conclude that, PCOS is a complex disorder, in multiple genetic, metabolic and hormonal controls fails to interact properly, however, interdisciplinary approach needed to manage the symptoms of the disease.

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women and it accounts for approximately 80% of cases of anovulatory infertility .[1] PCOS affects 5-10% of women of reproductive age [2]. Polycystic ovary syndrome (PCOS) is characterized by infrequent ovulation or anovulation, high androgen levels in the blood, and the presence of multiple persistent ovarian cysts. The Rotterdam criteria for PCOS are the currently accepted criteria are as follows and those meeting two of the following are considered to have PCOS:

- Olio and /or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries (presence of 12 or more follicles in each ovary, measuring 2±9mm in diameter and/or increased ovarian volume more than 10mL),

❖ And exclusion of other etiologies (congenital adrenal hyperplasias, androgen-secreting tumors, Cushing's syndrome [3]

PCOS has serious health consequences and it lowers health-related quality of life. Abnormal glucose tolerance and diabetes mellitus are present in 31% -35% and 7.5%-10%, respectively, of women with this condition. Affected women also have a high prevalence of hypertension, obestiy, ovariantheca cells, type 2 diabetes and dyslipidemia, which are known risk factors for cardiovascular diseases. During pregnancy, these women have an increased risk of spontaneous abortion and gestional diabetes . Hyperinsulinaemia, the consequence of insulin resistance, stimulates both ovarian and adrenal androgen secretion and suppresses sex hormone-binding globulin synthesis from the liver, resulting in an increase in free, biologically active androgens. This excess in local ovarian androgen production causes a premature follicular atresia and anovulation along with other clinical manifestations of hyperandrogenism such as hirsutism, acne, seborrhea and alopecia [4]. Due to chronic anovlation, women with PCOS are also thought to be at increased for endometrial cancer as consequence of unopposed estrogen exposure of the endometrium by a lack of progesterone secretion. Identification and correct diagnosis of PCOS has therefore important preventive and therapeutic implications for the affected women and their families [5]. The objective of this study was to perform a comprehensive review of the literature to determine therapeutic management for ovulation induction in infertile women of polycystic ovary syndrome.

**Ovarian physiology**

Ovaries are typically depicted as oblong structures measuring approximately 3 cm in long-axis and 2 cm in antero/posterior (AP) and transverse dimension. On angled long-axis scans, they are immediately medial to the pelvic vessels. They are particularly well depicted when they contain a mature follicle that is typically in the 1.5 to 2.0 cm range. The size of the ovary is related to the patient's age and phase of follicular development. When the ovary contains a mature follicle, it can become twice as large in volume than one that does not contain mature follicles. In premenopausal women, the normal ovary typically measures 3 × 2 × 1 cm. It may be up to 5 cm in length in one dimension, but should remain oval in shape. Rounded ovaries typically are encountered in patients with polycystic ovarian disease. It is not unusual to depict multiple immature, or atretic, ovarian follicles in the 3 to 5 mm range of the ovary. Measurements of the long, short and A/P dimension of the ovary determines ovarian volume by the ellipsoid formula (length × height × width × 0.5 = volume in cm3) . In premenopausal women, the normal ovary ranges from 10 to 12 cm3 in size, depending on the presence of a mature follicle, which can account for up to 2 cm or 4 cm3 of volume. The ovaries of postmenopausal women are usually smaller (2 × 2 × 1 cm) and featureless. The texture should be relatively featureless without presence of cystic or solid areas within the ovary [6]. Beginning with menarche, during spontaneous cycles there usually is development of one or sometimes two dominant follicles. TVS can depict the developing follicle starting when they measure between 3 and 5 mm. In the spontaneous cycle, usually there is one, or two, follicles that develop to measure approximately 10 mm in size. As the follicle matures, more fluid is elaborated into its center, and the number of granulosa cells lining the inner wall of the follicles increases. The oocyte, which is less than a tenth of a millimeter, is surrounded by a cluster of granulose cells. This complex is termed the cumulus oophorus. It measure approximately 1 mm and occasionally can be depicted along the wall of some mature follicles. Immediately before ovulation the cumulus separates from the wall and floats freely within the center of the follicle. Even with the enhanced resolution afforded by TVS, the attached or floating cumulus is only rarely visualized. Mature follicles typically measure from 17 to 25 mm in average inner dimension. After ovulation the follicular wall becomes irregular as the follicle walls becomes irregular as the follicle become "deflated". The fresh corpus luteum usually appears as a hypoechoic structure with an irregular wall and may contain some internal echoes corresponding to hemorrhage.

**Ovarian volume**

The human ovary is an organ which changes in size and activity throughout life; at birth, the ovary is 1 cm in length. The ovary decreases slightly in volume at 1 month of age, probably due to the clearance of maternal estrogen from the female neonate. There is a continuous slow growth of the ovaries throughout childhood: they enlarged, increase in weight 30-fold, and change in shape, so at puberty, they have reached the size, shape and weight of the adult ovary. In reproductive age ovaries are ovoid, they measure approximately 3-5 cm by 1.5-3 cm by 0.6-1.5 cm. [7].

**METHODS**

Literature search was performed in November 2013 in the following electronic databases: Medline, Ebsco, Pubmed, Dove Press and the Cochrane Library. We performed a search over the period December 1980 to May 2014 and only PCOS were included.

The Search was limited through the following selections; Based on Rotterdam Criteria, Insulin resistance, Polycystic ovary syndrome. Further relevant papers were located by hand-searching the reference lists of recent reviews and original articles written in English were included. Only human studies were included. Data from male factors were excluded.

We obtained hard copies of all the papers listed through our university or interlibrary loans. All sources of information obtained were read and evaluated by one of us

and successively checked independently by the other authors.

**PATHOPHYSIOLOGY**

Polycystic Ovarian Syndrome was initially recognized in 1935 and described as a reproductive disorder involving irregular or absent menses, infertility and hyperandrogenism over the past 2 decades, there has been a tremendous amount of research conducted with regard to understanding both the etiology as well as the treatment and management of this complex endocrine disorder. To date the exact pathogenesis of PCOS is still unknown, and its etiology has been an issue of debate among health care professionals. Findings from research have identified a number of biochemical abnormalities associated with this syndrome. The 3 main features of this syndrome include hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology. Various studies also suggest that both genetic and environmental factors may play a critical role in the development of PCOS.

Females with PCOS have abnormalities in the metabolism of the production of androgens and estrogen and in the control of androgen production. Patients may present with elevated serum concentrations of androgenic hormones (testosterone, androstenedione, and dehydroepiandrosterone sulfate [DHEA]. This patient population not only has higher levels of androgens, but also reduced levels of progesterone and estrogen. Hyperinsulinemia is now a well-recognized feature associated with PCOS, both in obese and non-obese females. Hyperinsulinemia and hyperandrogenism are both considered the hall mark features of this syndrome. Recent insights into the pathophysiology of PCOS have shown that insulin resistance plays a crucial role in the development of PCOS and contributes an increased risk of long-term issues such as type- 2 diabetes mellitus and an increased risk of CVD.

Hyperinsulinemia is prevalent among PCOS patients and is present in an estimated 50% to 70% of patients. The relationship between insulin resistance and PCOS was described more than 3 decades ago. During the 1990s, many clinical studies investigated the relationship between insulin levels and PCOS. Their findings have demonstrated the link between elevated insulin levels among those with PCOS and that elevated insulin levels may actually be a contributing factor to the production of excess testosterone.

Hyperinsulinemia is thought to cause or exacerbate hyperandrogenemia, and elevated insulin levels at the ovarian level lead to increased androgen production from the ovarianthecal cells. Studies have found that hyperinsulinemia augments androgen production in those with PCOS and suggest that insulin may act directly as a cogonadotropin augmenting leuteinizing hormone (LH) activity through stimulation of ovarian receptors of insulin and insulin-like growth factors and indirectly by enhancing the amplitude of serum LH pulses.[8]

**POSSIBLE PATHOGENESIS**

- ❖ Hypothalamic-pituitary axis abnormalities cause abnormal secretion of gonadotropin-releasing hormone and luteinizing hormone, resulting in elevated ovarian androgen production
- ❖ An enzymatic defect of ovarian (adrenal) steroidogenesis favors excess androgen production
- ❖ Insulin resistance drives metabolic and reproductive abnormalities in PCOS [9]

**DIAGNOSIS**

The revised diagnostic criteria of Rotterdam 2003 consensus for PCOS met two of the following three manifestations:

- ➢ Oligoovulation and /or anovulation clinical or biochemical signs of hyperandrogenism and polycystic ovaries.
- ➢ Irregular ovulation manifested as oligomenorrhea (<9menses per year) and amenorrhea ( no menstrual periods for 1 year).
- ➢ Clinical hyperandrogenism was defined by hirsutism. Polycystic ovaries were identified anatomically by the presence of ≥10 subcapsular follicles 2-8 mm in diameter by pelvic ultrasound. The diagnosis of the included 33 RPL-ovarian PCO women was based on the detect of polycystic ovaries by pelvic ultrasound.

**TESTOSTERONE**

Total testosterone is likely to be more reliable than a free testosterone given the difficulties seen with many of the assays used for the latter

- ❖ Testosterone values may be normal in PCOS
- ❖ Oral contraceptives will lower total testosterone, and interpretation in this setting is difficult (3months off oral contraceptives is best to get a “true” testosterone value).
- ❖ Most testosterone values in PCOS will be ≤150ng/dL (≤5.2nmol/L)
- ❖ Testosterone values of ≥200ng/dL (≥6.9nmol/L) warrant consideration of an ovarian or adrenal tumor. [9]

Free testosterone was determined with free androgen index (FAI)

FAI=100 ×total testosterone/sex hormone binding protein

**DEHYYDROEPIANDROSTERONE SULFATE (DHEA-S)**

- ❖ DHEA-S values may be normal or slightly elevated in PCOS
- ❖ DHEA-S values ≥800µg/dL (21.7µmol/L) warrant consideration of an adrenal tumor [9]

**PROLACTIN**

- ❖ Mild hyperprolactinemia has been reported in 5% to 30% of patients with PCOS. Prolactin is generally only 50% above the upper limit of normal. Furthermore, hyperprolactinemic PCOS patients having persistently elevated prolactin levels.

❖ Patients with prolactinomas may have polycystic ovaries on ultrasound [10]

**17-HYDROXYPROGESTERONE**

❖ A morning, fasting, unstimulated level of <200ng/dL (<6nmol/L) in the follicular phase reliably excludes late-onset 21-hydroxylase deficiency.

❖ Further evaluation of levels ≥200ng/dL involves adrenocorticotropic hormone (ACTH) stimulation with an intravenous 250µg dose and a 30 minute value (stimulated values ≥1,000ng/dL (≥30nmol/L) confirm the diagnosis.

❖ Oral contraceptives and glucocorticoids can affect values [11]

**24 HOURS URINE FREE CORTISOL**

❖ Mild elevations can be seen in PCOS with values ≥2times the upper limit of normal more consistent with Cushing's syndrome

❖ For mild elevations a dexamethasone- suppression corticotrophin-releasing hormone stimulation test is needed to distinguish mild cushing's syndrome from pseudo cushing's.

❖ Interpretation of serum (but not urine) cortisol levels in patients on oral contraceptives is problematic as cortisol-binding globulin may be increased falsely elevating the values (it is especially important that oral contraceptives be discontinued before dynamic testing is performed). [12]

**LUTEINIZING HORMONE/FOLLICLE STIMULATING HORMONE (LS/FSH) RATIO**

❖ A ratio ≥2.0 is suggestive of PCOS but is not highly sensitive or specific

❖ Gonadotropin levels are affected by oral contraceptives.

❖ Pelvic ultrasonography may be very helpful in the evaluation as well, but polycystic ovaries are not specific for PCOS with over 20% of "Normal" women having this finding. The number of follicles and ovary volume are both important in the ultrasound evaluation. [13]

**BIOCHEMICAL ASSAYS**

Plasma thyroid-stimulating hormone (TSH), T3, T4 luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measure by chemi-luminescence Immune assays (CLIA). Activated protein C resistance ratio (APCR) was measured by the ratio of the clotting time with and without APC. Anti-thrombin III, Protein C and Protein S were analyzed through clotting assays .Homocysteine and estradiol were measured by enzyme immunoassay (EIA).

**ISOLATION OF GENOMIC DNA**

Peripheral blood samples were collected in tubes containing EDTA, and genomic DNA was extracted using a standard Procedure.

**GENOTYPE ANALYSIS**

Polymerase chain reaction (PCR) assays were performed for three gene mutations. The mutations studied included the C677T and A1298C mutations of the MTHFR gene and the 675 4G/5G polymorphism of the PAI-I gene promoter. PCR amplifications of the respective genes were performed using specific primers (Table-1). The amplifications cycles were 94◦C for 30 s, 62 ◦C for 30s and 72◦C for 30 s, plus a final elongation time of 72◦C for 7 min. In case of PAI-I, PCR was run for 35 cycles with 67◦C as annealing temperature. PCR products were then digested by restriction enzymes Hing I and MboII for MTHFRC677T and A1298C, respectively as shown in Table.1. For further analysis of PCR products, they were electrophoresed on 1.5% agarose gels and polyacrylamide gels. In addition, ARMS-PCR with three primers was used for genotyping of PAI-I 4G/5G in two separated tubes. In this PCR, two forward and one reverse primers specific for the wild type and mutant variants were used.[14]

**METABOLIC CONSEQUENCES OF PCOS**

**I) INSULIN RESISTANCE AND PCOS**

The first association between hyperinsulinemia and PCOS was found a significant positive correlation between insulin, androstenedione, and testosterone levels among women with PCOS . Subsequent studies confirmed insulin resistance that is the cause of hyperinsulinemia. Studies in adipocytes from women with PCOS reveal adipocytes insensitivity to inhibition of lipolysis by insulin, as well as a decrease in maximal rates of adipocyte glucose uptake. Whilst these defects are also present in obesity ( WC> 88cm,HDL <50mg/dL, Triglycerides >150mg/dL) and type 2 diabetes (Fasting blood sugar >110mg/dL, BP>130/85mmHg) they can occur in PCOS in the absence of obesity and type 2 diabetes. Dunaif et al. reported decreased insulin receptor auto-phosphorylation in 50% of fibroblasts removed from PCOS women, which was due to increased receptor serine phosphorylation. Serine phosphorylation, as noted above, has been associated with decreased IRTK auto-phosphorylation. Infact, this is the probable mechanism of TNF-α induced insulin resistance since serine phosphorylation of P450c17 α hydroxylase ( the key regulatory enzyme of androgen biosynthesis) Increase enzymes activity leading to androgen biosynthesis, it is possible that a single defect (serine phosphorylation) can produce both insulin resistance and hyperandrogenism in a subgroup of PCOS women.[15]

**II)IMPARIED GLUCOSE TOLERANCE (IGT)**

There are increased rates of impaired glucose tolerance (IGT) and diabetes mellitus in women with PCOS. The underlying abnormality is postulated to be insulin resistance. These women may often have normal fasting glucose and HbA1c levels but are glucose intolerant following a glucose challenge.The compensatory hyperinsulinaemia drives many of the phenotypic changes seen, including ovarian hyperandrogenism (elevated insulin

drives ovarian theca cells androgen production) and acanthosis nigricans.

**III) OBESITY AND PCOS**

It's common diagnoses among infertility patients, accounting for a significant proportion of women seeking IVF embryo transfer treatment. Obesity is defined as $\geq 30 kg/m^2$. Body fat distribution was evaluated with waist – to-hip ratio. Waist measurement was performed from the thinnest site between the pelvic rim and the coastal margin and the hip measurement was performed at the level of the greater trochanters. BMI was calculated as : BMI= weight in kilograms/square of height in meters. As compared to normal weight patients, it is believed that obese patients stimulate poorly during ovulation induction with Intra uterine insemination (IUI) and IVF embryo transfer cycles. A study was conducted on 372 patients found mean number of follicles and oocytes retrieved were not related to BMI. Despite consensus agreement on the adverse effects of extremes of BMI on IVF success is controversial. A study on 333 patients has failed to find any effect of BMI on IVF pregnancy rate, whereas, another study on 180 patients demonstrated a negative effect only when the women were in the obese category. [16]

**a) Cardiovascular risk**

Cardiovascular risk factors are increased including hyperlipidaemia, increased circulating androgens. Insulin resistance and increased levels of inflammatory markers.Hypertriglyceridaemia, increased VLDL and LDL and decreased HDL are postulated to predispose to increased cardiovascular risk.

**b)Sleep apnoea**

The aetiology of PCOS is unknown but various theories have been put forth to explain the myriad of abnormalities encountered.

- Abnormalities in the hypothalamic pituitary axis (HPA) and uncontrolled ovarian steroidogenesis

These HPA abnormalities cause abnormal secretion of gonadotrophin releasing hormone (GnRH) and LH, resulting in increased ovarian production. LH stimulates the theca cell in ovary to synthesis androgens and FSH is responsible for the granulose cell synthesizing oestrogen via its actions on aromatase activity.

**c) Insulin resistance**

Insulin drives increased androgen production from the ovary and adrenal and may alter gonadotrophin secretion. In patients with PCOS, it has been revealed that there is selective tissue insulin sensitivity (skeletal muscle is resistant but ovary and adrenal are sensitive). Ovarian insulin sensitivity to the prevailing hyperinsulinaemia is thought to be one of the mechanisms that drive ovarian androgen production. Body mass index, hyperandrogenaemia and clinical hyperandrogenism are independent predictors of insulin resistance.

**d) Ovarian follicular cyst**

Abnormal androgen signaling is thought to be responsible for the increase in follicle number. It has also been postulated that follicles grow very slowly due to possibly deficient growth signals from the ovary. There have been some studies showing a positive association between follicle number and androgen concentrations. [17]

**ASSESSMENT OF OVARIAN RESERVE**

The assessment of ovarian reserve before subjecting patients to ovarian cauterisation has not been addressed. Most patients subjected to such a line of treatment are undergoing treatment for infertility, which might highlight the need for assessment of their ovarian reserve, especially in patients over 30 years of age, before subjecting them to ovarian trauma.

Usually patients have their levels of FSH and LH checked as one of the investigations to diagnose PCOD; in addition ovarian cauterisations in usually performed in patients who have already failed to respond adequately to clomiphene citrate. This might provide an opportunity to perform ovarian reserve screening tests such as basal FSH levels. Clomiphene citrate challenge test and gonadotrophin agonist stimulation test.

Elevated day 3 FSH concentrations are highly predictive of diminished ovarian reserve, as defined by poor gonadotrophin responsiveness and pregnancy rates in patients undergoing complex ovulation induction or one of the assisted reproductive technologies. Additionally, pregnancy rates were found to be highest in women with FSH levels less than 151U/L, and that it fell to less than 5% in those whose basal FSH levels were more than 251U/L [7]. FSH alone may be unreliable indicator of reproductive potential in older women [18]

**MANAGEMENT OF POLYCYSTIC OVARIAN SYNDROME (PCOS)**

It depends on the symptoms and mainly includes diet, weight management, exercise and bariatric surgery in morbidly obese patients (Table 2&3) . In addition, low anovulation in PCOS patients results from low follicle stimulating hormone resulting from excess levels of luteinizing hormone, insulin, and/or androgen. This is generally treated with a variety of medications including estrogen receptor antagonists, tamoxifen, aromatase inhibitors, glucocorticoids, or gonadotropins. Androgen-related problems such as hirsutism, acne, and/or alopecia are generally treated with anti-androgens that either bind androgen receptors or decrease androgen production. Alternative medicines including kinesiology, herbalism, homeopathy, reflexology, acupressure, acupuncture and massage therapy seem to be effective treatment in PCOS [19] .

**CLOMIPHENE CITRATE**

Ovulatory dysfunction is one of the most common causes of reproductive failure in sub-fertile and infertile couples. Women with PCOS have an increased incidence of ovulatory infertility. Clomiphene citrate (C/C) is the most common initial treatment used in anovulatory infertile women. The first clinical trial of C/C therapy demonstrated successful ovulation in 80% of women, half of whom achieved pregnancy during treatment.

## INSULIN SENSITIZERS IN PCOS

### Metformin

Metformin is a biguanide that is used to reduce plasma glucose concentrations in type 2 diabetics. There are some data to suggest that metformin may lead to slight improvements in peripheral insulin sensitivity. Studies in women with PCOS revealed reductions in androgen levels and improvements in ovulation when metformin was given for a duration of 10-24 weeks. However, only in some of these studies was the effect independent of the weight loss induced by metformin. In addition, metformin has been found to reduce the high rates of gestational diabetes in those with PCOS [21].

## PHARMACOLOGY

The first-line treatment of anovulation for patients wishing to conceive is clomiphene citrate, a selective modulator of the oestradiol receptor given at an initial dose of 50mg per day from days 2 to 6, 3 to 7 or 5 to 9 of the menstrual cycle, once it has been re-established. The dose can be increased to 50-250mg per day for 5 days if the patient still does not ovulate. To avoid multiple pregnancies, practitioners are strongly advised to monitor ovulation while administering clomiphene citrate, by measuring oestradiol hormone concentrations and performing atleast one pelvic ultrasonography[22].C/C is a non-steroidal triphenylethylene derivate that exhibits both estrogen agonist and antagonist properties. In general C/C acts solely as competitive estrogen antagonist. About 85% of an administered dose is eliminated after approximately 6 days, although traces may remain in the circulation for much longer. C/C is a mixture of two distinct steroisomers,enclomiphene is responsible for the ovulation inducing action of C/C. The levels of enclomiphene rise rapidly after administration and is cleared from the circulation soon thereafter. Zuclomiphene is cleared more slowly and the levels of this less active isomer remain detectable in the circulation for more than a month after treatment and may accumulates over consecutive cycles of treatment. The structural similarity to estrogen allows C/C to bind to estrogen receptors (ER). Incontrast to estrogen C/C binds ER for an extended period of time and eventually depletes ER concentrations. Depletion of the hypothalamic ER prevents correct interpretation of circulating estrogen levels. Reduced levels of estrogen block the negative feedback effect of estrogen on the anterior pituitary, stimulating an increased secretion of gonadotrophins thus augmenting follicular selection and stimulation. However,clomiphene citrate treatment fails, defined as failure to ovulate after 6months of treatment at an appropriate dose, the patient is regarded as resistant to it. By extension failure to conceive can also be regarded as treatment failure. Articles don't always make this distinction, however, and failure to conceive after clomiphene citrate may include either absence of ovulation or failure to conceive after ovulation. In these circumstances, ovarian drilling also called multiperforation or laparoscopic ovarian diathermy, can be suggested as first, second or third-line treatment for PCOS- related anovulation. This procedure, which can be performed by different approaches and with bipolar power, involves one or usually more perforations of the ovarian cortex.[23]

## SURGICAL TECHNIQUE OF OVARIAN DRILLING

The mechanism by which surgical treatment for PCOS related infertility acts is not clearly understood. It is thought that it may involve destruction of the ovarian stroma that produces the androgens. The following results always occur: decline in plasma LH and in pulsations; a temporary fall in inhibits; a (moderate) rise in FSH and sex, hormone-binding globulin; and a constant fall in androgens (especially testosterone) and in the Ferriman-Gallwey score [24]. Lower serum oestradiol concentrations are linked to a decline in aromatase activity. In practical terms, the LH/FSH ratio always returns to normal, with follicular development and ovulation resuming in 80% of cases. However, the physiological principles that make this surgical treatment effective have not yet been satisfactorily explained. What is known is that it relies on the destruction of some ovarian tissue and, for that to occur, the ovary must receive a certain quantity of energy administered by a minimally invasive route. As suggested by hendriks et al 2007, endocrine changes found after ovarian drilling seen to be governed by the ovaries themselves.

## LAPAROSCOPY

The benefit of laparoscopy is that is can be performed in all operating rooms, it doesn't require any specialist equipment and the entire abdominal cavity can be examined. Surgeons who regularly perform laparoscopies via this route will easily learn this technique. Moreover, laparoscopy can reveal some significant pelvic pathologies and therefore lead to modification of the therapeutic strategy. Its main disadvantages are the need to use curarimimetic agents, the absence of any available instrument that uses bipolar electrocoagulation and the difficulties sometimes faced in laparoscopy, especially on obese patients. [25]

Using transvaginal hydrolaparoscopy or fertiloscopy methods, have brought culdoscopy, a technique that fell out of favour in the 1970s, back onto the science . This procedure is performed on patients in the lithotomy position under general anaesthesisa. A veress needle is passed through the vagina into the pouch of Douglas, and 300ml of physiological saline at room temperature is injected. After withdrawing the needle, the surgeon inserts

the fertiloscope into the pouch of Douglas and introduces an optical device 2.9mm in diameter with a 30-degree lens.

The pelvis is then examined and a dye hydrotubation test performed. Because the fallopian tubes, the fimbria and the ovaries can all be seen clearly, a 5-french bipolar electrode can be used for microperforation of the ovarian cortex at 5 to 10 points. The bipolar energy used has a power of 100 and 130W, and the cortex is perforated to a depth of 8mm, producing a puncture with a diameter of 2mm. In comparision, ovarian drilling with monopolar electrodes and a laparoscopic technique appears effective when four perforations per ovary delivering 600J are performed [26]

The benefits of this approach are ; the option of using bipolar energy; the suitability of this technique for obese patients; the fact that it is less invasive; and the ability to use lighter anaesthesia. Its main disadvantages are: the need for specialist equipment; the fact that only the pelvis is available for examination; and the need fo surgeons to undergo training to learn and practice this procedure. However, the same technique can be performed by laparoscopy and shows equivalent results, except for the pregnancy rate, for which the follow up time is still insufficient. [27]

## PREDICTIVE FACTORS FOR OVARIAN DRILLING SUCCESS

Nine studies have examined the profile of patients likely to responded to ovarian drilling. Table 4. Summarizes the data, these were retrospective studies, only some of these studies which applied logistic regression, and one prospective study for patients resistant to clomiphene citrate . [28,29]

### Management of clinical hyperandrogenism

Oral contraceptive pills (OCPs) have been the traditional therapy for long-term treatment of PCOS in order to provide endometrial protection, regularize menses and improve dermatological abnormalities (hirsutism, acne) by reducing ovarian androgen production. Their main mechanisms of action include suppression of follicle-stimulating hormone, decrease of ovarian androgen secretion and free androgen levels and therefore protection of the endometrium from the risk of developing endometrial cancer [38]

### Management metabolic risk factors

Screening for diabetes and other cardiovascular risk factors (the metabolic syndrome) should be conducted in view of its prevalence in this population as discussed above. The management of glucose intolerance, dyslipidaemia and hypertension should follow current guidelines for these disorders. Patients should also be screened for sleep apnoea and referred for sleep studies when clinically indicated [40]

Cosmetic measures: This is probably the most utilised way of treating hirsutism and is often combined with pharmacotherapy.

i. Laser electrolysis with topical eflornithine cream (Vaniqua®) isthe most effective cosmetic measure for decreasing hair growth

ii. Other depilatory measures are: waxing, shaving and bleaching

iii. Minoxidil has been utilised in the treatment of androgenic alopecia

### Insulin sensitizers

Drugs that improve insulin resistance (metformin and thiazolidenediones) have been used to treat hirsutism as well. However metformin has limited success when compared to anti-androgens like spironolactone. A recent Cochrane review has shown that there was no difference between metformin and oral contraceptives in treating hirsutism. This has since been confirmed in a meta-analysis of patients with hirsutism (due to PCOS or idiopathic in nature), which also showed that metformin was inferior to both spironolactone and flutamide. In this meta-analysis, the effect of metformin on Ferriman-Gallwey scores was similar to placebo. Thus the clinical effectiveness of insulin-sensitisers for the treatment of hyperandrogenic symptoms remains to be proven.[41]

### Indian and global medicine [42,43]

The medical systems that are truly Indian in orgin and development are the ayurveda and the siddha systems. Ayurveda is practiced throughout India, but the siddha system is practiced throughout the worldwide in the tamil-speaking community migrated different countries.

**Table 1. Primer sequences and restriction enzymes used for detection of three thrombophilic polymorphisms**

| Polymorphism | PCR product (bp) | Restriction enzyme | RFLP products (bp) | Primer Sequences |
|---|---|---|---|---|
| MTHFR 677C/T | 198 | Hinfl | 198[a] 175,23 [b] | F-5'-AGGACGGTGCGGTGAGAGTG-3' |
| MTHFR 1298A/C | 164 | Mboll | 20,30,30,27,1,56[a] 20,30,30,84[b] | R-5'-TCCCGCAGACACCTTCTCCTTCA-3' |
| PAI-1-6754G/5G[a] | | | | F-5'-CCTTTGGGGAGCTGAAGGACTACTAC-3' |
| | | | | R-5'-CACTTTGTGACCATTCCGGTTTG-3' |
| | | | | F5g-5'-GTCTGGACACGTGGGGG-3' |
| | | | | F4g-5'-GTCTGGACACGTGGGGA-3' |
| | | | | R-5-TGCAGCCAGCCACGTGATTGTCTAG-3' |

**Table 2. National Institutes of Health Clinical Guidelines for long-term treatment of overweight and obesity [11]**

| Sl.No | Effective weight loss and long-term results- National Institutes of Health Guidelines |
|---|---|
| 1 | Sensible diet and changes eating habits for long term |
| 2 | Effective physical activity programme sustainable long term |
| 3 | Behaviour modification, reduction of stress, wellbeing |
| 4 | Combination of dietary and behavior therapy and increased physical activity |
| 5 | Social support by physician, family, spouse, peers |
| 6 | Smoking cessation and reduction in alcohol consumption |
| 7 | Avoidance of "crash diets " and short-term weight loss |
| 8 | Minor roles for drugs involved in weight loss |
| 9 | Avoidance of aggressive surgical approaches for majority |
| 10 | Adaption of weight-loss programmes to meet individual needs |
| 11 | Long-term observation, monitoring and encouraging of patients who have successfully lost weight |

**Table 3. Principles for treatment of infertility in obesity women [20]**

| **Principles for treatment of infertility in obese women** |
|---|
| • Assessment of BMI and waist circumference/waist hip ratio<br>• Assessment of metabolic risk profiles (lipid Profile, glucose intolerance), particularly in women with PCOS<br>• Encouraging weight loss through diet/exercise/lifestyle modification<br>• Energy deficit of 500-600kcal/day<br>• Moderate exercise/lifestyle modification<br>• Diet composition: Fat≤30% of energy (Saturated≤10% of energy, reduce trans fatty acids, increase mono-unsaturated and polyunsaturated fatty acids) carbohydrate-55% of energy, protein-15% of energy<br>• Reduction of alcohol intake and cessation of smoking<br>• Reduction of psychosocial stressors<br>• Use of a group environment in providing support, aiding weight loss and maintenance of weight loss.<br>• Tailoring intervention to a individuals weight and current dietary and exercise patterns (with use of dietitian of appropriate) |

**Table 4. Predictive factors for ovarian drilling success [30]**

| **Publication** | **PCOS recruited (n)** | **Duration of follow up (months)** | **Evaluation criterion** | **Favorable elements** | **Unfavourable elements** |
|---|---|---|---|---|---|
| Li et al (1998) (logistic regression) [31] | 118 | 12 | Pregnancy | Infertility <3years<br>LH > 10IU/L<br>Diathermy. laser | |
| Kriplani et al (2001,ID 186) (logistic regression) [32] | 66 | 54 | Pregnancy | LH>10IU/L<br>Infertility<3years | Associated tubal or masculine factors |
| Dale et al (2004) (Univariate analysis) [33] | 64 | 12-18 | Ovulation and pregnancy after LOD±IVF | | |
| Amer et al (2004) (retrospective, logistic regression) [34] | 200 | 12 | Ovulation and pregnancy | LH>10IU/l | BMI >35Kg/$m^2$ |
| Al-Ojaimi (2004) (Univariate analysis [35] | 181 | - | Ovulation | Obesity LH and LH/FSH intially elevated fall in LH and LH/FSH | Tesosterone>4.5 nM<br>Free androgen index>15<br>Infertility >3 years |
| Demirturk et al (2006) (Univariate analysis) [36] | 25 | - | Ovulation | Thinness | |
| Kato et al (2007) (Univariate analysis) [37] | 32 | - | Ovulation | Testosterone >50ng/dl | |

**Table 5. Anti-androgen therapy [39]**

| Mechanism of action | Drug | Dose | Adverse effect |
|---|---|---|---|
| Androgen receptor antagonists | Cyproterone acetate<br><br><br><br><br>Spironolactone<br>Flutamide | 2,50 or 100mg on days 1-11 of 28 day cycle with ethinylestradiol 30µg on days 1-21<br>100-200mg daily<br>Not recommended | Hepatic dysfunction<br>Feminisation of male fetus<br>Progesterone receptor agonist,Dysfunctional uterine bleeding<br>Electrolyte disturbance<br>Hepatic dysfunction |
| 5α-reductase inhibitors (Prevent conversion of testosterone to active dihydrotestoterone) | Finasteride | 5mg daily | Limited clinical experience; possibly less efficacious than other treatments |
| Suppress ovarian steroid production and elevate sex hormone-binding globulin | Oestrogen | See combination with cyproterone acetate above or Conventional oestrogen containing contraceptive | Venous thromboembolism<br>Hypertension<br>Weight gain<br>Dyslipidaemia<br>Increased breast and endometrial carcinoma |
| Suppress adrenal androgen production | Exogenous glucocorticoid to suppress ACTH | e.g Hydrocortisone 5mg at 0900 hrs and dexamethasone 0.5mg at 2200 hrs | Cushing syndrome |

**Table 6. The following herbs have all benefit PCOS sufferers by regulating hormone levels.**

| Herbs | Photograph | Botanical Name | Region | Hormonal effects | Advantage |
|---|---|---|---|---|---|
| Chaste berry |  | *Vitex agnus castus* (Lamiaceae) | Pituitary Gland | Controls the release of Luteinising hormone (LH) | Improve fertility Enchances Progesterone levels Decreasing estrogen and androgen levels |
| Saw Palemetto |  | *Sereno repens* | Cutaneous | Reduce excess levels of the male hormone testosterone | Decreasing excessive hair growth |
| Astaxanthin |  | *Haematococcus pluvialis* | Heart | Lowers male hormone testosterone | Powerful antioxidant |
| Rehmannia |  | *Rhodiola, Siberian Ginseng and Withania* | Adrenal Glands | Lowers adrenal stress | Adrenal tonics |
| Peony |  | *Paeonia lactiflora* (Paeoniaceae) | Anterior Pituitary | Reduces elevated testosterone | Modulates lactogenic hormone (after parturition) |

| | | | | | |
|---|---|---|---|---|---|
| Licorice |  | *Glycyrriza glabra* (Araliaceae) | Anterior Pituitary | Reduce androgen levels and improve the LH and FSH ratio | Regulate hormone and its adjuvant therapy of hirsutism |
| Gymnema |  | *Gymnema sylvestre* | Pancreas | Reducing carbohydrates and sugar cravings | Weightloss Improve insulin resistance |
| Tribulus |   | *T. terrestris* | Ovary | Restore menstrual regularity | Regulate ovulation |
| Spearmint Tea |  | *Mentha spicata* (Labiatae) | Cutaneous | Reduce testosterone | Antiandrogen properties |
| Ginseng Saponin |  | *Panax ginseng* (Araliaceae) | Ovarian Morphology and Nerve growth factor | Reduce androgen levels | Regulate hormone |
| Flaxseed |  | *Linum usitatissimum* (Linaceae) | Cutaneous and ovary | Reduce androgen levels | Decrease hirsutism, Insulin Decrease BMI and serum Testosterone levels |
| Aloe-vera |  | *Aloe barbadensis* (Liliaceae) | Ovary | Reduce testosterone | Restored estrus cyclicity,glucose sensitivity and steroidogenic activity |
| Cinnamom |  | *Cinnamomum zeylanium* (Lauraceae) | Pancreas | Improved effect of disturbed hormone | Reduce insulin resisstance |
| Milk Thistle |  | *Silybum marianum* (Asteraceae) | Ovary | Leutinizing hormone and progesterone | Increment in progesterone levels |
| Chamomile |  | *Matricaria chamomilla* (Asteraceae) | Ovarian tissue | Leutinizing hormone | Decrease signs of PCOS |

| | | | | | |
|---|---|---|---|---|---|
| Astragalus Polysaccharide |  | Astragalusspp (Fabaceae) | Pancreas | LH/FSH | Improving insulin resistance and Improved in high androgen levels |

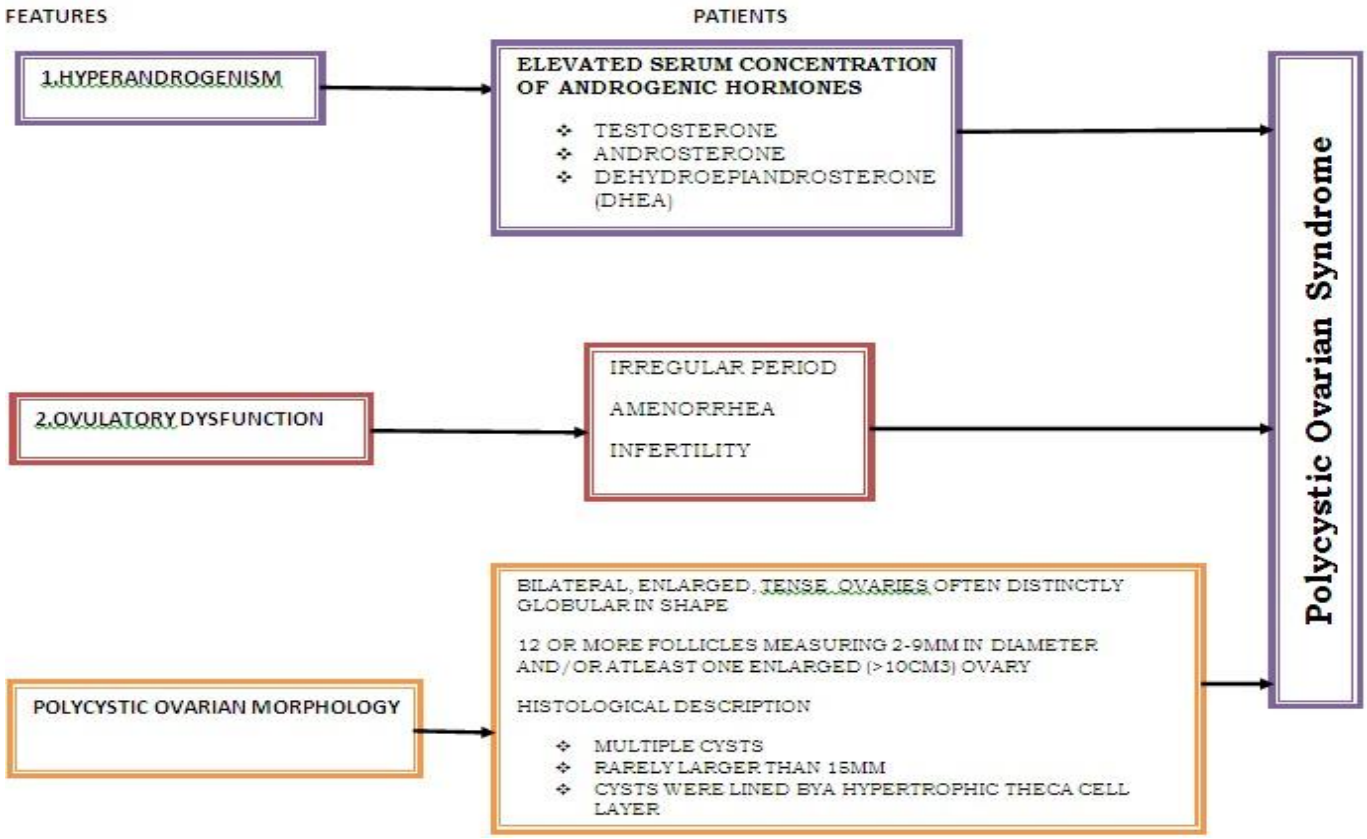



**Figure 1. The polycystic ovary may become enlarged with many small cysts.**

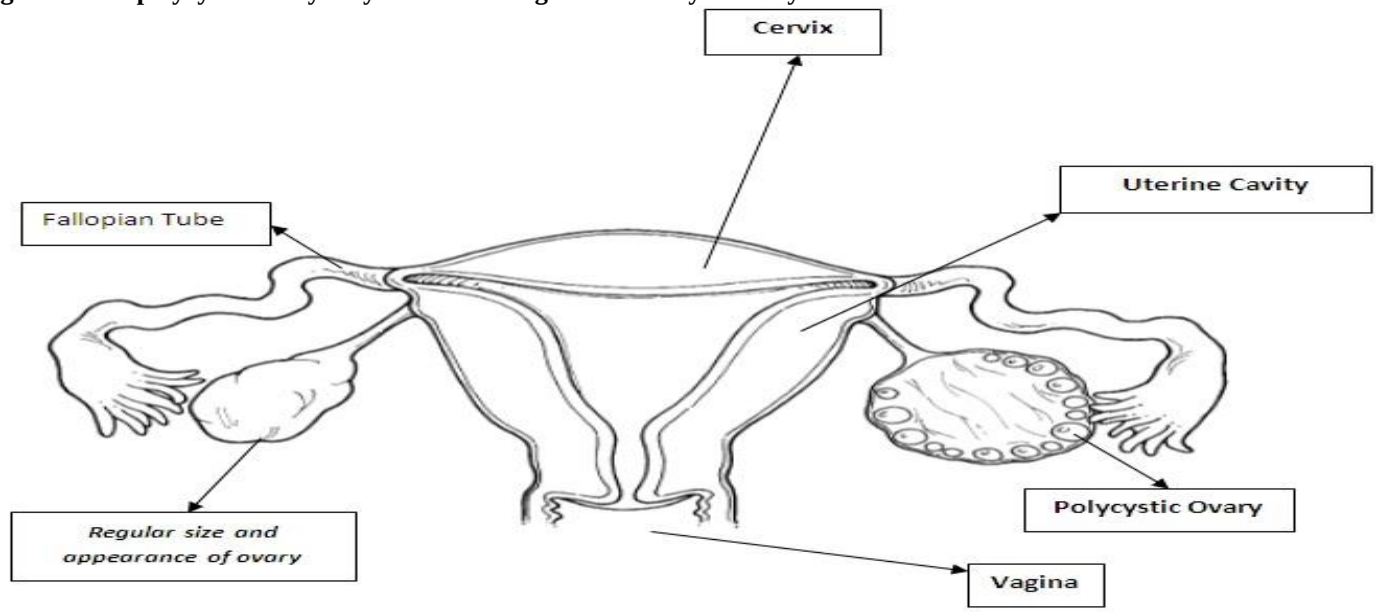
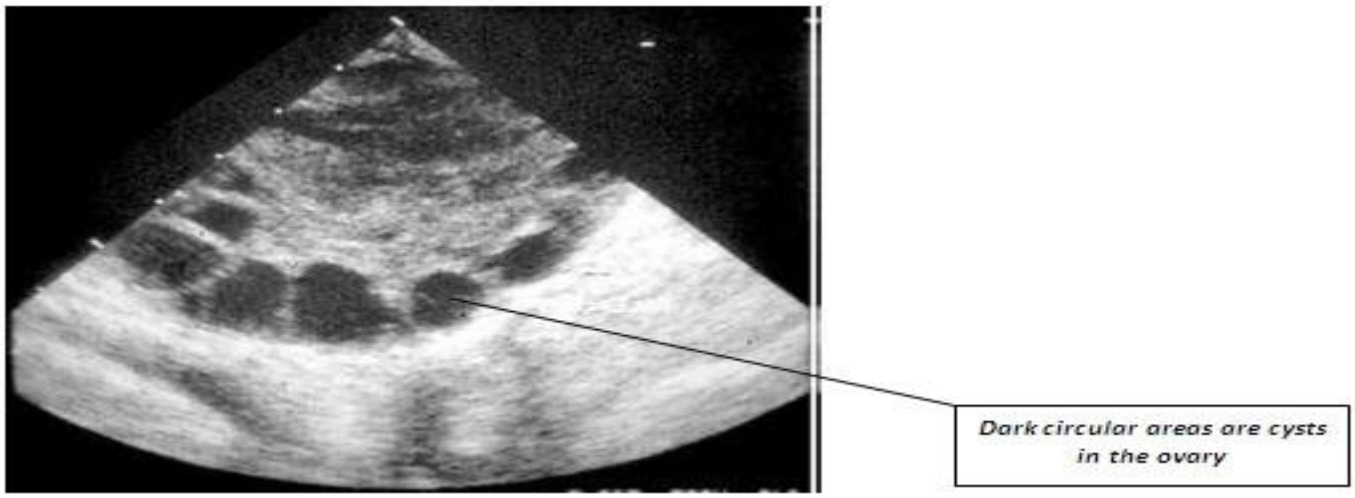


**Figure 2.Ultrasound picture of a polycystic ovary**




## CONCLUSION

Based on the literature authors conclude that, PCOS is a complex disorder, in multiple genetic, metabolic and hormonal controls fails to interact properly, however, interdisciplinary approach needed to manage the symptoms of the disease by pharmacological intervention and surgical intervention. Mean while, several ways to manage PCOS as well as decrease the complication associated with this syndrome were covered in this review. Life style modifications should be encouraged to take an active role in their health consequences by practicing diet modifications, weight loss and regular follow up of the clinicians to avoid the complication of the diseases.

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