Polycystic Ovary Syndrome: A Mysterious Ailment
Nargund College of pharmacy, Dattatreya nagar 2nd main, 100 ft ring road, BSK III stage, Bangalore, Karnataka, India
Received on:10-11-2011; Revised on: 15-12-2011; Accepted on:12-01-2012

ABSTRACT
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women between menarche and menopause. Clinical expression of this syndrome alters but commonly includes menstrual irregularities, infertility, and high levels of masculinising hormones. The involvement of androgen excess (hyperandrogenism), neuroendocrine abnormalities (alteration in GnRH pulse, LH, FSH) and genetics (FMR1) in the pathogenesis of PCOS is explained. It has tremendous negative impact on the physiology and metabolism of the body, including reproductive (infertility, hyperandrogenism, hirsutism and acne), metabolic (insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease) and psychological features (increased anxiety, depression). However, there is no perfect and well-defined diagnostic procedure for the identification of PCOS, considerable diagnostic procedures explained. Therapy should focus on both the short and long-term reproductive, metabolic, and psychological features. The aetiological role of insulin resistance and the impact of obesity on both hyperinsulinaemia and hyperandrogenism explained. Management focused on the drug therapy with alternative treatment, diet modification, and life style alterations.

Key words: PCOS, Menstrual irregularities, Infertility, Hyperandrogenism, Insulin resistance

INTRODUCTION
Polycystic ovary syndrome (PCOS) is a frustrating experience for woman, often complex for managing clinicians and is a scientific challenge for researchers. As research in PCOS is rapidly advancing, it is vital that research evidences translated to knowledge and action among women, healthcare professionals and policy makers. PCOS is the most common endocrine abnormality in reproductive-age women.

DEFINITION
Polycystic ovary syndrome (PCOS; Stein-Leventhal syndrome; sclerocystic ovarian disease) is by definition a syndrome for which there is no single diagnostic criterion to confirm clinical diagnosis. PCOS diagnosed by the presence of ultrasound evidence of polycystic ovaries or hyperandrogenism. PCOS is characterised by an accumulation of incompletely developed follicles in the ovaries due to anovulation, and is associated with increased ovarian androgen production. Clinical manifestations include infrequent or absent menses, obesity, and signs of androgen excess which include acne or seborrhoea. Women with PCOS commonly have insulin resistance, and elevated serum luteinising hormone (LH) levels, and are at an increased risk of type II diabetes and cardiovascular events.

PREVALENCE
Polycystic ovary syndrome (PCOS) is the most common endocrine abnormality in women of reproductive age, and its prevalence traditionally estimated at 4% to 8% from studies performed in Greece, Spain, and the USA. The prevalence of PCOS is increasing the world over and is showing a galloping increase in parallel with the rising prevalence of type 2 diabetes mellitus (T2DM). Use of different diagnostic criteria may partly account for it, as has recently been shown (18%) in the first community-based prevalence study based on current Rotterdam diagnostic criteria. Unfortunately, 70% of women in this recent study were undiagnosed. While the upper limit of prevalence for this study imputed using estimates of polycystic ovaries (PCO) for women who had not had an ultrasound, non-imputed prevalence calculated as 11.9 ± 2.4%. PCOS also noted to affect 28% of unselected obese and 5% of lean women. In 2006, based on US data and traditionally lower prevalence estimates, the anticipated economic burden of PCOS in Australia was AU$400 million (menstrual dysfunction 31%, infertility 12% and PCOS-associated diabetes 40% of total costs), representing a major health and economic burden. With regards to fertility, the estimated cost per birth in overweight women with PCOS is high.

Etiology
The exact aetiology of PCOS is unknown. Genetic and environmental factors combine with potential other contributors, including ovarian dysfunction, hyperandrogenism and hypothalamic pituitary abnormalities, to contribute to the etiology of PCOS. Although no single genetic abnormality has been identified in PCOS, a family history of type 2 diabetes is common.

Most women with PCOS have insulin resistance. This plays a key etiological role, contributing to reproductive (hyperandrogenism, anovulation and infertility) and metabolic features (type 2 diabetes, metabolic syndrome and cardiovascular risk factors). Insulin resistance is both genetic and lifestyle related, yet specific causes of insulin resistance and optimal therapies to address it remain unclear.

As noted, elevated insulin levels drive androgen production and increase free androgen levels by reducing sex hormone-binding globulin (SHBG) level. The combination of increased levels of androgens and insulin underpin the features of PCOS (figure I, II).

Intra-uterine exposure of a female foetus to an excess of androgens is an aetiological hypothesis finding increasing favour. Although the source of excess androgens in utero is unknown, animal experiments have shown that inducing exposure of the foetus to excess androgens produces all the manifestations of PCOS in the female progeny.

SIGNS AND SYMPTOMS:
Polycystic ovarian syndrome presents a complex and baffling array of symptoms. The condition is associated with some of the common symptoms include

Menstrual disturbance
The majority of women with PCOS have an abnormal menstrual cycle and the most frequent pattern is infrequent menstruation associated with anovu-

Nagamani Kopparapu
Nargund College of pharmacy, Dattatreya nagar 2nd main, 100 ft ring road, BSK III stage, Bangalore, Karnataka, India
PCOS is a complex multifactorial disorder influenced by the synergistic impact of environmental factors on a predisposed genetic background, which modulates both hormonal and metabolic processes. A complete understanding of the underlying pathophysiology of PCOS is still lacking. There are several theories to explain the pathogenesis of PCOS: (1) Hyperandrogenism, 2) Neuroendocrine abnormalities and 3) Genetics. We will discuss each of these theories in more detail.

### Hyperandrogenism:
Investigations from nonhuman primates have shown that prenatal exposure to androgen excess in uterus leads to the development of the human PCOS phenotype in adult monkeys, but it may produce hypermenorrhea (very frequent menstrual periods) or other symptoms. Approximately three-quarters of patients with PCOS (by the diagnostic criteria of NIH/NICHD 1990) have evidence of hyperandrogenemia.

<table>
<thead>
<tr>
<th>Area of action</th>
<th>Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy homeostasis</td>
<td>Glucose uptake in muscles, glycerogen formation in liver, glucose uptake in fat cells</td>
<td>Defective in insulin resistance</td>
</tr>
<tr>
<td>Hormonal effects</td>
<td>Inhibition of lipolysis, stimulation of adrenal androgen production, sensitivities follicle to respond to LH at 4mm diameter rather than 9.5mm diameter, Inhibition of apoptosis of theca cells, stimulation of pituitary LH secretion, Inhibition of liver SHBG production, stimulates 5-alpha reductase, increasing tissue conversion of testosterone to dihydrotestosterone, suppresses HDL cholesterol, Increases PAI-1, Acanthosis nigricans, skin tags</td>
<td>Normally occurs at low insulin levels, Not universal, depends on woman having other genes, follicular developed is arrested at 8mm diameter, cysts lined by theca cells, further stimulation of ovarian androgens, Increases active testosterone, Explanation of testosterone when testosterone and FAI are normal, vascular disease, Increased thrombotic disease, severe insulin resistance, Moderate insulin resistance</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Metabolic syndrome
This appears as a tendency towards central obesity and other symptoms associated with insulin resistance. Serum insulin, insulin resistance and homocysteine levels are higher in women with PCOS.

### High levels of masculinising hormones

- **Infertility**
  PCOS is the most common cause of anovulatory infertility. It accounts for 90-95% of women attending infertility clinics with anovulation. However, 60% of women with PCOS are fertile (defined as the ability to conceive within 12 months), although time to conceive is often increased. In those with PCOS and infertility, 90% are overweight. Obesity also independently exacerbates infertility, reducing efficacy of infertility treatment and inducing a greater risk of miscarriage.

- **Adrenal hyper responsiveness to adrenocorticotropic hormone**
  Adrenal hyper responsiveness to adrenocorticotropic hormone (ACTH) occurs in 25% of women with PCOS, resulting in excess dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEA-S), and androstenedione. It is the important source of hyperandrogenism in non-obese subjects. Preclinical models clearly indicate that estradiol and DHEA leads to development of cysts in the ovary.

- **Obesity**
  Furthermore, although the ovaries and adrenal glands are the principal sources of excess androgen production in women with PCOS, enhanced 5alpha-reductase activity in the liver and peripheral tissues (e.g., adipose tissue) may also increase conversion of testosterone to the biologically more potent androgen, dihydrotestosterone (DHT) which is responsible for the production of cysts in PCOS.

### Three Major causes of hyperandrogenism
- GnRH-mediated LH hyper secretion.
- Overproduction of Testosterone precursors. (Mainly because of an intrinsic abnormality of P450c17a.)
- LH-mediated androstenedione production leads to inhibin augmentation.
- Hyperinsulinemia is one of the major causes of hyperandrogenism by following mechanisms.
- Directly by acting as a co-gonadotropin augmenting LH activity within the ovary,
- Indirectly by increasing serum LH pulse amplitude.

### Insulin resistance and hyperinsulinemia
Inherited resistance to glucose metabolism with compensatory hyperinsulinemia, often aggravated by obesity found to be the cause of PCOS.

- Obesity and/or hyperandrogenaemia aggravate, but are not the primary cause, of insulin resistance. Most of the hormonal and functional abnormalities in PCOS are direct or indirect results of hyperinsulinaemia (see Table 1).
- Recent, PCOS women with normal insulin sensitivity shown to have ovarian hyper response to insulin.

### Table-I .The Effects of hyperinsulinemia

- Normal hyperinsulinemia
  - Glucose uptake in muscles
  - Glycerogen formation in liver
  - Glucose uptake in fat cells
- Moderate insulin resistance
  - Glucose uptake in muscles
  - Glycerogen formation in liver
  - Glucose uptake in fat cells
  - Lipolysis
- Severe insulin resistance
  - Glucose uptake in muscles
  - Glycerogen formation in liver
  - Glucose uptake in fat cells
  - Lipolysis
  - Hyperinsulinemia
  - Increased thrombotic disease
  - Severe insulin resistance
  - Moderate insulin resistance

- Glucose uptake in muscles: Low production of androgens leads to increase of glucose uptake in muscles, glycogen formation in liver, glucose uptake in fat cells.
- Glucose uptake in fat cells: Low production of androgens leads to increase of glucose uptake in fat cells.
- Lipolysis: Low production of androgens leads to increase of lipolysis.
- Hyperinsulinemia: Low production of androgens leads to increase of hyperinsulinemia.
In genetically susceptible patients, hyperinsulinaemia stimulates the enzyme complex cytochrome P450c 17α in both the ovary and the adrenal cortex, increasing androgen production (see Figure II). Insulin-resistant women without this genetic susceptibility do not develop PCOS. Hyperinsulinaemia also stimulates pituitary LH secretion that, in turn, further stimulates ovarian androgen production through the cytochrome P450c 17α complex.

Insulin also stimulates the enzyme 5α-reductase (see Figure II), which converts testosterone to dihydrotestosterone, the androgen that stimulates acne, hair growth and scalp hair loss. This explains the common phenomenon of hirsutism in the presence of normal testosterone and free androgen index levels.

The central role of hyperinsulinaemia in PCOS is highlighted in women with type 1 diabetes, who need peripheral hyperinsulinaemia to achieve normal glycaemia when insulin is not secreted directly into the portal vein from the pancreas.

Hirsutism, biochemical hyper androgens and menstrual abnormalities are present in 20%-30% of women with type 1 diabetes, and 50% have polycystic ovaries. [28]

The diagnosis of insulin resistance is imperfect science. Impaired glucose tolerance, impaired fasting glucose, and type 2 diabetes diagnose insulin resistance with certainty, but, unfortunately, at a very late stage when beta cell numbers are falling. Increased insulin responses to a GTT (fasting insulin > 9 mIU /L, peak insulin > 60 mIU /L or two-hour insulin >one hour) give a positive diagnosis, but miss 10%-15%, mostly in the very physically active.

Insulin resistance is one of the most reliable measures of insulin resistance in women not on the OCP (oral contraceptives). The clinical findings of skin tags, acanthosis nigricans and skin pigmentation is an integral part of the assessment of all women with PCOS.

**Neuroendocrine Abnormalities**

The hypothalamic-pituitary-ovarian axis
The pituitary gonadotroph plays a central and important role in reproductive function. It is responsible for secretion of FSH and LH by stimulating hypothalamic GnRH by integrated feedback mechanisms. FSH is responsible for conversion of androgen to oestrogen by stimulating aromatase enzyme and promotes the initial follicular development.

LH has its role in luteal phase by promoting progesterone secretion and in follicular phase by inducing thecal androgen production and initiates oocyte maturation at mid cycle. [29]

Alteration of GnRH pulse frequency is the most common endocrine abnormality observed in PCOS women. This rapid GnRH pulse frequency favours excess LH secretion over FSH secretion. It leads to elevated LH level and LH:FSH ratio.

This excess LH is responsible for the production of androgens from ovarian theca cells. Aromatization of androgen to oestrogen is impaired due to deficiency of FSH. It finally leads to Hyperandrogenism. [32]

**Luteinising Hormone (LH)**
In PCOS women, there is significant increase in serum luteinizing hormone (LH) level. This is due to an increased amplitude and frequency of LH pulses. It observed in 40–60% of PCOS women. [30]

Decreased sensitivity of the GnRH leads to persistently rapid GnRH pulse
frequency that is responsible for LH hyper secretion, which is a hallmark of the disorder and finally it leads to hyperandrogenism.

Other causes of LH hyper secretion:
(i) Aromatization of androgens to estrogens, that results in everlasting estrogen overproduction.
(ii) Decreased central opioid and dopaminergic tone,
(iii) Leptin-induced GnRH modulation, or
(iv) Insulin-mediated increase in serum LH pulse Amplitude. \[26\]

Genetics
It is difficult to determine genetic origins of PCOS. Although research has focused on association of CYP17, CYP11A, CYP21 gene expression; but they fail to show confirm evidence with PCOS. \[30\] PCOS has also been associated with a specific FMR1 sub-genotype. The research suggests that women who have heterozygous-normal/low FMR1 have polycystic-like symptoms of excessive follicle-activity and hyperactive ovarian function. \[31\]

The development of ovarian cysts
Follicular cells become responsive to LH stimulation only after the follicle grows to a diameter of 9.5 mm, after which the mid-cycle LH surge stimulates two sets of mitoses of the theca and granulosa cells lining the follicle, creating the pre-ovulatory follicle. If ovulation does not occur, that is, the follicle does not rupture, the theca and granulosa cells undergo apoptosis – programmed cell death – and the follicle collapses. Hyperinsulinaemia sensitises the follicular cells to respond to LH stimulation earlier, at a diameter of 4 mm, so that the follicle enlarges to only 8 mm diameter and hence is not sufficiently mature to rupture and ovulate. Hyperinsulinaemia prevents apoptosis of the theca cells; leaving a sub cortical follicular cyst lined with theca cells without granulosa, cells (see Figure II).

In the absence of granulosa cells to convert androstenedione to oestriol and oestradiol, theca cells convert androstenedione to androgens (see Figure I).

Diagnosis
There is no perfect and well-defined diagnostic procedure for the identification of PCOS. Therefore, it leads to confusion to many clinicians for the management of PCOS. The hallmark of disease is hyperandrogenism and chronic anovulation. These two parameters play a crucial role in diagnosis of PCOS in the absence of pituitary and adrenal disease. \[33\]

Gynaecologic ultrasonography
It is to investigate the following
- The Ovarian follicles; the distributed ovarian function and ovulation.
- According to the Rotterdam criteria, 12 or more small follicles found to seen in an ovary on ultrasound examination. \[34\]
- The follicles may be oriented in the periphery, giving the appearance of a ‘string of pearls’. The numerous follicles contribute to the increased size of the ovaries, that is, 1.5 to 3 times larger than normal

Laparoscopic examination of ovaries
- This examination may reveal a thickened, smooth, pearl-white outer surface of the ovary. However, it is not consider for finding out PCOS.

Serum blood levels of androgens
The hallmark of this syndrome is Hyperandrogenism. Hyperandrogenism can also determine by majorly, by assessment of free testosterone / free androgen index (FAI) and minor estimation of androstenedione and DHEAS. Determination of SHBG is essential for calculation of FAI. \[35\] FAI correlated with degree of obesity. \[36\]

Hormonal levels
- Follicle stimulating hormone (FSH) to luteinizing hormone (LH) levels estimation at day 3 of menstruation generally 1:1, but sometimes even greater in PCOS women. \[37\]
- Assessments for finding risks
Fasting biochemical screen and lipid profile [38]

2-hour oral glucose tolerance test (GTT)
It should perform in patience with risk factors (obesity, family history, history of gestational diabetes) [14] may indicate impaired glucose tolerance (insulin resistance) in 15-33% of women with PCOS. [39] Insulin resistance could observe in both normal weight and overweight patients.

Fasting insulin level or GTT with insulin levels (also called IGTT).
Elevated insulin levels not only helpful to predict response to medication but also indicate women who will need higher dosages 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.

Glucose tolerance testing (GTT) instead of fasting glucose can increase diagnosis of increased glucose tolerance and frank diabetes among patients with PCOS according to a prospective controlled trial. [17]

Other causes of irregular or absent menstruation and hirsutism, such as hypothyroidism, congenital adrenal hyperplasia (21-hydroxylase deficiency), Cushing’s syndrome, hyperprolactinemia, androgen secreting neoplasms, and other pituitary or adrenal disorders, should be investigated. [14, 38, 39]

PROGNOSIS
PCOS has widespread detrimental effects on the physiology and metabolism of the body and their resulting long-term consequences. Environmental influences play an important role in the multi-system dysfunctions, with obesity, abnormal gonadotropin dynamics, excessive androgen production, and insulin resistance presenting as the key features of the disorder.

Insulin Resistance / Diabetes
- A review published in 2010 concluded that women with PCOS had an elevated prevalence of insulin resistance and type II diabetes, even when controlling for body mass index (BMI). [34,40]

- Patients with PCOS along with type-I diabetes found to have increased serum total and free testosterone concentration and androstenedione levels, but they found to have normal sex hormone-binding globulin (SHBG) and dehydroepiandrosterone sulphate (DHEAS) levels. [40] Therefore, there is a strong correlation among PCOS, obesity, diabetes. Obesity increases insulin resistance and dyslipidemia in patients with or without PCOS. PCOS also makes a woman, particularly if obese, prone to gestational diabetes. [42]

Hypertension
It occurs in patients particularly if obese and/or during pregnancy. [42, 43]

Dyslipidemia
In patients with PCOS, there is disordered metabolism of cholesterol and triglycerides (TG). There is higher LDL, VLDL, and lower HDL [43]. PCOS patients show decreased removal of atherosclerosis-inducing remnants, seemingly independent of insulin resistance/Type II diabetes. [44,45]

Cardiovascular disease
PCOS women have 2-fold risk of arterial disease when compared to normal women [34-42] independent of BMI. [46]

It is well-known fact that women with PCOS are more prone to atherosclerosis. This is mainly due to the presence of male hormones in increased concentration than normal. The atherosclerosis may further lead to stroke, heart attack, eye and kidney problems. [47]

Liver Disease
PCOS patients have abnormal cholesterol and TG, the ability to metabolize these molecules in liver will be impaired. Therefore, the extra lipids will be stored in liver cells. Usually there is limited capacity to store lipids in liver. Therefore, this further contributes to perturbations in the liver’s metabolic capacity. [42,44]

Bulimia
Bulimia nervosa is eating disorders characterized by recurrent episodes of binge eating (rapid consumption of a large amount of food in a discrete period, usually less than two hours). PCOS aggravate bulimic behaviour. As PCOS women have increased androgen levels, they have the capacity of appetite stimulating levels, which may further leads to weight gain. [41,42]

Pregnancy Complications
It includes increased prevalence of early pregnancy loss (EPL), gestational diabetes (GDM), pregnancy-induced hypertensive disorders (PAP/PIH) and the birth of small-for gestational-age (SGA) babies. The increased risk of EPL has contributed to obesity, hyperinsulinemia and raised PAI-1 levels, elevated LH concentrations and endometrial dysfunction. [48]

Endometrial hyperplasia and endometrial cancer (cancer of the uterine lining)
In PCOS women, these are possible due to over accumulation of uterine lining, and lack of progesterone resulting in prolonged stimulation of uterine cells by estrogen. [34, 42, 49, 50] It is not clear if this risk is directly due to the syndrome or from the associated obesity, hyperinsulinemia, and Hyperandrogenism. [51-54]

Loss of Hearing
As PCOS is associated with abnormality of hormones, it further creates problem in inner ear, which leads to hearing problem. [55]

Acanthosis nigricans
Characterised by patches of darkened skin under the arms, in the groin area, on the back of the neck. [34]

Depression/Depression with Anxiety [14]

Autoimmune thyroiditis [56]

MANAGEMENT OF PCOS

Hyperandrogenism:
- Anti-androgens: It found that Flutamide, a non-steroidal anti-androgen was effective in treating hirsutism. Its use at a dose of 250 mg daily for 18 months in 18 non-obese adolescents with functional ovarian hyperandrogenism lead to improvement in both clinical and biochemical hyperandrogenism. Efornithine (Vaniqa) is a topical cream that used to slow hair growth. Efornithine works by inhibiting ornithine decarboxylase, which is essential for the rapidly dividing cells of hair follicles. Cyproterone acetate (CPA) and ethynylestradiol used as an anti-androgen. [57]

- Spironolactone is the one most commonly used anti-androgen in adolescent women in US. It acts by competing with receptor for dihydrotestosterone, and blocks the androgen receptor and exhibit the anti-Androgenic effect. It also acts as an aldosterone antagonist. Its anti-androgenic effect can be improved by increasing sex
Anovulation and fertility

- Investigation on vitamin supplements revealed that there is a direct correlation between fertility and multivitamin supplement. Regular use of multivitamin may decrease risk of infertility. Vitamin B / folic acid are an important element in the multi-vitamins.[59]
- The most common and first-line method for inducing ovulation in anovulatory woman is by using clomiphene citrate (anti estrogen). It acts by blocking the negative feedback effect of oestrogen on anterior pituitary stimulation. This further leads to increase in secretion of gonadotrophins. In anovulatory women, Clomiphene improves ovulation in approximately 80% of cases and leads to pregnancy in approximately 50% after 6 cycles.[60]
- An investigation on Naltrexone shown that, it has a tendency to induce ovulation in women with PCOS. Further, ovulation improved by giving in combination with clomid. Naltrexone can reduce weight, insulin level and improve the LH/FSH stimulation hormone ratio, in PCOS women. [81]
- Aromatase inhibitors anastrozole and letrozole used either alone or along with clomiphene citrate. Combination leads to reduction in gonadotrophin requirement.[60]
- CYP17a inhibitors: Ketoconazole acts by inhibition of adrenal as well as ovarian cytochrome P450 hydroxylase enzyme and by inhibition of ovarian aromatase activity. In resistant women, there is no improvement in pregnancy rates even though it used in combination with clomiphene citrate. Therefore, these combinations are rarely used.[60]
- Surgical therapy: It aimed mainly at restoring ovulation. Various laparoscopic methods including electrocautery, laser drilling [62], and multiple biopsy, are used with the goal of creating focal areas of damage in the ovarian cortex and stroma. Potential complications include formation of adhesions (although this is less common than with traditional surgical approaches) ovarian atrophy. Multiple pregnancy rates are lower with ovarian drilling than with gonadotropin treatment. [63]

Menstrual irregularities

An infrequent menstrual cycle not only leads to PCOS but also carry a 3-fold increased risk of endometrial carcinoma. Four (4) menses per year are required to control this increased risk. Oral contraceptives are always effective at normalizing menstrual cycle. Use of oral contraceptives has its limitation in hyperactive coagulation state. 7-10 days course of medroxyprogesterone is no improvement in pregnancy rates even though it used in combination with clomiphene citrate. Therefore, these combinations are rarely used.[60]

Use of oral contraceptives with a non-androgenic progestin to suppress ovarian function restores regular menstrual cycles and normalizes androgen levels. Greek investigators found 150 mg desogestrel combined with 30 mg ethinylestradiol to be effective in lowering androgen levels, regulating menses, and decreasing hirsutism in adolescents. It is well tolerated, and did not worsen the lipid profile, weight, or waist-to-hip ratio.[57]

Anovulation and fertility

- Investigation on vitamin supplements revealed that there is a direct correlation between fertility and multivitamin supplement. Regular use of multivitamin may decrease risk of infertility. Vitamin B / folic acid are an important element in the multi-vitamins.[59]
- The most common and first-line method for inducing ovulation in anovulatory woman is by using clomiphene citrate (anti estrogen). It acts by blocking the negative feedback effect of oestrogen on anterior pituitary stimulation. This further leads to increase in secretion of gonadotrophins. In anovulatory women, Clomiphene improves ovulation in approximately 80% of cases and leads to pregnancy in approximately 50% after 6 cycles:[60]
- An investigation on Naltrexone shown that, it has a tendency to induce ovulation in women with PCOS. Further, ovulation improved by giving in combination with clomid. Naltrexone can reduce weight, insulin level and improve the LH/FSH stimulation hormone ratio, in PCOS women. [81]
- Aromatase inhibitors anastrozole and letrozole used either alone or along with clomiphene citrate. Combination leads to reduction in gonadotrophin requirement.[60]
- CYP17a inhibitors: Ketoconazole acts by inhibition of adrenal as well as ovarian cytochrome P450 hydroxylase enzyme and by inhibition of ovarian aromatase activity. In resistant women, there is no improvement in pregnancy rates even though it used in combination with clomiphene citrate. Therefore, these combinations are rarely used.[60]
- Surgical therapy: It aimed mainly at restoring ovulation. Various laparoscopic methods including electrocautery, laser drilling [62], and multiple biopsy, are used with the goal of creating focal areas of damage in the ovarian cortex and stroma. Potential complications include formation of adhesions (although this is less common than with traditional surgical approaches) ovarian atrophy. Multiple pregnancy rates are lower with ovarian drilling than with gonadotropin treatment. [63]

Insulin resistance

- Hyperinsulinemia may be one of the aspects that lead to hyperandrogenemia. Because the correction or suppression of hyperinsulinemia by either weight loss or medications, leads to lowering of androgen level and improves the fertility. This has succeeded by using metformin in adolescents. Apart from this, even Thiazolidinedionines found to reduce the functional adrenal hyperandrogenism in adult women.[51]
- Magnesium had shown to reduce insulin resistance. PCOS women contain lower ratio of Mg to Ca in comparison with normal women. Supplementation of Mg helps in balancing the Mg and Ca.[64,65]
- Carnitine plays a role in decreasing symptoms of PCOS by improving IR,[66]
- NAC (n-acetyl-cysteine) shown to effect on IR, improvement in ovulation, reduction of pregnancy complications, and reduction of “advanced glycation products” (AGEs).[67]
- “D-chiro-inositol” or DCI improves insulin sensitivity in women with PCOS. As DCI supply is spotty and too expensive, d-pinitol comes into a role that is a precursor of DCI. Therefore, by taking supplemental d-pinitol, there is an increase in DCI,[66]

Role of inositol

- The inositol phosphoglycans (IPGs) are putative mediators in non-classic insulin signalling cascade for glucose uptake and use.
- Oral nutritional supplementation of inositol with part of the vitamin B complex (B8) found to enhance insulin sensitivity and improve the clinical and hormonal characteristic of patients with PCOS [61]
- It plays a role in inducing ovulation, improving quality of eggs to avoid the miscarriage (with folic acid).[69]

Combination therapy

As there is no particular drug for effective treatment of hyperandrogenemia and IR, investigators are tested combination therapy that include flutamide/metformin, ethinylestradiol/drospirenone with or without flutamide. The therapy results in improvement in hyperandrogenemia, but variable in insulin resistance.[57]

Role of vitamin D

Accumulating evidence suggests that, vitamin D deficiency may contribute to the development of the metabolic syndrome. Among them in one study found insufficient levels of 25-hydroxyvitamin D (< 30 ng/ml) in almost three quarters of PCOS patients.[71] Vitamin D3 has proved to act as genomic stimulator of the insulin response in the control of glucose transport. Recent study revealed that the combined supplementation of both calcium and vitamin D3 found to be beneficial in optimizing glucose metabolism and irregular menstruation. [72]

Diet modification

Current lifestyle recommendations for PCOS propose allow fat (~30% of energy, saturated fat ~10% of energy), moderate protein (~15%) and high carbohydrate intake (~55%) and increased consumption of fibre, whole grain breads, cereals, fruit and vegetables for reduction of associated mortality and morbidity and improvement of insulin sensitivity.[71]

Lifestyle modification

A woman with PCOS requires not only medical management but also more importantly “lifestyle management”. A change in attitude towards exercise and food will help her achieve physiological normality and improve her
emotional status. As fat cells store estrogen, which can have a direct influence on PCOS and fertility. Losing, even a moderate amount of weight reduces the person’s risk of cardiovascular disease, non-insulin dependent diabetes (type 2) and reduction in stored estrogens. Weight loss also helps to lower the level of insulin, which, in turn, reduces the ovaries’ production of testosterone. Weight loss through lifestyle modification should be a primary treatment aim for PCOS. [7,34]

CONCLUSION:
PCOS is not just an endocrine disorder, but a combination of metabolic and psychosocial detrments. PCOS is the best attempt so far to integrate conflicting views of this syndrome into an understanding that will help the general physician, endocrinologist, dermatologist, gynecologist, and radiologist in treating patients. PCOS linked with familial origins, the multiple clinical presentations, and the reproductive and metabolic sequelae. Traditional and newer forms of treatments described, including the widespread use of metformin, the new wonder drug that restores ovulation and fertility in many women while improving metabolic sequelae with few serious side effects. Patients need regular follow-up with their physicians for early detection and management of any untoward sequelae associated with the syndrome. Additionally self-management by modifying diet and lifestyle will appear to be achieving significant success.

REFERENCES:
54. Imran Pirvany, M.D., and Togas Tulandi, M.D. Laparoscopic treatment of polycystic ovaries: is it time to relinquish the procedure? Fertility and sterility, 80(2), august 2003
64. Kalliopi Kotsa, M.D., Ph.D., Maria P. Yavropoulou, M.D., Olympia Karahalios, Public Health Department, University Hospital Korinthos, Greece, “Blood pressure, hyperinsulinemia and the polycystic ovarian syndrome.”, *Trends in Endocrinology & Metabolism*, 13(6) August 2002. doi:10.1016/j.tem.2002.06.001.