Chapter (1)

Polycystic ovarian syndrome

(A) Definition and historical background:

PCOS is a heterogeneous disorder that affects several body systems and leads to reproductive and metabolic complications. It is also the most common cause of chronic anovulation and hyperandrogenism in young women. (Mitra S et al., 2015)

In 1935, Stein and Leventhall first defined a disorder, which would eventually become known as the polycystic ovarian syndrome (PCOS). These gynecologists described 7 women suffering from infertility and amenorrhea and determined, upon surgical exploration, that these women had enlarged ovaries with several superficial cystic structures. Stein and Leventhall performed ovarian wedge resections on these patients, in the belief that they were removing obstructions or cysts from the ovary, which would allow for normal ovarian function to resume. After the surgery, all women resumed their cyclic menses and 5 conceived. (Rupa K et al., 2018).

In 1990, an expert conference sponsored by the National Institute of Health (NIH) established that the major criteria to diagnose PCOS included clinical hyperandrogenism (determined by the presence of hirsutism) and/or blood total testosterone (TT) excess associated with ovarian dysfunction (OD) (defined by the presence of oligo-amenorrhea and chronic anovulation), provided that all other well-known disorders characterized by androgen excess are excluded. (Sheety D et al., 2017)

In 2003, the expert conference in Rotterdam added a third criterion, based on the ovarian morphological appearance by ultrasonography (defined as polycystic ovarian morphology - PCOM). Intriguingly, the Rotterdam panel decided that PCOS could be defined when at least two major features were present, whatever their combination. (The Rotterdam ESHRE/ASRM 2004)
In a short period of time, the Rotterdam criteria became very popular, despite the number of possible different phenotypes being greatly expanded, from classic to milder forms, characterized by the absence of a hyperandrogenic state. A few years later, the Androgen Excess and PCOS society (AEPCOS) emphasized the relevance of hyperandrogenism as a primary criterion to define PCOS. (Azziz R et al., 2009)

(B) Epidemiology of PCOS:

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-aged women around the world; prevalence of PCOS varies widely depending on ethnicity, body composition, and the definition used for diagnosis. (Matsuzaki T et al., 2017)

PCOS affects 6–10% women of childbearing age. Furthermore, it is believed to be one of the leading causes of infertility worldwide. (Barthelmess E et al., 2014)

An Australian study examined the prevalence of PCOS in a retrospective birth cohort employing the NIH, Rotterdam, and AES diagnostic criteria. These data revealed prevalence based on NIH diagnostic criteria of 8.7% ± 2.0%, less than the 11.9% ± 2.4% and 10.2% ± 2.2% using Rotterdam and AES criteria, respectively. (March et al., 2010).

Approximately 85–90% of women with oligomenorrhea have PCOS, while 30–40% of women with amenorrhea suffer from PCOS. More than 80% of women showing symptoms of androgen excess have PCOS. Roughly, 90–95% of anovulatory women presenting to infertility clinics have PCOS. (Tosi F et al., 2016)

(C) Diagnostic criteria for PCOS:

Diagnosis of polycystic ovary syndrome is based primarily on the clinical history and physical examination. The major clinical features of polycystic ovary syndrome are hyperandrogenism and menstrual dysfunction. (Legro RS et al., 2013)
It is generally accepted that PCOS is not a specific endocrine disease but a syndrome represented by a collection of signs and symptoms and that no one sign, symptom, or test is diagnostic. (Escobar-Morreale HF 2012)

There has been considerable controversy over the 3 different definitions that have been proposed by professional organizations for the diagnosis of PCOS. (RCOG; 2014)

1. **The National Institutes of Health (NIH):**

   NIH in 1990 proposed the following diagnostic criteria for PCOS:
   - Chronic anovulation.
   - Clinical and/or biochemical signs of HA.
   - Exclusion of other causes of HA such as congenital adrenal hyperplasia, androgen-secreting tumors and hyperprolactinemia.

2. **Rotterdam Criteria:**

   The European Society of ESHRE/ASRM held a consensus meeting at Rotterdam in 2003 and developed revised criteria incorporating a wider spectrum of phenotypes in PCOS. Two out of three criteria would be needed to make the diagnosis after exclusion of the other causes for HA:
   - Oligo-amenorrhea and/or anovulation.
   - Clinical and/or biochemical signs of HA.
   - Polycystic ovarian morphology (PCOM) by US.

3. **Androgen Excess and PCOS Society Criteria (AES-PCOS)**

   The Androgen Excess Society (2006) recommended diagnosing PCOS by the presence of 3 features:
   - Clinical and/or biochemical signs of HA.
   - Ovarian dysfunction (oligo/anovulation and/or PCOM).
   - Exclusion of other causes of HA.
Review of literature

<table>
<thead>
<tr>
<th>Criteria</th>
<th>NIH 1990</th>
<th>Rotterdam 2003</th>
<th>AES 2006</th>
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<tr>
<td>Oligomenorrhea</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
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<tr>
<td>Clinical or biochemical HA</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
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<tr>
<td>PCOM</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
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<td>Exclusion of other causes, i.e., CAH</td>
<td>+</td>
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*Table (1): Diagnostic criteria of PCOS (Azziz R et al., 2016).*

These three diagnostic criteria identified different phenotypes of women with PCOS. Although the NIH criteria identified the hyperandrogenic women who are at higher metabolic risk, the Rotterdam criteria also identified women with ovulatory dysfunction and PCOM (Cupisti S et al., 2011).

In December 2012, the NIH sponsored an expert panel that endorsed the acceptance of the Rotterdam criteria because they encompass a broad spectrum of phenotypes representing PCOS (Selma et al., 2016).

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Phenotype-1</th>
<th>Phenotype-2</th>
<th>Phenotype-3</th>
<th>Phenotype-4</th>
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<td></td>
<td>Frank PCOS</td>
<td>Classic PCOS</td>
<td>Ovulatory PCOS</td>
<td>Mild PCOS</td>
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<tr>
<td>Oligomenorrhea</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Clinical or biochemical HA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>PCOM</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prevalence</td>
<td>46–71%</td>
<td>7–40%</td>
<td>7–18%</td>
<td>7–16%</td>
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<tr>
<td>Long-term health risks</td>
<td>known</td>
<td>Known</td>
<td>unknown</td>
<td>Unknown</td>
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*Table (2): Phenotypes from NIH evidence-based methodology workshop on polycystic ovary (Lujan ME et al., 2010).*
(D)Etiology of PCOS:

I- Hereditary Factors of PCOS:

Polycystic ovary disease runs in families and a number of genetic abnormalities appear to result in features of the syndrome and account for the heterogeneity of the symptoms. (Dantas WS et al., 2015)

Familial clustering of PCOS suggests a genetic basis for this disorder. Several susceptibility genes have been implicated, particularly in the region of the insulin receptor gene, insulin gene, follistatin, fibrillin-3 and other members of the transforming growth factor beta signaling family. (Subbulaxmi T, 2015).

The field of the genetics of PCOS has relatively recently moved into the era of genome-wide association studies. This has led to the discovery of 16 robust loci for PCOS. Some loci contain genes with clear roles in reproductive (LHCGR, FSHR, and FSHB) and metabolic (INSR) dysfunction in the syndrome. (Jones and Goodarzi, 2016).

II. Endocrinological causes of PCOS:

1. Increased activity of the GnRH/LH pulse generator in PCOS:

Elevated LH levels or an elevated LH/FSH ratio is a common clinical feature in PCOS and a key indicator of neuroendocrine dysfunction. The mechanisms underlying the persistent increase in LH pulse frequency and amplitude in PCOS are not well understood. There are however, three current hypotheses. (Baskind NE et al., 2016) (Pankaj et al., 2015).

One hypothesis is that HI enhances GnRH neuron activity or pituitary responsiveness to GnRH.

A second hypothesis is that low levels of progesterone in the absence of ovulation and follicular remodeling result in the loss of progesterone negative feedback to GnRH secretion. Progesterone is
considered a critical regulator of GnRH pulse frequency. LH pulse frequency inversely correlates with progesterone levels during the menstrual cycle.

A third hypothesis suggesting that HA alters neuronal circuitry critical for relaying steroid hormone negative feedback to GnRH neurons.

2. Ovarian abnormalities:

The proposed mechanism is through abnormal activation of ovarian enzymes especially 17 α-hydroxylase which catalyses the conversion of progesterone into 17α-OH progesterone then to androstenedione. (Mark et al., 2015).

III. Metabolic factors:

1. Obesity:

Haq et al. (2007) performed a study included 508 women with polycystic ovary disease. They concluded that the highest rate of abnormal clinical and biochemical features of polycystic ovary disease were seen in obese women with body mass index BMI above 30 (68.5%). These obese women need more attention for their appropriate management.

Obesity may influence the risk of PCOS via IR and compensatory hyperinsulinemia that augments ovarian/adrenal androgen production and suppresses sex hormone binding globulin (SHBG), thereby increasing androgen bioavailability. (Anderson et al., 2014).

2. Hyperinsulinemia (HI):

IR is defined as a decreased ability of insulin to mediate its metabolic actions on glucose uptake, glucose production and lipolysis requiring increased amounts of insulin to achieve its proper metabolic action. In fact, increased circulating insulin levels characterize IR if pancreatic β-cells are functionally intact. (Livadas S et al., 2014)

IR may occurs secondary to resistance at the insulin receptor, decrease hepatic clearance of insulin and/or decrease pancreatic sensitivity. (Mani H et al., 2013)
Both obese and non-obese women with PCOS are more IR and HI than age and weight-matched women with normal ovaries. Thus, there appear to be factors in women with PCOS that promote IR and that are independent of obesity. (Durmus U et al., 2016)

Pancreatic beta cell dysfunction has been described in women with PCOS, whereby there is increased in basal secretion of insulin yet an independent postprandial response. This defect remains even after weight loss despite an improvement in glucose tolerance. (Stepto NK et al., 2013)

3. Abnormal Estrogen Clearance and Metabolism:

The clearance and metabolism of estrogen can be impaired by other pathologic conditions, such as thyroid or hepatic disease; it is for this reason that a careful history and physical examination are important elements in the differential diagnosis of anovulation. Both hyperthyroidism and hypothyroidism can cause persistent anovulation by altering not only metabolic clearance but also peripheral conversion rates among the various steroids. (Speroff Let al., 2011)

IV. Chronic inflammation:

The inflamed adipose tissue induces a systemic chronic inflammatory response. Several proinflammatory markers and mediators have been demonstrated to be elevated in women with PCOS (Christina and Emily 2015).

V. Psychological stress:

The participation of stress as an etiological factor for ovarian pathologies in patients with PCOS give strong support for participation of sympathetic nerves in the ovarian function both in normal and pathological status. Psychological stress may be associated with elevated levels of urinary 3-methoxy-4-hydroxyl-phenoglycerol (MHPG) excretion and platelet serotonin. As MHPG correlated with LH and DHEA-S, Greiner et al. (2005) hypothesised that psychological stress and neurotransmitter levels may be linked to some of the hormonal
derangement including inappropriate gonadotropin secretion and elevated adrenal androgen levels in women with PCOS.

**(E) Pathophysiology of PCOS:**

Phenotypic heterogeneity between cases has limited the ability to make definitive conclusions regarding its etiology and pathophysiology.

(Ramanand SJ et al., 2013)

The pathophysiology of PCOS is complex and reflects the interactions between genetic, metabolic and environmental factors. Among these factors, disordered gonadotropin secretion, HA, insulin resistance and hyperinsulinemia, ovarian dysfunction, and follicular arrest are prominent. (Conway GS et al., 2014)

One of the most consistent biochemical features of PCOS is the hypersecretion of androgens. The hyperandrogenism and anovulation that accompany PCOS may be caused by abnormality in four endocrinologically active compartments: (1) the ovaries, (2) the adrenal glands, (3) the peripheral fat, and (4) the hypothalamus–pituitary compartment. (Franks et al., 2008).

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**Figure (1):** Drawing illustrates the hypothalamic-pituitary-gonadal axis in PCOS (Lee and Rausch, 2012).
The insulin resistance results in a compensatory hyperinsulinemia, which augments LH-stimulated androgen production in an ovary genetically predisposed to PCOS. Insulin also inhibits hepatic synthesis of SHBG, increasing the amount of unbound (free) or bioactive testosterone in the circulation and increasing the effect of circulating androgens (Munzker J et al., 2012).

Figure (2): Drawing illustrates the role of insulin resistance in PCOS. Insulin increases the action of LH at the ovary, favoring the production of androgens. In addition, insulin-mediated inhibition of sex hormone–binding globulin (SHBG) synthesis in the liver increases the fraction of free androgens in the serum. Increased adiposity worsens insulin resistance and thus exacerbates the metabolic and endocrine derangements of PCOS (Lee and Rausch, 2012).

The pathogenesis of ovulatory dysfunction could be caused by the abnormal secretion of gonadotrophins, intraovarian androgen excess, direct effect of insulin, or a combination of these factors. (Panidis D et al., 2012)

Morphologically, the characteristic feature of polycystic ovaries is an apparent failure to select a dominant follicle and the accumulation of antral follicles 2–8 mm in size. It is assumed that this appearance reflects
an androgen-induced arrest in antral follicle development (Franks et al., 2008).

(F) Clinical-Endocrinal Features:

PCOS is typically first identified during the early reproductive years. The clinical scenario of PCOS is very heterogeneous and the symptoms are related to the ovarian dysfunction and HA (Goodman NF et al. 2015)

Clinical Expression Usually Includes Oligo or anovulation, Hyperandrogenism (either clinical or biochemical) and Presence of polycystic ovaries (Escobar-Morreale HF et al. 2012)

Hyperandrogenism

In adult women, clinical evidence of hyperandrogenism includes hirsutism, alopecia, and acne; these should be considered as indicating a condition of excess androgen production and the effect of androgens on the pilosebaceous unit. (Lee H et al. 2016)

Hirsutism

Hirsutism is the growth of excessive terminal hairs on the face or body in a male pattern distribution. (Casarini L et al., 2014)

It is the most obvious clinical indicator of androgen excess and is an important feature of PCOS. It is present in 70% of women with PCOS, and patients usually complain of cosmetically disturbing hirsutism. (Escobar-Morreale HF et al. 2012)

Typically, the onset of hirsutism in PCOS follows menarche, develops gradually, and intensifies with weight gain; substantial numbers of terminal hairs over the chin, neck, lower face, and sideburns (particularly if extending medially) indicate the presence of androgen excess. Excessive hair growth on the lower back, sternum, abdomen, shoulders, buttocks, perineal area, and inner thighs is considered abnormal. (Goodman NF et al 2015)
Ferriman Gallwey used a scoring system evaluating 11 body areas, including the upper lip, chin, chest, upper back, lower back, upper arm, forearm, upper and lower abdomen, thighs and lower legs. A score of 0 : 4 was assigned to each area examined, based on the visual density of terminal hairs, such that:

- A score of zero represented the absence of terminal hairs.
- A score of 1 few scattered hairs.
- A score of 2 scattered hairs with few concentrated areas.
- A score of 3 complete but light coverage.
- A score of 4 heavy complete coverage.

Terminal hairs can be distinguished clinically from vellus hairs primarily by their length (i.e. >0.5 cm), coarseness, and pigmentation. In contrast, vellus hairs generally measure <0.5 cm in length, are soft and non-pigmented. Then 2 areas excluded (lower legs and forearms) in the modification. (Pasquali R et al., 2012).

Figure (3): Modified Ferriman-Gallwey score (Speroff L et al., 2011).
Acne

The extent to which PCOS may increase risk for developing acne is therefore uncertain. When acne persists after adolescence or is exacerbated in the midtwenties or midthirties, hyperandrogenemia is common, and acne may be considered a clinical sign of hyperandrogenism. (Goodman NF et al., 2015)

Alopecia

Androgenic alopecia, describing scalp hair loss in women, also can result from hyperandrogenism and is a recognized but uncommon feature of PCOS. (Azziz R et al., 2006)

Ovulatory and Menstrual Dysfunction

Ovulatory dysfunction represents a major clinical concern for most patients. As many as 85% of women with PCOS have clinical evidence of menstrual irregularities. (Legro RS et al., 2013)

The most common abnormalities are oligomenorrhea and amenorrhea; clinicians diagnose oligomenorrhea when menstrual cycles last longer than 35 days or occur less than eight times a year (during adolescence the threshold is higher and a cycle length up to 40 days may be considered normal). (Goodman NF et al., 2015) Between one-quarter to one-third of all women with oligomenorrhea or menstrual dysfunction have PCOS. (Li R et al., 2013)

Measurement of serum progesterone during the midluteal phase (days 21–22) is the best way to assess ovulation. Whereas progesterone levels >2.5 ng/mL may indicate ovulation, values ≥7 ng/mL are generally needed for regular luteal function. (Goodman NF et al., 2015)

Women with PCOS may ovulate spontaneously; how frequently this occurs is unknown, but ovulations have been reported in up to 32% of “cycles”. (Speroff L et al., 2005)
Amenorrheic women with PCOS usually have the most severe hyperandrogenism and higher antral follicle counts when compared with women presenting with oligomenorrhea or regular menstrual cycles. (Hart R et al., 2015)

PCOS is characterized by an increased number of pre-antral and small antral follicles, those which primarily produce AMH. Thus, elevated serum AMH level, as a reflection of the stock of pre-antral and small antral follicles, is two- to fourfold higher in women with PCOS than in healthy women and is found in all PCOS populations. (Dewailly D et al. 2014)

AMH is an indicator of ovarian reserve and follicle growth. There is actually a very good correlation between serum AMH levels and ultrasonographic measure of the antral follicular count (AFC). This can be explained because circulating AMH is mostly produced by granulosa cells of follicles from 2 to 9 mm in diameter (60%), and those small follicles are precisely the ones counted on the ultrasound when the AFC is done. (Lee H et al. 2016)

Measurement of serum AMH is even more sensitive and specific than the AFC as it also reflects pre-antral and small antral follicles (<2 mm), which are hardly seen in ultrasound. Serum AMH is therefore a deeper “probe” for the growing follicular pool than the AFC. (Day FR et al. 2015)

Elevated AMH values (>4.5 ng/mL) may be useful as a substitute for ovarian morphology when no accurate ovarian ultrasound is available. Serum AMH level is also correlated to the severity of PCOS symptoms and is higher when hyperandrogenism or oligo-anovulation is present. (Dewailly D et al. 2014)

**Polycystic Ovarian morphology (PCOM)**

Approximately 75% of anovulatory women have multicystic or polycystic ovaries. Women with PCOS have an increased proportion of primordial follicles and the density of pre-antral and small antral follicles
in the polycystic ovary is six times that of the normal ovary. (Maciel GA et al., 2014)

Small follicles do not develop into ovulatory follicles (growth of these follicles is arrested before they mature and also have a reduced rate of apoptosis compared with those in a normal ovary; this gives rise to the typical morphology of a polycystic ovary. (Homburg R et al., 2014)

In 2003, Rotterdam PCOS criteria updated the definition of PCO as the presence of 12 or more follicles (AFC) in each ovary measuring 2–9 mm in diameter and/or an increased ovarian volume (10 mL) in at least one ovary. (Rotterdam ESHRE/ ASRM, 2004).

New AES guidelines, which are based upon a review of the data published using new ultrasound technology, have increased the threshold count of small ovarian follicles to 25. Ovarian size threshold has not been influenced by new technologies, and 10 mL remains the threshold between normal and increased ovary size. (Dewailly D et al. 2014)

Polycystic ovaries result from chronic anovulation that persists for a sufficient length of time. This morphology is commonly found in normal women. (Casarini L et al., 2014)

Polycystic ovaries are observed in 20–30% of the population and the prevalence in general population appears to decrease with age; it may be estimated that about 20% of women with polycystic ovaries have PCOS; even 14% of women using oral contraceptives also meet the ultrasonographic criteria for polycystic ovaries. Moreover, polycystic ovaries are commonly observed during normal pubertal development. (Li R et al., 2013)

**Other Features of the Polycystic Ovary Syndrome**

PCOS has other common features besides hyperandrogenism and ovulatory dysfunction that are not included in any diagnostic criteria, including abnormal patterns of gonadotropin secretion, insulin resistance,
and related metabolic abnormalities, such as dyslipidemia. (Escobar-Morreale HF et al., 2012)

Abnormal Gonadotropin Secretion

Devoted to the pathophysiology of the disorder, increased serum LH concentrations, low normal FSH levels, and increased LH/FSH ratios are typical. (Franks et al., 2008).

The resulting low estrogen and progesterone levels do not produce a negative feedback on LH secretion and this is the major cause for the high serum LH concentrations in women with PCOS. (Speroff L et al., 2011).

Gonadotropin levels or ratios are not a reliable diagnostic criterion; they neither make nor exclude the diagnosis. (Escobar-Morreale HF et al. 2012)

Biochemical Hyperandrogenism

Circulating androgen levels can also help to identify those hirsute women with PCOS. Hyperandrogenemia should be evaluated biochemically in all women suspected of having PCOS. (Slominski et al., 2013)

Ideally, assessments of free testosterone (T) levels are more sensitive than the measurement of total T for establishing the existence of androgen excess. Testosterone levels are elevated in most, but not all, women with PCOS. (Pasquali R et al., 2016)

Insulin Resistance

PCOS is associated with increased risk of impaired glucose tolerance (IGT), gestational diabetes mellitus (GDM), and type 2 diabetes (T2D). (Siklar et al., 2015)
Insulin resistance and compensatory hyperinsulinemia are common but not universal features of women with PCOS. The overall prevalence of insulin resistance among women with PCOS is between 50% and 75%, and greater in obese than in lean women with PCOS. (Lee and Rausch, 2012).

In 1980, the association between HI and PCOS was first noted by Burghen et al. (1980) who found a significant positive correlation between insulin, androstenedione and testosterone levels among PCOS women (Samer et al., 2016).

IR is considered the main pathogenic factor in the background of increased metabolic disturbances in women with PCOS which can explain HA, menstrual irregularity and other metabolic manifestations seen in this disease. But it is not diagnostic criterion for PCOS (Miro et al., 2014).

Figure (4): Overview of peripheral IR in PCOS (Speroff L et al., 2011)
Although obesity is a major factor for the development of IR in PCOS, it is now well known that a component of IR is independent of body weight. *(Lim SS et al., 2013)*.

Insulin resistance was diagnosed according to the FG to FI ratio. If a participant's FG /FI will be 4.5 or less, she will be classified as being IR; and if her FG/FI will be greater than 4.5, she will be classified as being non-IR. *(Hudecova M et al., 2011)*.

**Dyslipidemia**

Dyslipidemia is perhaps the most common metabolic abnormality observed in women with PCOS, nearly 70% have at least one borderline or elevated lipid level. *(Moran LJ et al., 2016)*

Insulin resistance and hyperinsulinemia are associated with decreased high-density lipoprotein (HDL) cholesterol and elevated triglyceride levels, and numerous studies have observed such abnormalities in women with PCOS. *(Ollila MM et al., 2016)*

Triglyceride, low-density lipoprotein (LDL), and non-high-density lipoprotein (HDL) cholesterol changes are higher compared with non-PCOS women. *(Livadas S et al., 2014)*

Assessing waist circumference and non-HDL cholesterol appear to be the most useful clinical indicators of this metabolic disturbance. *(ASRM, 2015)*

**Obesity**

Obesity is a common feature of PCOS; many women with PCOS are overweight or obese. *(Naderpoor N et al., 2015)*

There is widespread variability in the prevalence of overweight (BMI 25–30 kg/m2) and obese (BMI ≥ 30 kg/m2) women in PCOS
populations across different countries; the prevalence of obesity is approximately 50% overall. (Legro RS et al., 2016)

Obesity is associated with PCOS, but its causal role has yet to be determined; explanations include reverse causality (i.e., PCOS increases susceptibility to weight gain) and synergistic but independent roles for obesity and PCOS in infertility. (Dokras A et al., 2016)

Hyperinsulinemia itself contributes to obesity by the anabolic effect on fat metabolism through the adipogenesis process: the result is an increased uptake of glucose into adipocytes, the production of TG and the inhibition of hormone-sensitive lipase (Arner, 2005)

Greater abdominal or visceral adiposity is associated with greater IR, which could exacerbate the reproductive and metabolic abnormalities in PCOS. (Morgante G et al., 2015)

Visceral fat or abdominal fat is metabolically distinct from subcutaneous fat; it is resistant to the anti-lipolytic effects of insulin and releases excessive amounts of FFAs which leads to IR in the liver and muscle. In response to it, in the liver, there is an increased gluconeogenesis and in the muscle there is an inhibition of insulin-mediated glucose uptake. (Ezeh U et al., 2016).

Metabolic Abnormalities

The increased metabolic risk might be related to obesity as well as to genetic and environmental factors. (Lizneva D et al., 2016)

Metabolic disorders are often associated to PCOS (up to 50%), including an increased rate of insulin resistance, regardless of obesity. (Zhao X et al. 2010)

The Metabolic syndrome is accepted as a cardiovascular risk factor and requires three of the following five clinical characteristics: elevated waist circumference (population specific, >88 cm), systolic and/or diastolic blood pressure (≥130 mm Hg systolic; ≥85 mm Hg diastolic), fasting blood glucose (≥100 mg/ dL) or previously established diabetes
mellitus, fasting serum triglycerides (≥150 mg/dL), and decreased serum high-density lipoprotein cholesterol levels (<50 mg/dL). (Casarini L et al., 2014)

Many women with PCOS have some degree of dyslipidemia. Many also have central obesity, and some even meet criteria for the diagnosis of the metabolic syndrome. Metabolic dysfunction in women with PCOS leads to exaggerated risk for CVD with aging. (Speroff L et al., 2008)

Effect on Mental Health

The prevalence of behavioral disorders, depression, and anxiety is higher in women with PCOS than in the general population. Such mood disorders, capable of impairing quality of life, can be prominent in adolescents faced with issues of self-presentation, in young adult women concerned with fertility, and in women of all ages with respect to eating, overweight, and clinical manifestations of androgen excess. (Conte F et al., 2015)

Cancer Risks

Women with PCOS have multiple risk factors for endometrial cancer that include obesity, metabolic abnormalities (such as diabetes, hyperinsulinemia, hypertension, and obesity), and history of oligomenorrhea with prolonged exposure to unopposed estrogen (chronic anovulation). Studies have noted a 2.7-fold increased risk for developing endometrial cancer versus the general population. (Yildiz BO et al., 2012)

Presumably, the mechanism relates to constant, unrelenting estrogen stimulation of the endometrium, predisposing to abnormal patterns of growth. Endometrial hyperplasia and even endometrial cancer can be encountered in young anovulatory women. (Legro RS et al., 2013)

Consequently, for those with long-standing anovulation, endometrial sampling to exclude endometrial hyperplasia is a prudent precaution. The decision on whether to perform an endometrial biopsy should not be
based on the patient’s age but on the duration of potential exposure to unopposed estrogen stimulation. (Casarini L et al., 2014)

**Effect on Fertility**

PCOS is the commonest cause of anovulatory infertility and eugonadotropic hypogonadism, and it is often diagnosed for the first time in the fertility clinic. (Morley LC et al., 2017)

Seventy-five percent of these women suffer infertility due to anovulation. This may be explained by the effects of obesity, metabolic, inflammatory, and endocrine abnormalities on ovulatory function, oocyte quality, and endometrial receptivity. (Balen AH et al., 2016)

Ovarian hyperandrogenism and hyperinsulinemia may promote premature granulosa cell luteinization, and paracrine dysregulation of growth factors may disrupt the intrafollicular environment and impair cytoplasmic and/or nuclear maturation of oocytes. (Weghofer A et al., 2007)

These features are not universal, and oocyte quality, fertilization, and implantation rates in an individual woman with PCOS can be normal. (Tso LO et al., 2015)

**(G) Management of PCOS:**

Since PCOD accounts for approximately 25-30% of infertility in women, the treatment of this condition is of both medical and social importance. (Speroff L et al., 2011)

**The overall goals of treatment are:**

- To reduce the production and circulating levels of androgens.
- To protect the endometrium against the effects of unopposed estrogen.
- To support the lifestyle changes to achieve normal body weight.
- To lower the risk for cardiovascular disease.
Review of literature

- To avoid the effects of hyperinsulinemia on increasing the risks of cardiovascular disease and diabetes mellitus.
- Induction of ovulation to achieve pregnancy. (Speroff et al., 2011).

I- General measures:

**Life-style modification:**

Life-style modification is very important in the treatment for PCOS, as weight loss and exercise show a striking improvement in ovulatory function and features of hyperandrogenism. Specifically, dietary modification, moderate exercise and cessation of smoking are lifestyle modification recommended in women with PCOS. (Casarini L, 2014)

**Weight reduction:**

Several studies have shown that weight loss in women with PCOS improves the endocrine profile, the menstrual cycle, the rate of ovulation, and the likelihood of a healthy pregnancy (Legro RS et al., 2016).

Even a modest loss of 5% of total body weight can achieve a reduction of central fat, an improvement in insulin sensitivity, and restoration of ovulation. Lifestyle modification is clearly a key component for the improvement of reproductive function in overweight women with anovulation and PCOS. (Graff SK et al., 2016)

II- Medical treatment:

**Treatment of infertility in patients with PCOS:**

(a) **Pre-treatment considerations:**

A semen analysis should be performed before ovulation induction therapy is recommended; tubal patency should also be assessed in either hydrosalpingography or laparoscopy before embarking on any form of ovulation induction therapy. (Legro RS et al., 2016)

(b) **Ovulation induction:**

Women with the polycystic ovary syndrome (PCOS) have normo-gonadotrophic and normo-estrogenic anovulation constitute the largest
group of anovulatory women encountered in clinical practice. (Teede HJ et al., 2011)

Current clinical protocols involve an orderly Step-by-Step (Stepwise) approach to ovulation induction in women with PCOS that includes:

**Step I:** Weight reduction if body mass index (BMI) is >27 kg/m.

**Step II:** Antiestrogen.

**Step III:** Insulin sensitizers as a single agent.

**Step IV:** Insulin sensitizers in combination with clomiphene.

**Step V:** Gonadotropin therapy.

**Step VI:** Insulin sensitizers in combination with gonadotropins.

**Step VII:** Laparoscopic ovarian drilling.

**Step VIII:** In vitro fertilization (IVF). (Speroff et al., 2011).

➢ **1-Antioestrogens:**

[a] **Clomiphene citrate (CC):**

The first choice drug in women with newly diagnosed polycystic ovary syndrome is the antioestrogen clomifene citrate. Clomifene citrate enhances release of pituitary gonadotrophins, resulting in follicular recruitment. Three quarters of women with polycystic ovary syndrome will ovulate with clomifene citrate (Balen AH et al., 2016).

Complications of treatment are rare and usually mild. Patients who do not ovulate on the maximum dose of 150 mg are considered to be clomifene citrate resistant. (Legro RS et al., 2016).

Clomiphene citrate can cause inadequate endometrial thickness in 15-50% of patients and have negative effects on the quality or quantity of the cervical and endometrial mucosa. These complications may be attributed to the anti-estrogenic effect and the relatively longer half-life of clomiphene citrate, thus decreasing endometrial thickness by its long-
term effect in decreasing the number of estrogen receptors (Kalem MN et al., 2016).

Clomiphene citrate is the traditional first line treatment for chronic anovulation that characterizes polycystic ovary syndrome. However, 20% -25% of polycystic ovary syndrome women fail to ovulate with incremental doses of clomiphene citrate. In addition, clinical data revealed a discrepancy between ovulation rates (75% - 80%) and conception rates (30% - 40%) during clomiphene citrate treatment. For these patients a few limited therapies can be tried before moving on to gonadotropin therapy or laparoscopic ovarian drilling. (RCOG, 2014).

[b] Aromatase Inhibitors:

Aromatase inhibitors have been proposed as an alternative treatment to CC therapy, as the discrepancy between ovulation and pregnancy rates with CC has been attributed to its antiestrogenic action and estrogen receptor depletion. (Speroff L et al., 2011)

The aromatase inhibitors suppress estrogen production and thereby mimic the central reduction of negative feedback through which CC works. (Conway G et al., 2014)

Letrozole, the most widely used antiaromatase for this indication, has been shown to be effective in inducing ovulation and pregnancy in women with anovulatory PCOS and inadequate CC response and improving ovarian response to FSH in poor responders. (Goodman NF et al., 2015)

Anastrozole is currently being examined as a possible alternative (Balen AH et al., 2016).

➢ 2- Insulin-sensitizing agents:

Insulin-sensitizing agents have been recently proposed as the therapy of choice for polycystic ovary syndrome (PCOS). Since insulin resistance and associated hyperinsulinemia are recognized as important pathogenetic factors of the syndrome. Moreover, since almost all obese
PCOS women and more than half of those of normal weight are insulin resistant, be suggested in most patients with PCOS. (Naderpoor Net al., 2016).

Insulin sensitizer treatment has been associated with a reduction in serum androgen levels and gonadotropins, and with an improvement in serum lipids and in prothrombotic factor plasminogen-activator inhibitor type I, whatever the insulin sensitizer used. This therapy has also been associated with a decrease in hirsutism and acne, and with a regulation of menses and an improvement of ovulation and fertility. Notable improvements in all these parameters have also been described after a change in lifestyle approach, particularly in the presence of obesity. Lifestyle interventions should therefore be combined with insulin sensitizers in PCOS when obesity is present. (Morley LC et al., 2017)

**Insulin Sensitizers include:**

1-**Metformin:** (will be discussed)

2-**Thiazolidinediones (TZDs) (pioglitazone and rosiglitazone):**

   Another class of insulin-sensitizers that is less well-studied. Improved hyperinsulinemia-mediated ovarian androgen production, decreased plasma and free testosterone levels, and increased sex hormone binding globulin (SHBG) levels (Tang T et al., 2012).

   pioglitazone is as effective as metformin in improving insulin resistance and hyperandrogenism in women with PCOS, however, pioglitazone cause increases in body weight, BMI, and waist to hip ratio (Morley LC et al., 2017).

3-**Gonadotrophins:**

Ovulation induction using gonadotrophins is mainly indicated in cases of clomifene resistance and in those who fail to conceive or have intolerable side effects with clomifene. (Balen AH et al., 2016)
Gonadotropin therapy is associated with an increased risk of multiple follicular development and multiple pregnancies. Furthermore, PCOS patients are particularly prone to ovarian hyperstimulation syndrome (OHSS). The risk of severe OHSS is about 5–8 per cent and is a life-threatening condition, unless appropriate measures such as fluid control and anti-coagulant measures are taken. (Kalem MN et al., 2016)

The tendency of PCOS patients to over-respond to gonadotropin treatment is mainly due to the larger size of the FSH sensitive cohort of small antral follicles so careful monitoring of treatment and dosage manipulation is therefore necessary. (RCOG, 2014)

III- Surgical treatment:

It has been known since 1939 that surgical resection of the ovarian tissue in PCOS women increases the percentage of ovulatory cycles, often restores regular menstruations and increases the pregnancy rate (Legro RS et al., 2013).

Nowadays classical wedge ovarian resection has been virtually abandoned because its performing requires laparotomy, the procedure is associated with a certain risk and may lead to the development of periadnexal adhesions (Goodman NF et al., 2015).

Laparoscopic ovarian drilling (LOD) is mainly indicated in clomifene-resistant patients where it has been shown to have a similar efficacy to gonadotropins with the advantage of a lower multiple pregnancy rate. (Flyckt RL et al., 2014)

LOD can result in ovulation in approximately 80 percent and a clinical pregnancy in 60 per cent of cases. Apart from inducing ovulation, LOD can also lead to correction of the biochemical abnormalities in PCOS, such as high LH and androgen concentrations. (Mitra S et al., 2015)

The exact mechanism by which LOD may stimulate ovulation is not entirely known, but it is possible that the thermal damage associated with
the procedure may lead to release of inflammatory intra-ovarian cytokines, with a paracrine effect on androgen production and eventual normalization of pituitary LH secretion. (Moazami Goudarzi Z et al., 2014)

Patients with high LH are more likely to respond to LOD, while those with marked obesity, marked hyperandrogenism and/or long duration of infertility are more likely to be resistant. (Badawy A et al., 2011)

Figure (5): Shows appearance of an ovary with laparoscopic ovarian drilling (Badawy A et al., 2011)

VI-In-vitro fertilization /embryo transfer (IVF/ET):

If all the above measures fail for the infertile PCOS patient, the in-vitro fertilization is a last resort providing excellent results. (Balen AH et al., 2016)