Middle East Fertility Society Journal (2011) **16**, 19–37

Middle East Fertility Society

Middle East Fertility Society Journal

www.mefsjournal.com
www.sciencedirect.com

OPINION ARTICLE

Polycystic ovary syndrome and impact on health

Gautam N. Allahbadia [a,*], **Rubina Merchant** [b]

[a] *Medical Director, Deccan Fertility Clinic, Rotunda – Center for Human Reproduction, Mumbai, India*
[b] *Embryologist, Rotunda – Center for Human Reproduction, Mumbai, India*

Received 21 July 2010; accepted 5 October 2010
Available online 11 November 2010

KEYWORDS

Polycystic ovary syndrome;
Endocrine dysfunction;
Reproductive dysfunction;
Biochemical dysfunction;
Metabolic dysfunction;
Obesity;
Adolescence;
Etiology;
Pathophysiology;
Metabolic syndrome;
Inheritance;
Treatment;
Origin

Abstract Polycystic ovary syndrome (PCOS) is a multifactorial, heterogeneous, complex genetic, endocrine and metabolic disorder, diagnostically characterized by chronic anovulation, polycystic ovaries and biochemical and clinical manifestations of hyperandrogenism. It has a tremendous negative impact on the physiology and metabolism of the body as it may evolve into a metabolic syndrome with insulin resistance, hyperinsulinemia, abdominal obesity, hypertension and dyslipidemia presenting as frequent metabolic traits and culminating in serious long-term consequences, such as type 2 diabetes mellitus, endometrial hyperplasia and cardiovascular disease. The key endocrine abnormalities include dysregulation of the gonadotropin-releasing hormone (GnRH) pulse generator to feedback inhibition by ovarian steroids, resulting in luteinizing hormone (LH) hypersecretion, and decreased follicle-stimulating hormone (FSH), and ovarian stromal–thecal hyperactivity, resulting in ovarian hyperandrogenism, all of which may lead to significant biochemical, reproductive and metabolic dysfunction.

Though it is detected in approximately 5–10% of women of reproductive age, recent evidence from experimental observations in animals, buttressed by human studies, suggest a deep-rooted developmental origin of PCOS, the pathophysiology of which progresses from infancy to adulthood. In utero fetal programming or dysregulation of the hypothalamic–pituitary–gonadotropic axis at crucial developmental stages, mediated by the interaction of genetically determined hyperandrogenism and environmental factors (obesity), may have a significant role in the development

* Corresponding author. Address: Medical Director, Rotunda – Center for Human Reproduction, 201, 2nd floor, B Wing, 36 Turner Road, Bandra (W), Mumbai 400 050, India. Tel:. +91 22 26552000/26405000; fax: +91 22 26553000.
E-mail address: drallah@gmail.com (G.N. Allahbadia).

Peer review under responsibility of Middle East Fertility Society.
doi:10.1016/j.mefs.2010.10.002

ELSEVIER **Production and hosting by Elsevier**

of the final expression of the PCOS phenotype and its long-term consequences, the symptoms of which may vary throughout lifespan, largely influenced by obesity, metabolic alterations and ethnicity. Several candidate genes involved in steroid hormone biosynthesis and metabolism, action of gonadotropins and gonadal hormones, obesity and energy regulation and insulin secretion and action, in addition to many others, have been implicated in the pathogenesis of the syndrome, suggesting a genetic basis for PCOS.

Though several pharmacological therapies are available to alleviate the symptoms of PCOS and components of the associated metabolic syndrome, lifestyle modifications, including diet and exercise, have been proved most effective and should be employed as a first line intervention, and particularly so, since obesity has a central role in the pathogenesis of the disease. Active interventions to diagnose and treat the disorder from childhood before it is manifested in adolescence and imprinted in adulthood, should be the goal in combating PCOS and its related disorders.

1. Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous, multifactorial, complex genetic and endocrine disorder, characterized by menstrual disturbances, clinical and biochemical manifestations of hyperandrogenism (1) and polycystic ovaries. The detrimental and widespread effects of PCOS on the physiology and metabolism of the body have led to its recognition as a metabolic syndrome with detectable abnormalities, such as insulin resistance, hyperinsulinemia, obesity, dyslipidemia [decreased high-density lipoprotein (HDL) cholesterol and hypertriglyceridemia] and hypertension that culminate in serious long-term consequences, such as increased risk of development of type 2 diabetes mellitus (2), endometrial hyperplasia and coronary artery disease (3). PCOS affects 5–10% of women of reproductive age (4), menstrual disorders and biochemical and clinical hyperandrogenism being reported in 60.6% of PCOS women (5). Familial aggregation of this syndrome is well established and there are ethnic and racial variations in the prevalence of the syndrome and its symptoms (6).

Initially recognized as an endocrine disorder of premenopausal women (2), the definition of PCOS has now been expanded from a disorder that presents at menarche and ends at menopause to a disorder that may be present from birth to senescence (7).

The Rotterdam ESHRE/ASRM criteria for confirming the diagnosis of PCOS following certain exclusion criteria are presented in Table 1. However, though the ultrasound morphological characteristics, detailed in Table 1, may be a typical appearance of PCOS ovaries, this finding is not specific, since it may occur in $>20\%$ of healthy girls (4).

The spectrum of clinical signs and symptoms differs widely among women with PCOS and can also vary over time within the same individual woman in the presence of particular precipitating factors, the most significant of which is an alteration in body weight (8). There is evidence that a history of weight gain frequently precedes the onset of clinical manifestations of PCOS and obese PCOS women have more severe hyperandrogenism and a significantly higher incidence of anovulatory cycles, oligomenorrhea and/or hirsutism compared to normal-weight women (9).

Clinical observations support a potential fetal origin of PCOS. In utero programming of the female fetus may affect differentiating target tissues, resulting in combined reproductive and metabolic abnormalities and producing a comprehensive adult PCOS-like phenotype (10). Although a woman may be genetically or environmentally predisposed to PCOS, it is the development of insulin resistance due to the deposition of adipose tissue that leads to the expression of the PCOS phenotype. The natural history of PCOS can be further modified in postnatal life by factors affecting insulin secretion and/or action, most importantly, nutrition (2). The largely overlapping causes of PCOS, evidence of the involvement of multiple genes affecting endocrine and metabolic pathways and the heterogeneous nature of the syndrome make it difficult to establish a single cause for PCOS. The following sections will discuss the various disorders of PCOS and their possible etiologies.

2. Clinical discussion

2.1. Impact of PCOS

The impact of PCOS on growth is reflected by its 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. Though the multi-system dysfunctions in PCOS are strongly interlinked by the pathogenesis of these individual disorders, they may be broadly classified into: endocrine dysfunction, reproductive dysfunction, metabolic dysfunction and biochemical dysfunction.

2.1.1. Endocrine dysfunction

Although the pathogenesis of PCOS is still controversial, an array of neuroendocrine abnormalities have been implicated as a major component of the syndrome. Recent data suggest that PCOS is marked by anomalies of both feed forward and feedback signaling between GnRH/LH and ovarian androgens (11). The key endocrine abnormalities of the reproductive axis include accelerated GnRH pulsatile activity, hypersecretion of LH, theca-stromal cell hyperactivity and hypofunction of the FSH-granulosa cell axis (12). The causes and effects of endocrine dysfunction in PCOS are illustrated in Fig. 1.

2.1.1.1. LH Hypersecretion. In normal ovulatory women, an increase in GnRH pulse frequency during the follicular phase

Table 1 The Rotterdam ESHRE/ASRM criteria for the diagnosis of polycystic ovary syndrome (ESHRE/ASRM, 2004).

1. Oligo-anovulation
2. Clinical/or biochemical evidence of hyperandrogenism
3. Polycystic ovaries on ultrasound examination. *Ultrasound morphological criteria* fulfilling sufficient specificity and sensitivity: 12 or more follicles in each ovary, each measuring 2–9 mm in diameter, and /or increased ovarian volume (> 10 mL). *Histopathological criteria:* observation of an increased numbers of follicles, hypertrophy and luteinization of the inner theca cell layer, and a thickened ovarian tunica

Exclusion criteria to confirm the diagnosis

For elevated androgens
- Late onset congenital adrenal hyperplasia (CAH)
- Androgen-secreting tumours
- Cushing's syndrome

For oligo/anovulation
- Thyroid disorder
- Elevated prolactin

favors LH synthesis, while a decrease in GnRH pulse frequency in the luteal phase as a result of the progesterone effect favors FSH synthesis (13). In PCOS, decreased sensitivity of the GnRH pulse generator to feedback inhibition by ovarian steroids and a steroid-permissive milieu result in a persistently rapid GnRH pulse frequency and perturbations in gonadotropin secretion, such as *LH hypersecretion*, a hallmark of the disorder (14) and a cause of hyperandrogenism (13). This may also help to explain the genesis of PCOS during puberty (14). Patients with PCOS exhibit an accelerated frequency and/or higher amplitude of LH pulses, augmentation of LH secretory burst mass, a more disorderly LH release, elevated in vitro LH bioactivity and a preponderance of basic LH isoforms (11). Mean serum concentrations of immunoreactive and bioactive LH in adolescents with PCOS have been reported as three ($P < 0.001$) and two times higher ($P = 0.002$), respectively, than their corresponding values in controls (15).

Additional possible causes of LH hypersecretion (Fig. 1):

(i) aromatization of androgens to estrogens, resulting in permanent estrogen overproduction, which favors LH hypersecretion, stimulates ovarian stromal hyperplasia (16) and leptin production,
(ii) diminished central opioid and dopaminergic tone (17),
(iii) direct leptin-induced GnRH modulation (18), or
(iv) an insulin-mediated increase in serum LH pulse amplitude.

High endogenous LH levels may have detrimental effects on oocyte maturity, fertilization, pregnancy and miscarriage rates (19).

2.1.1.1.1. LH hypersecretion in adolescence. Insensitivity of the GnRH pulse generator to sex steroid suppression during pubertal maturation could be a potential mechanism for the perimenarchal abnormalities seen in hyperandrogenic adolescent girls who appear to exhibit early manifestations of PCOS. (20). Elevated serum LH levels in women with hyperandrogenemia due to 21-hydroxylase deficiency, a classical cause of adrenal hyperandrogenism, further provides indirect evidence for such in utero programming of the hypothalamic–pituitary (HP) axis in humans (21).

2.1.1.2. Decreased FSH. An increase in GnRH pulse frequency results in decreased FSH production, the effects of which have been indicated in Fig. 1.

2.1.1.3. Hyperandrogenism. Hyperandrogenism, the primary clinical manifestation of dysregulation of steroid production in PCOS (22), is one of the most consistently expressed PCOS traits and a result of LH hypersecretion (13). LH hypersecretion has been positively correlated with elevated serum 17-hydroxyprogesterone, androstenedione and testosterone concentrations, which also characterize adolescents with PCOS. Concomitant uncoupling of the pair wise synchrony of LH and testosterone, LH and androstenedione, and testosterone and androstenedione secretion in bihormonal analyses, point to a deterioration of both orderly uniglandular and coordinate bihormonal output in PCOS (11). A several hundred fold increase in the activities of steroidogenic enzymes P450c17 and 3β-hydroxysteroid dehydrogenase, and a disproportionate increase C17, 20 lyase activity, have been observed in long-term cultures of theca cells (23). Measurement of free testosterone or the free androgen index is a sensitive method of assessing hyperandrogenemia (19).

2.1.1.3.1. Possible causes of hyperandrogenism (Fig. 1).

(i) GnRH-mediated LH hypersecretion.
(ii) Increased synthesis of testosterone precursors due to a dysregulation of theca cell androgen production intrinsic to the ovary, owing to an intrinsic abnormality of P450c17α or an abnormality of autocrine/paracrine factors, which regulate P450c17α- the rate-limiting enzyme in androgen biosynthesis. This may be the primary factor driving the enhanced testosterone secretion in PCOS.
(iii) Inhibin augmentation of LH-mediated androstenedione production as observed in cultured human theca cells.
(iv) Hyperinsulinemia, which has been proposed as the primary event leading to hyperandrogenism. Mechanisms by which it may contribute to increased androgen production include:

- directly by acting as a co-gonadotropin augmenting LH activity within the ovary,
- indirectly by enhancing serum LH pulse amplitude,
- stimulation of cytochrome P450c17α activity in the ovaries or adrenals of women with PCOS, thus impacting steroidogenesis. Dysregulation of adrenal P450c17α and functional adrenal hyperandrogenism has been observed in about two-thirds of hyperandrogenic women,

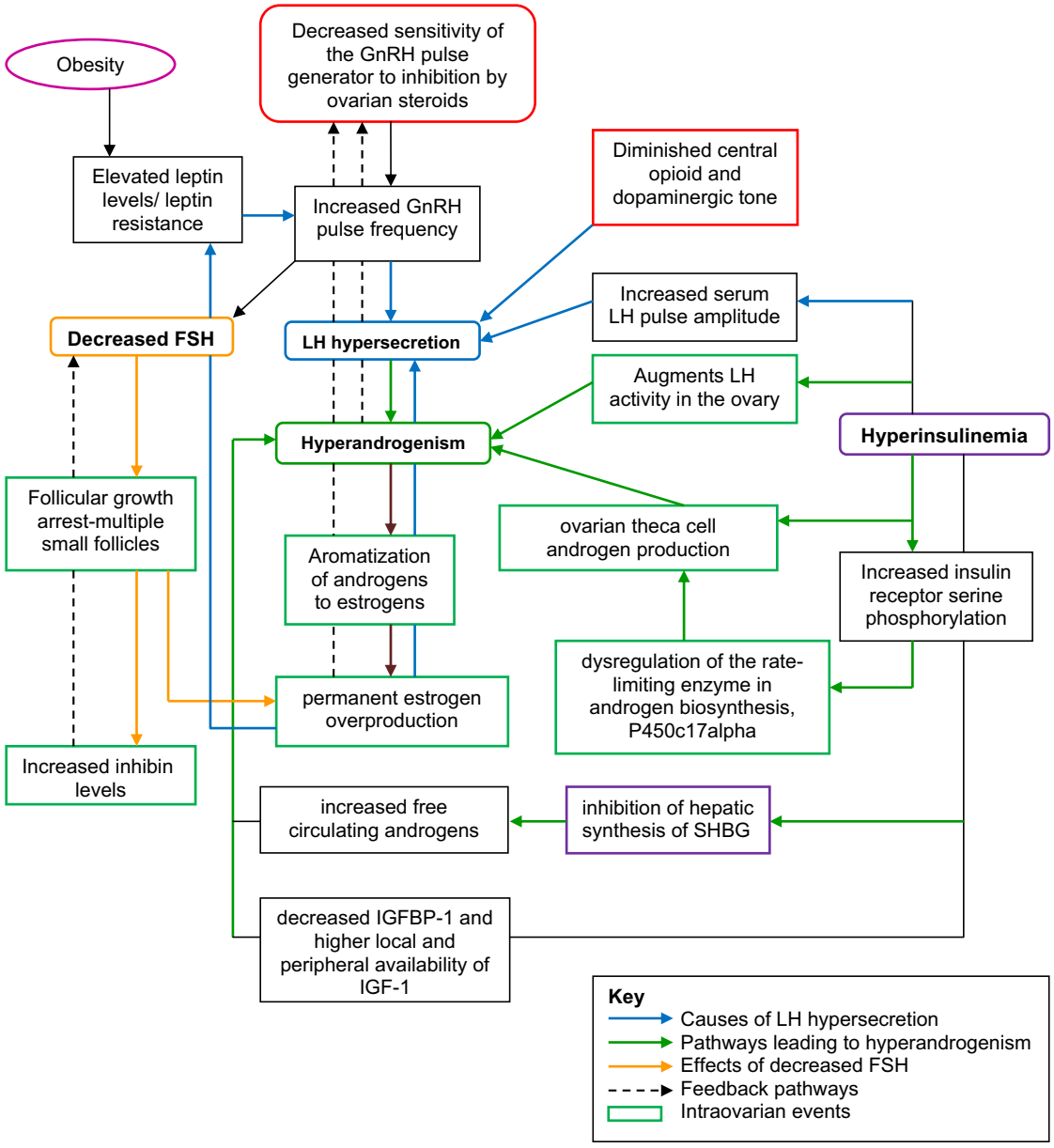

Figure 1 Endocrine dysfunction in PCOS.

- insulin cross-reactivity, owing to a similarity between the insulin growth factor (IGF-1) and insulin receptor or modulation of ovarian steroidogenesis via its own receptors on granulosa and theca cells.

(v) Increased serine phosphorylation of the insulin receptor, resulting in activation of both ovarian and adrenal P450c17α enzymes and promoting androgen synthesis. It is, therefore, possible that a single post-receptor defect, namely serine phosphorylation, could be responsible for both the insulin resistance and androgen excess in PCOS.

(vi) Genomic variants in genes related to the regulation of androgen biosynthesis, function, the availability of androgens to target tissues, insulin resistance, the metabolic syndrome and proinflammatory genotypes may be involved in the genetic predisposition to functional hyperandrogenism and PCOS (Table 2).

The occurrence of hyperestrogenism together with hyperandrogenism in PCOS suggests that abnormalities in local regulatory factors of steroidogenesis affect granulosa as well as theca cells (22). Hence, the hyperandrogenic state associated with PCOS is predominantly of ovarian origin, and the primary cause of androgen excess lies within the ovarian theca-interstitial cells. However, the positive role of LH hypersecretion and hyperinsulinemia in augmenting androgen production cannot be ignored and all these mechanisms may work together to influence the resultant hyperandrogenism.

2.1.1.3.2. Physical manifestations of hyperandrogenism. The overall impact of hyperandrogenism is manifested as hirsutism and acne in the genetically predisposed. *Hirsutism* can be defined as excessive growth of facial and/or body (neck and lower abdomen) terminal hair in a male distribution pattern and is prevalent in 70% of the women with a diagnosis of PCOS. Insulin resistance with compensatory hyperinsulinemia, as a

result of excessive weight gain, may result in the suppression of sex hormone binding globulin (SHBG), elevation of free biologically active testosterone and the final manifestation of hirsutism. While the degree of hirsutism may be influenced by the relative activity of the 5α reductase enzyme that converts testosterone to the more active metabolite dihydrotestosterone (DHT), ethnic and genetic differences in the activity of the 5α reductase enzyme may modify the evaluation of the degree and impact of hirsutism. Insulin and insulin-like growth factors stimulate 5α reductase activity (24).

Hirsutism may be accompanied paradoxically with *androgenic alopecia,* a progressive pattern of hair loss of scalp terminal hair (male pattern baldness) due to the opposite effect on the scalp follicles.

Acne vulgaris, is a chronic inflammation of the sebaceous glands of the pilosebaceous unit (PSU), occurring in early adolescence, the severity of which may be linked largely to the degree of hyperactivity of the sebaceous glands in the PSU. The pathogenesis of Acne vulgaris begins with overstimulation of the androgen receptors in the PSU, resulting in excess sebum production, follicular keratinization and, cornification associated with impaired drainage and hence, comedone formation. The main etiological factor in this sequence of events is excess androgen [testosterone, androstenedione, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS)] of ovarian and/or adrenal origin. Though present initially on the face, because of increased 5α reductase type 1 activity compared to other skin areas, 50% of the women

Table 2 Genetic Etiology of PCOS.

Gene mutation	Mutation effect	Phenotypic expression
(i) Gene polymorphisms in insulin receptor substrate genes (IRS1 and IRS2) (ii) Mutations in the minisatellite in the regulatory region of the insulin gene (INS-VNTR)	Impaired insulin metabolism	Insulin resistance
Activating mutation of the kinase responsible for the insulin receptor (IR) serine/threonine phosphorylation	Impaired signal transduction and post-binding defect in insulin action	
Causes of increased androgen biosynthesis Activating mutation of the kinase responsible for the insulin receptor (IR) serine/threonine phosphorylation	Preferential hyperphosphorylation of the enzyme P450c17 Impaired post-translational regulation of 17,20-lyase activity (CYP17)	Hyperandrogenism
Pentanucleotide repeat polymorphisms (TTTTA)n in the regulatory region of CYP11a (encoding cytochrome P450scc enzyme)	Cytochrome P450scc enzyme upregulation	
Multiple sequence variants at five susceptibility loci, especially steroidogenic enzyme genes (CYP21 heterozygosity, HSD3B2, IRS-1, GRL and ADRB3 variants) and elevated expression of the CYP11A 3BHSD2, and 17,20-lyase (CYP17) genes	Increased gene transcription	
Increased transcription of steroidogenic enzyme genes, aldehyde dehydrogenase 6 and retinol dehydrogenase 2, coding for CYP17 and CYP11A promoter regulator activity	Increased expression of 17α-hydroxylase	
Mutations in the centromeric region of insulin receptor gene (19p13.3)	Abnormal signal transduction mechanisms leading to altered expression of theca cell steroidogenesis genes	
Causes of increased androgen action 5α reductase gene (SRD5A1-2) mutations	Elevated 5α reductase activity	
21-Hydroxylase (CYP21) gene mutation	21-Hydroxylase (CYP21) deficiency	
UGT2B15 gene mutation	Disruption in androgen inactivation glucuronidation enzyme (UGT2B) mechanism	
Causes of increased androgen receptor activity Androgen receptor gene polymorphisms		
Genetic variations in the gene receptor for AMH/BMP signaling alterations in the expression of estrogen receptors in the granulosa and theca cells	Increased AMH levels and follicle number	Disturbed folliculogenesis
Phosphatase and tensin homolog deletions on chromosome 10 (PTEN) induced by insulin	Increased PTEN levels in granulosa cells and proliferation of granulosa cells	

with hyperandrogenism, have acne over the neck, chest and upper back (24).

Because of the dichotomy in the final pathogenetic pathway where DHT is further reduced to 3α androstenediol and its glucuroneride, only in patients with hirsutism but not with acne, these two clinical scenarios present simultaneously, especially in PCOS, but they do not always appear concomitantly. Thus, acne and hirsutism appear to be expressions of the different metabolic fate of DHT.

Acanthosis nigricans is a mucocutaneous eruption that occurs most frequently in the axillae, skin flexures and the nape of the neck and is manifested by increased pigmentation and papillomatosis. It is a marker associated with insulin resistance and compensatory hyperinsulinemia, occurs in 1–3% of women with PCOS, and may be a more frequent finding in adolescent girls with PCOS.

Since these manifestations of hyperandrogenism are largely cosmetic, they are a cause of significant social embarrassment, emotional distress and resultant psychosocial sequelae, warranting an important priority in the overall management of women and adolescents with PCOS (24).

2.1.2. Reproductive dysfunction (Fig. 2)

Women with PCOS frequently present with reproductive dysfunction. Ovarian function might be disturbed, with resultant abnormal folliculogenesis and steroidogenesis. Although it is

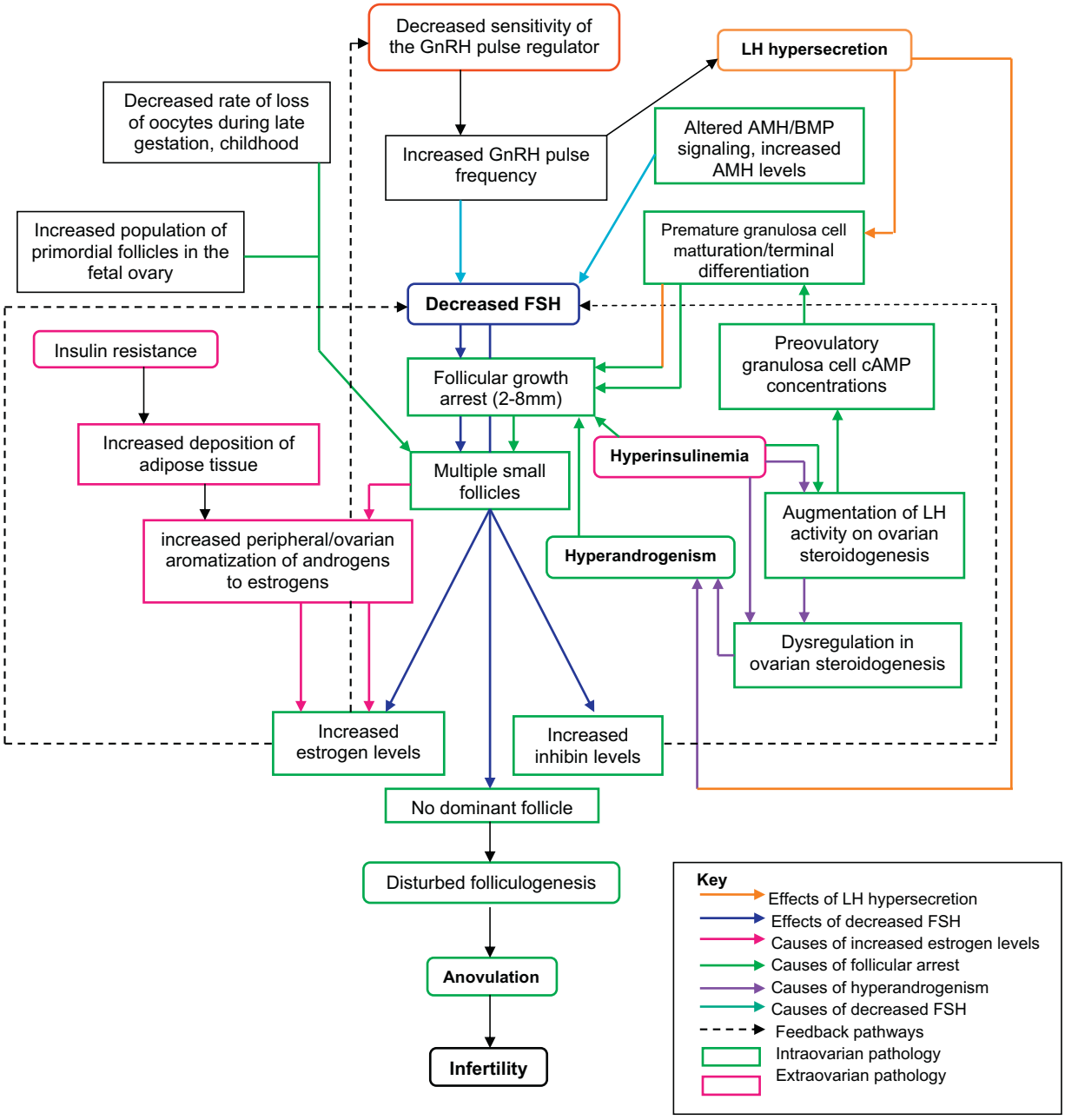

Figure 2 Reproductive dysfunction in PCOS.

difficult to define the exact pathogenesis of anovulation, many possible mechanisms have been postulated. LH hypersecretion, hyperandrogenemia, hyperinsulinemia, obesity, decreased plasminogen activator inhibitor (PAI) activity and endothelial dysfunction, all of which are interlinked, have been implicated in the pathophysiology of disordered ovarian and endometrial function and reproductive failure as a whole in PCOS women (25).

2.1.2.1. Menstrual abnormalities. Menstrual irregularity is the most common gynecological presentation of PCOS, oligomenorrhea being observed in approximately 85–90% of women with PCOS, while as many as 30–40% of amenorrheic patients have PCOS (26). It may be developmentally linked to either high maternal weight in late pregnancy, possibly linked to obesity and weight-related reproduction problems in children, or reduced placental and fetal growth, which may be linked to the more severe symptoms of PCOS in the daughter, usually resulting in an early clinical diagnosis of the syndrome.

2.1.2.2. Abnormal follicular dynamics. Poly cystic ovaries display an increased number of preantral and antral follicles compared with normal ovaries, suggesting that early and late follicular development are disturbed. (27) Perturbations in gonadotropin secretion in PCOS, such as decreased FSH levels and LH hypersecretion, owing to a dysregulation of the GnRH pulse regulator, may result in abnormal follicular dynamics culminating in anovulatory infertility (28). Decreased FSH levels, follicular growth arrest at the 2–8 mm stage and production of excessive estrogen and inhibin by multiple, small follicles inhibit FSH secretory dynamics sufficiently to prevent the selection of a dominant follicle (22) and contribute to impaired follicular development.

Insulin resistance with the resultant increased deposition of adipose tissue, and increased aromatization of androgens to estrogens peripherally, (29) or in the granulosa cells, due to the effect of multiple follicles, may contribute to hyperestrogenism. Estradiol hypersecretion may be reflective of advanced maturation of medium-sized antral follicles (28). Anovulation in women with PCOS is characterized by the arrested growth of antral follicles and though the underlying basis for the abnormalities in anovulatory PCOS remains uncertain, it is possible that there are intrinsic differences in folliculogenesis between polycystic and normal ovaries, which affect preantral as well as antral follicles.

It has also been suggested that LH and insulin hypersecretion probably play a secondary role in PCOS by amplifying the preexisting ovarian dysregulation. LH hypersecretion may result in follicular growth arrest either directly by causing premature granulosa cell maturation and luteinization, or indirectly by LH-induced hyperandrogenism. Insulin hypersecretion augments the action of LH on steroidogenesis in isolated granulosa cells, and may further compromise the growth of medium-sized antral follicles by the generation of 'preovulatory' concentrations of cAMP within the granulosa cell, thereby leading prematurely, to terminal differentiation of granulosa cells (28). The minisatellite of insulin gene (INS VNTR), especially class III alleles and III/III genotypes might determine the predisposition to anovulatory PCOS (6). The genetic causes of disturbed folliculogenesis have been listed in Table 2.

Dysregulation of ovarian theca cell androgen production, which may be induced by LH, hyperinsulinemia, or defects in genes regulating androgen biosynthesis, results in hyperandrogenism, often associated with an increase in the number of follicles which evade atresia (22) (Fig. 2). It is speculated that since the transforming growth factor beta (TGF-β) family members, anti-Müllerian hormone (AMH) and bone morphogenetic proteins (BMPs), inhibit FSH sensitivity, their signaling may contribute to the aberrant follicle development in these women, though the pathophysiology of this process is poorly understood (27).

In normal menstrual physiology, the monotropic rise of plasma FSH during the luteal–follicular transition is critical for follicular development and subsequent ovulation. In hyperandrogenemic girls destined to develop PCOS, unlike in normal early puberty, the nocturnal increase in ovarian steroids may not be adequate to suppress the GnRH pulse generator, leading to a persistently rapid LH pulse frequency, impaired FSH production and inadequate follicular development (14). Evidence for a disorder of early follicular development in the polycystic ovary is consistent with an increased population of primordial follicles in the fetal ovary (2) or a decreased rate of loss of oocytes during late gestation, childhood and puberty (30). However, it remains to be determined whether this phenomenon is the cause or the effect of increased exposure to androgens within the ovary (2). The sequence of events that culminate in anovulation and hence, infertility, have been illustrated in Fig. 2.

2.1.2.3. Infertility. Polycystic ovary syndrome is probably the most common cause of anovulatory infertility (6), associated with an increased risk of miscarriage after either spontaneous or assisted conception (25) and the development of ovarian hyperstimulation syndrome (OHSS) in assisted conception (31). A higher incidence of first trimester spontaneous abortions (25–73%) has been reported in women with polycystic ovaries or PCOS (32). Abnormalities in LH secretion were found in 81% of women with recurrent fetal loss, and higher androgen levels were observed in women who had recurrent miscarriages, both with and without PCOS. Anovulatory infertility, due to arrested folliculogenesis in PCOS, is frequently found in association with insulin resistance (IR) and obesity (33).

A series of intraovarian growth factors [insulin-like growth factors (IGF), AMH, growth differentiation factor 9 (GDF-9) and inhibin] and extra-ovarian factors (GH, IGF-1 and insulin) seem to act together in a process that triggers anovulation or early pregnancy loss through the impairment of folliculogenesis, oocyte maturation, steroidogenesis and endometrial receptivity but whether these abnormalities are the direct cause of anovulation and pregnancy loss, or the consequence of deranged steroidogenesis has to be determined (12). Whereas underweight is associated with poor fetal growth and increased pregnancy loss, overweight is more strongly associated with diseases in pregnancy, pregnancy loss, stillbirth and high birth weight (34). The role of PCOS in infertility and early pregnancy loss is presented in Table 3.

2.1.3. Metabolic dysfunction (Fig. 3)

2.1.3.1. Metabolic syndrome. The metabolic syndrome (MBS), also called Syndrome X or Insulin Resistance Syndrome, refers

to the clustering of a number of cardiovascular risk factors, with insulin resistance, hyperinsulinemia, abdominal obesity, hypertension and atherogenic dyslipidemia presenting as frequent metabolic traits. The metabolic syndrome is also associated with an increased risk of development of type 2 diabetes and cardiovascular disease (35). Insulin resistance (71%) is the most common metabolic abnormality in PCOS patients followed by obesity (52%) and dyslipidemia (46.3%), with an incidence of 31.5% for the metabolic syndrome (36). The major risk factors leading to the metabolic syndrome or cardiovascular dysmetabolic syndrome are physical inactivity and an atherogenic diet, and the cornerstone clinical feature is abdominal obesity or adiposity. (37). The National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III criteria for the metabolic syndrome necessitates the presence of three or more of the following features to qualify for MBS: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, high blood pressure and impaired fasting glucose (Table 4).

The prevalence of MBS in women with PCOS (43%) has been reported to be nearly 2-fold higher than in age-matched women in the general population. A nearly 8-fold greater prevalence of MBS in women with PCOS aged 20–29-years (44.8% vs. 5.9%, respectively) and a nearly 4-fold increased prevalence in women with PCOS aged 30–39 years was observed compared to age-matched women in the general population. A significant age-related trend ($P < 0.001$) has been reported in the prevalence of MBS, increasing from 23% in PCOS women < 20 years, to 45% in women aged 20–29 years, and then to 53% in PCOS women aged 30–39 years. Moreover, women with MBS had significantly higher BMI values and tended to present more often with hirsutism and Acanthosis nigricans than those lacking this condition (35). Abnormalities in waist circumference (98%), high-density lipoprotein-cholesterol (HDL-C) (95%), blood pressure (70%), triglycerides (56%) and glucose (11%) have been reported in women with PCO and MBS (38).

2.1.3.1.1. Insulin resistance. One of the important consequences of obesity, the prevalence of which is progressively increasing around the world, is the development of insulin resistance (IR). Insulin resistance is central to the pathogenesis of PCOS, has a multifactorial pathogenesis, is a precursor of diabetes mellitus and is additionally associated with components of the metabolic syndrome, such as cardiovascular risk, hypertension and endothelial dysfunction, which is considered the initial step in the process of atherosclerosis and a shorter lifespan. A significantly higher ($P < 0.01$) prevalence of obesity, central obesity, hypertension and, high triglycerides and

Table 3 Causes of infertility and early pregnancy loss in PCOS.

Disorder	Effect
LH hypersecretion	Adverse effect on the developing oocyte • inhibition of the oocyte maturation inhibitor • premature oocyte maturation anovulation Premature follicular differentiation, premature luteinization:follicular arrest Adverse effect on the developing endometrium • increased endometrial advancement Hyperandrogenism Hyperestrogenism
Hyperandrogenism	Impaired folliculogenesis and granulosa cell function Detrimental effect on endometrial function
Insulin resistance	Hyperandrogenism Independent risk factor for recurrent pregnancy loss
Hyperinsulinemia	LH hypersecretion Hyperandrogenism Adverse affects on endometrial function by • potentiation of LH and androgen effects • influencing PAI activity
Obesity	Menstrual disorders Increased risk of miscarriage after spontaneous or assisted conception by • predisposition to insulin resistance • induced reduction in SHBG thus, hyperandrogenemia
Increased inhibin levels	Anovulation
Increased plasminogen activator inhibitor (PAI), (fibrinolysis inhibitor)	Early recurrent unexplained/spontaneous miscarriage by • provoking thrombotic placental insufficiency abnormality, • impaired trophoblastic development and poor placentation in early • pregnancy
Aberrant growth factor expression	
Reduced/delayed GDF-9 expression	Follicular arrest before granulosa cells gain competence to initiate apoptosis Decreased long-term developmental potential of the oocytes
Hyperexpression of antiapoptotic factors (EGF and TGF-α)	Blocking of apoptosis and atresia
Expression of insulin-like growth factor (IGF) and its intrafollicular receptors	Inhibitory effect on IGF and FSH actions: follicular arrest
Increased TNF-α	Modulation of theca cell steroidogenesis Decreased estradiol levels

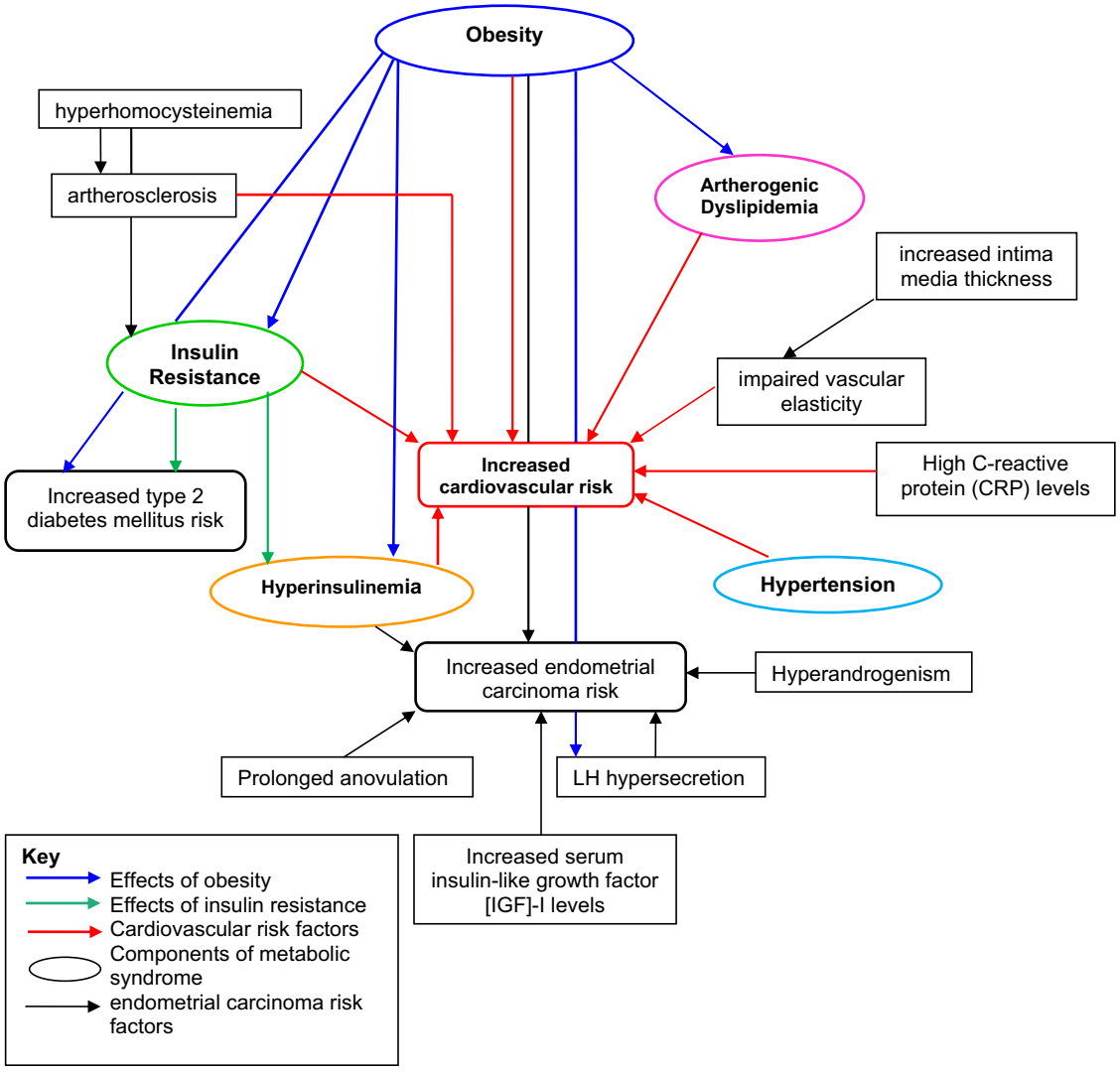

Figure 3 Metabolic dysfunction in PCOS.

low prevalence of HDL-C has been reported in Asian Indians with the insulin resistance syndrome (IRS) (39).

Anovulatory women with PCOS are relatively hyperinsulinemic and more insulin resistant than weight-matched control subjects (40). Approximately 50–70% of all women with PCOS have some degree of insulin resistance, and this hormone insensitivity probably contributes to the hyperandrogenism that is responsible for the signs and symptoms of PCOS (41). The association between increased insulin resistance (IR) and PCOS is a consistent finding in all ethnic groups (42).

2.1.3.1.1.1. Etiology of insulin resistance. The proposed mechanisms contributing to insulin resistance are peripheral target tissue resistance, decreased hepatic clearance and increased pancreatic sensitivity (43). Studies on the molecular mechanisms of insulin resistance in PCOS suggests that the peripheral insulin resistance in these patients may be due to a post-binding defect in insulin receptor-mediated signal transduction, specifically, a dysregulation of insulin receptor phosphorylation (increased insulin-independent serine phosphorylation and decreased insulin-dependent tyrosine phosphorylation) and, consequently, decreased tyrosine kinase activity of the receptor, inhibition of normal signaling and a significant decrease in insulin responsiveness (40). Serine phosphorylation also appears to increase the activity of P450c17α, the key regulatory enzyme in androgen biosynthesis, which is present in both, adrenal and ovarian steroidogenic tissues (43). Polymorphisms in genes involved in insulin secretion or insulin receptor metabolism have also been implicated (44). It has been hypothesized that the hyperandrogenemic endocrine environment during prenatal life and puberty has a profound effect on body fat distribution, predisposing to insulin resistance (45). The etiology and effects of insulin resistance in PCOS are depicted in Fig. 3

2.1.3.1.1.2. Detection. A fasting glucose-to-insulin ratio of <7 is a useful index of insulin resistance in adolescents (7). Although uncertainty exists, early detection and treatment of insulin resistance in this population could ultimately reduce the incidence or severity of diabetes mellitus, dyslipidemia, hypertension and cardiovascular disease. Though several tests have been used to measure insulin sensitivity, the oral glucose tolerance test (OGTT) is the best simple, office-based method of assessment in women with PCOS because it pro-

Table 4 The National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III criteria for the metabolic syndrome in women with PCOS.

1. Abdominal obesity >88 cm (waist circumference)
2. Triglycerides ⩾150 mg/dL (1.7 mmol/L)
3. High-density lipoprotein-cholesterol (HDL-C) < 50 mg/dL (1.29 mmol/L)
4. A systolic blood pressure ⩾130 mmHg or a diastolic blood pressure ⩾85 mmHg
5. Fasting glucose: ⩾100 mg/dL (⩾5.6 mmol/L)

Three out of these five criteria qualify for the syndrome. Participants who reported using antihypertensive or antidiabetic medication (insulin or oral agents) were counted as having high blood pressure or diabetes, respectively.

vides information about both insulin resistance and glucose intolerance (41).

2.1.3.1.2. Hyperinsulinemia. Inherent defects in insulin synthesis/secretion, insulin resistance and obesity may all contribute to hyperinsulinemia. Hyperinsulinemia, whether through weight gain or because of inherent defects in insulin action, stimulates both adrenal and ovarian cytochrome P450c17α activity and may explain the progression to PCOS in girls with premature adrenarche at the time of pubertal gonadotropin activation (46). By inhibition of hepatic synthesis more peripherally, insulin reduces serum SHBG, favoring free circulating androgens and decreases insulin-like growth factor binding protein-1 (IGFBP-1), allowing more IGF-1 to be available both locally and peripherally (47). It may additionally influence LH hypersecretion by increasing LH pulse amplitude or potentiate the effects of LH on ovarian steroidogenesis, inducing hyperandrogenism (Fig. 1). Long-term hyperinsulinemia in humans, as is the case in PCOS patients, stimulates leptin secretion from adipose tissue (48), elevated levels of which have been associated with adverse effects on reproductive function (Fig. 4). The role of hyperinsulinemia in the pathogenesis of infertility is illustrated in Figs. 2 and 4. Although both insulin resistance and hyperinsulinemia have significant pathogenic roles in PCOS, women with hyperinsulinemia are not necessarily all hyperandrogenic and only 52% of those with type 2 diabetes mellitus have clinical manifestations of androgen excess (49).

2.1.3.1.3. Dyslipidemia. Dyslipidemia is a disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. These changes may be manifested by the elevation of serum total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (TG) concentration and a decrease in the HDL cholesterol concentration. As compared to women without PCOS, 85% of PCOS women have dyslipidemia characteristic of the metabolic syndrome. Obesity has an important influence on the lipid profile with approximately 50% of patients with PCOS being overweight or obese with abdominal fat accumulation. Insulin is positively correlated with total cholesterol, LDL and TG, and negatively correlated with HDL in IR patients. Hyperinsulinemia, due to IR, has been associated with lipid and lipoprotein abnormalities in women with PCOS. Insulin-related lipid changes in PCOS women account to about 25%. Dyslipidemia in women with PCOS may result from the independent effects of androgen excess and insulin resistance, secondary to excess androgen action, or altered activity of hepatic lipase or lipid transfer protein. Dyslipidemia was found to be a major prognostic risk factor for cardiovascular disease (CVD) (50) (Fig. 3).

2.1.3.1.4. Obesity. Obesity contributes significantly to both insulin resistance and hyperandrogenism in overweight women with and without PCOS, with more than 50% of PCOS women being overweight [body mass index (BMI) > 25 kg/m^2] or obese (BMI > 27 kg/m^2) with a tendency for an increased waist–hip ratio (WHR) or abdominal obesity. It has been shown to be an independent predictor of conversion of normoglycemia to impaired glucose tolerance or type 2 diabetes mellitus (DM), contribute to a significant proportion of menstrual disorders in women with PCOS, and worsen the clinical presentation of PCOS, suggesting a pathogenetic role of obesity in the development of PCOS and related infertility (9) (Fig. 4). Up to 30% of obese PCOS women have impaired glucose tolerance and 7.5% are likely to develop frank diabetes by their forties (51). Obese PCOS women have more severe hyperandrogenism. There is universal agreement that central fat deposition (defined as a waist–hip ratio >85, or a waist circumference ⩾ 80 cm) is a marker of the metabolic syndrome. Compared with weight-matched controls, overweight women with PCOS have increased cardiovascular risk factors and evidence of early cardiovascular disease (CVD), potentially related to insulin resistance (9) (Fig. 3), and in association with the resultant insulin resistance, may be a significant factor leading to the 7-fold increased risk of death after a myocardial infarction (52).

A high prevalence of insulin resistance and impaired glucose tolerance among obese women with risk factors, such as obesity (BMI > 30 kg/m^2) or fasting glucose >5.5 mmol/L and a relevant family history, makes an oral glucose tolerance test and a metabolic screen mandatory (51).

2.1.3.1.4.1. Role of leptin in PCOS. Leptin is a hormone secreted mainly from the adipose tissue, serum levels of which are influenced by obesity, insulin resistance and the levels of sex steroids (androgens and estrogens) and insulin. It is mainly involved in the regulation of body weight by decreasing appetite and increasing energy expenditure. Besides regulating the energy metabolism of the body, leptin has important actions on the reproductive system, which makes it an important link between the adipose tissue and hypothalamus–pituitary–gonadal (HPG) axis (43). Long-term hyperinsulinemia in humans, as is the case in PCOS patients, stimulates leptin secretion from adipose tissue (48). Significantly higher leptin (P = 0.0028), and insulin concentrations, insulin: glucose ratio (IGR), and a significant correlation between leptin and fasting insulin concentrations, IGR, WHR and LH have been reported in obese PCOS women than in normal-weight women with PCOS. There is a significant negative correlation between leptin and LH concentrations, independently of either BMI or IGR, suggesting a possible involvement of leptin in LH hypersecretion (18). Estrogens increase, whereas androgens suppress leptin production, suggesting sexual dimorphism in leptin levels (43).

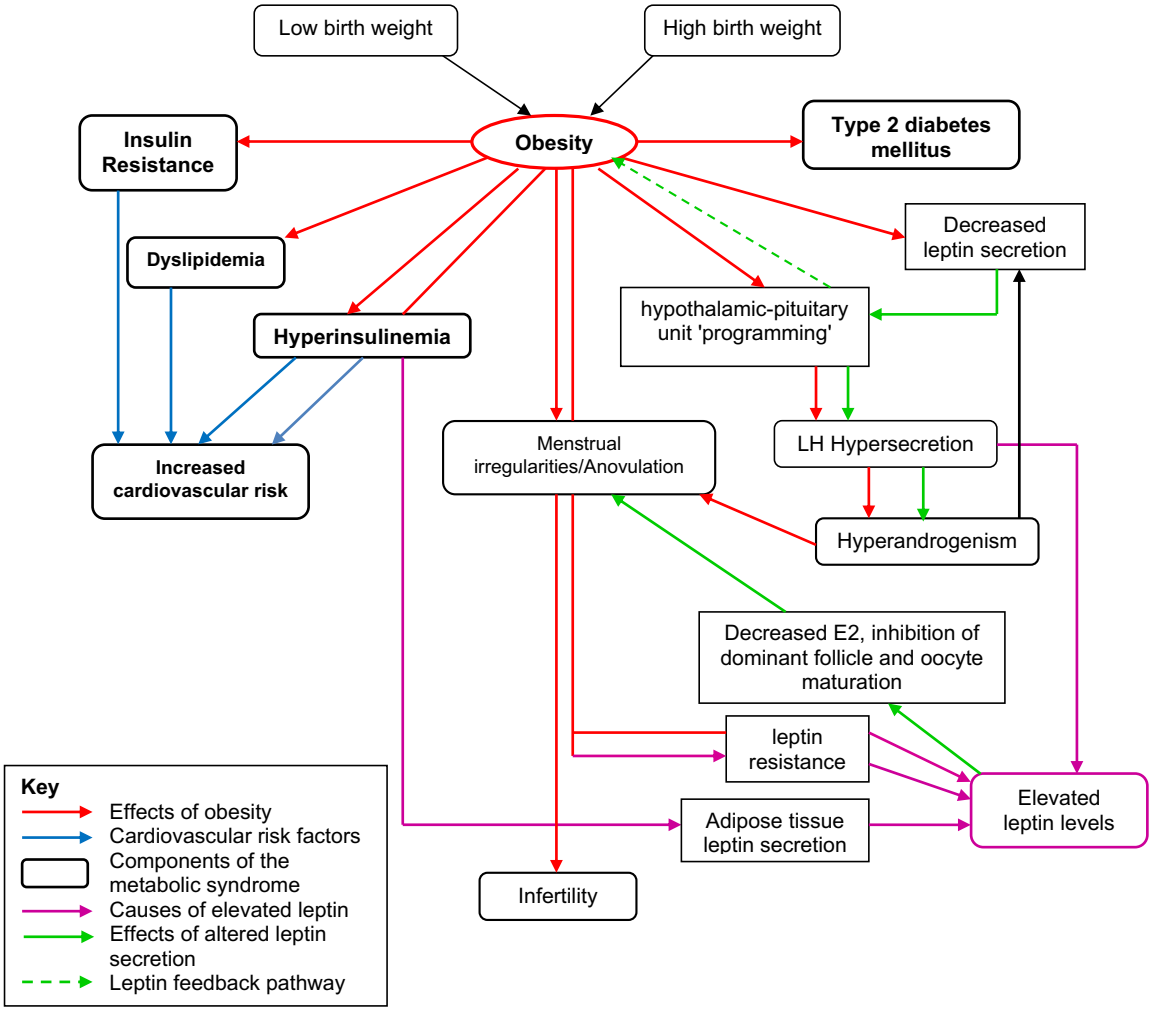

Figure 4 The role of obesity in PCOS.

The direct and indirect effects of leptin on the HPG axis, such as acceleration of GnRH pulsatility (but not the pulse amplitude) in a dose dependent manner, suggest that leptin may play an important role in the pathogenesis of PCOS. Gonadotropic cells express leptin receptors and leptin may directly stimulate LH, and to a lesser extent, FSH. Depending on its serum levels, leptin may exert a bimodal action on the HPG axis; at low doses, leptin may have a permissive threshold effect on the central nervous system (CNS) that regulates gonadotropin secretion, whereas high serum leptin levels (leptin resistance) as seen in obese people, may have an inhibitory effect on the gonads. Leptin resistance, possibly due to abnormalities in the leptin receptor, may be a characteristic of human obesity (43). Higher abdominal fat accumulation in obese PCOS patients may result in decreased leptin secretion, which sends inappropriate satiety signals to the brain resulting in increased body weight and serum leptin levels, which may impair gonadal function and ovulation.

At the ovarian level, high leptin concentrations may suppress estradiol production and interfere with the development of dominant follicles and oocyte maturation by reducing the response to gonadotropin stimulation. The presence of leptin receptors on human ovarian follicles, expression of leptin mRNA in follicular cells at the time of dominant follicle selection and evidence of the secretion of leptin by granulosa cells indicate a possible direct paracrine role for leptin in ovarian physiology (53). Since androgens suppress leptin production and long-term hyperinsulinemia stimulates it, the net result would be a balance between the effects of BMI, androgens and insulin. The role of leptin in the pathophysiology of PCOS is demonstrated in Fig. 4. However, further studies are required in this area to clarify the complex interaction of adipose tissue and leptin with the HPG axis in PCOS patients.

2.1.3.1.5. Cardiovascular disease (CVD) risk. Cardiovascular risk factors associated with PCOS include insulin resistance, central obesity, hypertension, dyslipidemia, hyperhomocysteinemia, increased intima media thickness and impaired vascular elasticity (54). Obesity may contribute to a significant increase in cardiovascular risk either directly, or via its impact on the various components of the metabolic syndrome (Figs. 3 and 4). PCOS is associated with a 50% increased risk for coronary heart disease (CHD) compared to age and BMI-matched women without PCOS. Hyperhomocysteinemia in PCOS, related to insulin resistance, or high androgen levels, varies with ethnicity and is a recognized risk factor for atherosclerosis. It may hence, play an important role in the

Table 5 The causes and effects of biochemical dysfunction in PCOS.

Disorder	Cause(s)	Effects
Elevated androgen levels	Abnormalities in androgen biosynthesis/secretion/ metabolism/action (genetic/biochemical aberrations)	Hirsutism Androgenic alopecia Acanthosis nigricans
	LH hypersecretion	Anovulation Premature follicular differentiation, premature luteinization:follicular arrest
	Inhibition of hepatic synthesis of SHBG Increased follicular FSH receptors expression of insulin-like growth factor (IGF) and its intrafollicular receptors Decreased IGFBP-1, higher availability of IGF-1 both locally and peripherally	Follicular growth and estrogen biosynthesis
Increased inhibin levels	Multiple follicles, follicular arrest, premature differentiation Increased primordial follicles in fetal ovary/decreased loss during gestation/ childhood	Anovulation
Increased AMH levels	Genetic	Hyperandrogenism Disturbed folliculogenesis via inhibition of FSH-induced aromatase activity and E2 synthesis
Blocking of apoptosis and atresia	Hyperexpression of antiapoptotic factors epidermal growth factor (EGF) and transforming growth factor-α (TGF-α)	Multiple small follicles Disturbed folliculogenesis
Hyperinsulinemia	Inherent defects in insulin synthesis/secretion Insulin resistance Obesity	LH hypersecretion Hyperandrogenism Decreased IGFBP-1, higher availability of IGF-1 both locally and peripherally
Increased tumour necrosis factor-α (TNF-α)		Modulation theca cell steroidogenesis Decreased estradiol levels
Reduced/delayed growth differentiation factor 9 (GDF-9) expression		Follicular arrest before granulosa cells gain competence to initiate apoptosis Decreased long-term developmental potential of oocytes
Increased ovarian NGF production		Antral follicle growth arrest

development of cardiovascular disease (39). Multiple, prospective, epidemiological studies have demonstrated that high C-reactive protein (CRP) levels, a marker of inflammation, predict the incidence of myocardial infarction, stroke, peripheral arterial disease and sudden death (55). Elevated CRP levels in the PCOS group (36) suggest that women with PCOS may indeed be at risk for early-onset CVD. Both CRP and homocysteine have been shown as independent risk factors for CVD.

Despite advances in diagnostic techniques and identification of structural markers to address the prevalence of cardiovascular risk factors in PCOS women, owing to limitations, such as poor documentation of clinical CV events and a relatively young age of women at follow-up in most studies, the incidence of carotid disease in PCOS women has not consistently been demonstrated and no increased association with CV mortality reported (54).

2.1.3.1.6. Type-2 diabetes mellitus. Polycystic ovary syndrome is associated with an approximately 7-fold increased risk of type 2 diabetes mellitus (DM) (6). Insulin resistance and pancreatic β-cell dysfunction are major risk factors for the development of type 2 DM. In a follow-up of 67 women with PCOS [54 with normal glucose tolerance (NGT) and 13 with impaired glucose tolerance (IGT)] for a mean of 6.2 years, 17% of those with NGT at baseline developed IGT or type 2 DM over time, while 54% of those with IGT at baseline had progressed to type 2 DM. Further support for the high prevalence of abnormal glucose tolerance in PCOS comes from the 10-fold increased risk of developing gestational diabetes mellitus (GDM) in PCOS women compared to the general population (baseline risk ~3%) (56). The minisatellite of insulin gene (INS VNTR), especially class III alleles and III/III genotypes might determine the concomitant risk for the development of type 2 DM (6).

In addition to a significantly higher glucose intolerance ($P = 0.00001$), significantly larger mean waist circumference ($P = 0.0004$), higher tendency for hypertension ($P = 0.001$), hypertriglyceridemia ($P = 0.02$) and a lower level of HDL ($P = 0.04$) have been reported in women with a history of GDM compared to controls. Of the women who had GDM, 49% had metabolic syndrome, 58.5% had polycystic ovaries and 40% had PCOS, significantly higher ($P = 0.00001$) than the values observed in control women (6%, 13% and 3%,

respectively). This confirms an association between GDM and subsequent PCOS and metabolic syndrome (57).

2.1.4. Biochemical dysfunction

The causes of biochemical dysfunction in PCOS and its effects on the endocrine, reproductive and metabolic dysfunction are illustrated in Figs. 1–3 and presented in Table 5.

2.1.5. Cancer

An association between PCOS and type 1 endometrial cancer, particularly low-grade endometrial stromal sarcoma and carcinosarcoma, epithelial ovarian cancer risk and breast cancer has often been reported in the literature. Prolonged anovulation with continued estrogen secretion, unopposed by progesterone, may enhance the development and growth of endometrial cancer, particularly in young women. LH hypersecretion, chronic hyperinsulinemia, obesity, hyperandrogenism and increased serum insulin-like growth factor [IGF]-I levels may represent risk factors for endometrial cancer (Fig. 3). However, an estimate of the relative risk of endometrial cancer in women with PCOS has yet to be worked out (58) and there is no consensus with regard to the increased incidence or mortality from endometrial cancer in PCOS women or the subgroup of PCOS in whom hormonal treatment may be required to reduce the perceived risk of endometrial carcinoma (59). While data with regard to epithelial ovarian cancer risk are conflicting but generally reassuring, the few available data appear to exclude a strong association between PCOS and breast cancer (58).

2.2. Etiology and pathophysiology of PCOS

Polycystic ovary syndrome is a multifactorial, polygenic, heterogeneous endocrine disorder. While several mechanisms, including disorders in the HPG axis, ovarian and adrenal androgen production, insulin action, and several candidate genes regulating androgen and insulin biosynthetic pathways, have been implicated in the pathogenesis of the disorder, hyperandrogenism and insulin resistance, largely modulated by obesity, appear to be central to the pathophysiology of the disease. Although many extra-ovarian factors have been identified to influence the disorder, the ovary remains central to the pathogenic events and although a woman may be genetically or environmentally predisposed to develop PCOS, it is the development of insulin resistance, due to the deposition of adipose tissue that leads to the expression of the PCOS phenotype. Hence, it is possible for a woman to have PCOS and then with weight loss lose some of the features PCOS, and consequently, not express the PCOS phenotype.

2.2.1. Origin in adolescence

The signs and symptoms of PCOS often emerge during the peri-pubertal years, with premature pubarche (PP) (appearance of pubic or maxillary hair before 8 years of age in girls without other signs of puberty) being the earliest recognized manifestation (1). Adolescent girls with a history of premature pubarche are at high risk for developing the full PCOS phenotype, including ovarian hyperandrogenism and chronic anovulation (60) (Table 6). Of the girls initially evaluated for premature pubarche, 45% have been reported with oligomenorrhea and higher basal concentrations of 17-hydroxyprogesterone, androstenedione and testosterone on follow-up, in addition to low SHBG and IGFBP-1 levels. It has been reported that oligomenorrhea in adolescents is not a stage in the physiologic maturation of the hypothalamic–pituitary–ovarian axis but an early sign of PCOS associated with subfertility (61). In hyperandrogenemic girls, destined to develop PCOS, unlike in normal early puberty, the nocturnal increase in ovarian steroids may not be adequate to suppress the GnRH pulse generator, leading to perturbations in gonadotropin secretion (a persistently rapid LH pulse frequency and impaired FSH production) (14) and consequently, the clinical and metabolic manifestations of PCOS. The origin of PCOS in adolescence is illustrated in Fig. 5. Marked weight gain, inherent defects in insulin action and the resultant hyperinsulinemia may result in early maturation of the zona reticularis (premature adrenarche), predisposing to hyperandrogenism, PP and the clinical and biochemical manifestations of PCOS in adolescence. Insulin resistance and hyperinsulinemia are important pathophysiological features that are common to both PP and PCOS (1) and recent evidence supports the notion that premature pubarche in girls may be a forerunner of the metabolic syndrome and may precede the development of clinical ovarian androgen excess in adolescence (62,63). Pre-perimenarchal acquisition of centripetal obesity amplifies coronary heart disease (CHD) risk factors and hypofibrinolysis in hyperandrogenemic girls with probable familial PCOS and precocious puberty (64).

Both normal puberty and PCOS have in common hyperpulsatile gonadotropin secretion, hyperactive ovarian and adrenal androgen production, insulin resistance or hyperinsulinemia and consequently low IGF-BP-1 and SHBG. Because of the

Table 6 Characteristics of adolescent girls with a history of premature pubarche.

1. Elevated dehydroepiandrosterone levels, higher basal concentrations of 17-hydroxyprogesterone, androstenedione and testosterone on follow-up
2. Low SHBG and IGFBP-1 levels
3. Hyperinsulinemia
4. Oligoamenorrhea (especially in overweight girls with hirsutism or acne)
5. History of low birth weight
6. Family history of diabetes mellitus
7. Family history of premature cardiovascular disease
8. Family history of PCOS and/or obesity
9. Reduced fetal growth followed by excessive postnatal catch-up in height and particularly, in weight
10. Increased plasminogen activator–inhibitor type 1 (PAI-1) activity (an early biochemical marker of cardiovascular risk in PCOS)

shared features of the two conditions, it has been hypothesized that puberty triggers PCOS in predisposed girls (61).

2.2.2. Origin in utero

Although PCOS manifests clinically during adolescence with maturation of the hypothalamic–pituitary–ovarian axis (2), data from experimental observations in prenatally androgenized sheep and female rhesus monkeys, supported by data from human studies (45), suggest that the natural history of PCOS may originate in intrauterine life (10). Experimentally induced fetal androgen excess in female rhesus monkeys early in gestation produces a comprehensive adult PCOS-like phenotype that includes both reproductive (hyperandrogenism, oligomenorrhea, enlarged, polyfollicular ovaries, LH hypersecretion and impaired embryo development) and metabolic dysfunction (insulin resistance accompanying abdominal obesity, impaired insulin response to glucose and hyperlipidemia) found in PCOS women (65,66). Exposure to androgen excess late in gestation mimicked these programmed changes, except for LH and insulin secretion defects (66).

The postulated fetal origin of PCOS is illustrated in Fig. 5. Prenatal androgenization of the female fetus, induced by genetic (genetically determined ovarian androgen hypersecretion) and environmental factors (obesity), or the interaction of both, may thus program differentiating target tissues and variably perturb multiple organ system programming, thereby providing a single, fetal origin for a heterogeneous adult syndrome (66). The severity of hyperinsulinemia and insulin resistance may further be influenced by both genetic factors (such as polymorphism in the insulin gene regulatory region) and obesity (45). Early intrauterine fetal (mis) programming determines not only cardiovascular and metabolic regulation in later life,

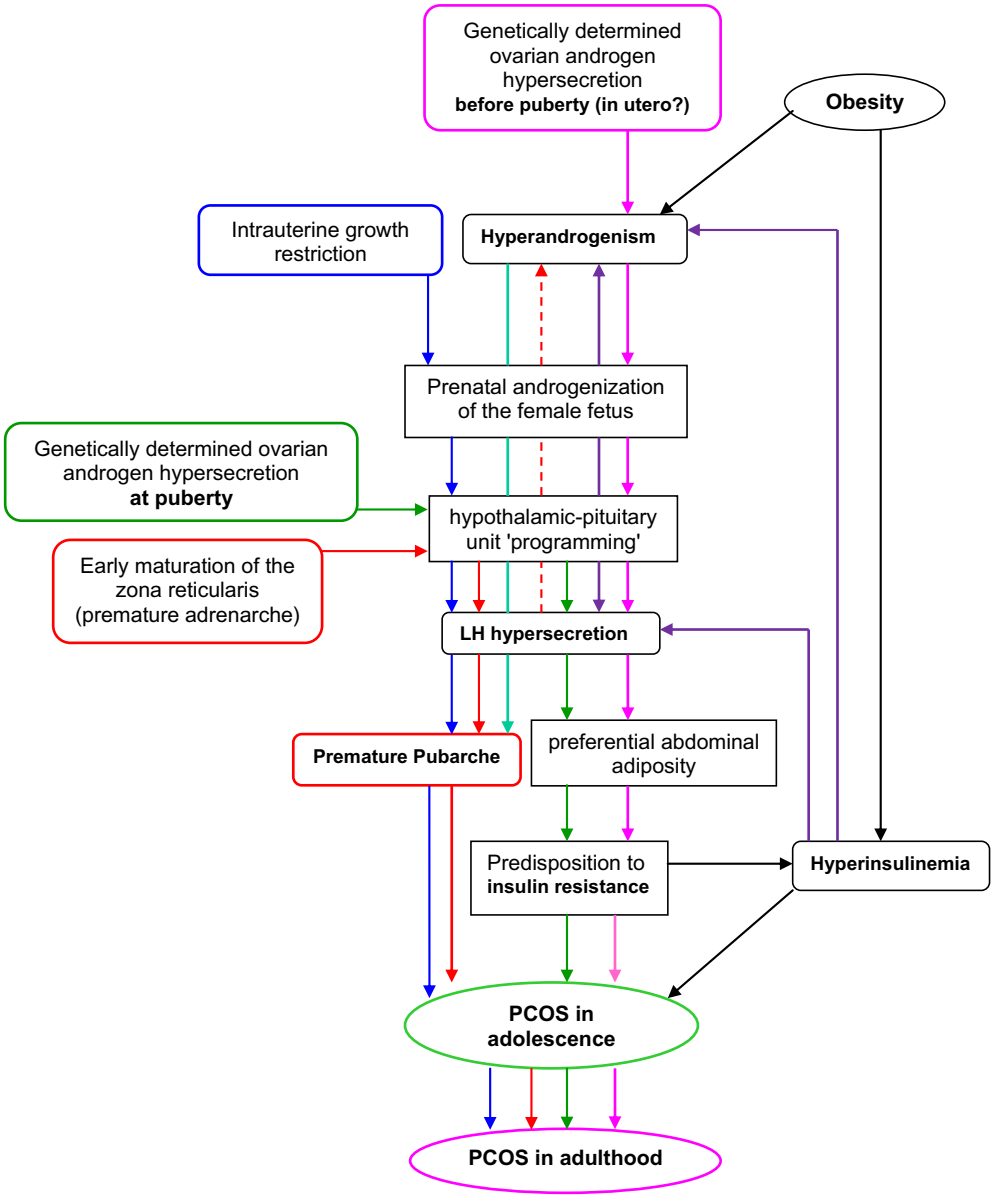

Figure 5 Possible pathway for the origin of PCOS.

but also reproductive function. Intrauterine growth restriction may be associated with precocious maturation of gonadal function and an earlier onset of puberty and menarche, while prenatal androgen excess may negatively influence the development of the ovaries, the female genital phenotype itself (67), and reduce hypothalamic sensitivity to steroid negative feedback resulting in LH hypersecretion. The combined reproductive and metabolic abnormalities may culminate in ovarian hyperandrogenism, premature follicle differentiation and follicular arrest in adulthood (68). At present, it is unclear whether the maternal environment directly influences the development of PCOS in the offspring because though the placenta presents an effective barrier to maternal androgen excess, metabolic disturbances during pregnancy could affect the development of the syndrome in the fetus (2).

2.2.3. The role of obesity

There is now compelling evidence that growth patterns in early life are associated with risk of the metabolic syndrome in adulthood (69). Lower birth weight seems to be associated with later risk for central obesity, which also confers increased cardiovascular risk, possibly mediated through changes in the hypothalamic–pituitary axis, insulin secretion and sensing, and vascular responsiveness. The seeming paradox of increased adiposity at both ends of the birth weight spectrum-higher BMI with higher birth weight and increased central obesity with lower birth weight (70), further underlines the impact of birth weight on fat distribution and predisposition to disease in later life. It has been suggested that the course of evolution of insulin resistance and type 2 diabetes involves fetal, postnatal and adult components (71), and factors in postnatal life, such as nutrition, that affect insulin secretion and/or action, may modify the natural history of PCOS (2). However, the relative importance of prenatal vs. postnatal factors for such associations remains controversial (69). The central role of obesity in the pathogenesis of PCOS is illustrated in Fig. 4.

2.2.4. Genetic etiology

Polycystic ovary syndrome is a complex oligogenic disorder in which, a small number of key genes interact with environmental factors (notably obesity), the balance of which, determine the typically heterogeneous, clinical and biochemical phenotype (72). Multiple biochemical pathways have been implicated in the pathogenesis of PCOS. Several genes from these pathways have been tested, including genes involved in steroid hormone biosynthesis and metabolism (StAR, CYP11, CYP17, CYP19, HSD17B1-3 and HSD3B1-2), gonadotropin and gonadal hormones action (ACTR1, ACTR2A-B, FS, INHA, INHBA-B, INHC, SHBG, LHCGR, FSHR, MADH4 and AR), obesity and energy regulation (MC4R, OB, OBR, POMC and UCP2-3), insulin secretion and action (IGF-1, IGF-1R, IGFBPI1-3, INS VNTR, IR, INSL, IRS1–2 and PPARG) and many others (6). Several lines of evidence suggest that there is an underlying genetic cause for PCOS (73) (Table 2).

Collectively, these findings are consistent with the concept that a gene or several genes are linked to PCOS susceptibility. A strong genetic basis for PCOS also comes from the fact that the syndrome clusters in families (6).

However, though the roles of more than 70 candidate genes have been evaluated for a causal role in PCOS during the past decade, because of genetic and phenotypic heterogeneity and underpowered studies, the results of many of these studies remain inconclusive (74). Most of these genes represent only minor modifying loci; the evidence supporting linkage is not overwhelming and needs to be buttressed in larger studies. Because the mutations/genotypes associated with PCOS are rare, and their full impact on the phenotype incompletely understood, routine screening of women with PCOS or stigmata of PCOS for these genetic variants is not indicated at this time. Currently, the treatment implications for individually identified genetic variants are uncertain and must be addressed on a case by case basis (75).

2.2.4.1. Mode of inheritance. The mode of inheritance of the disorder is still uncertain, although the majority of studies are consistent with an autosomal dominant pattern (75) with incomplete penetrance (66), modified perhaps by environmental factors. Studies of first-degree relatives of women diagnosed with PCOS reveal familial clustering of the disease, particularly hyperandrogenemia, with 46% of ascertainable sisters of PCOS women reported as hyperandrogenemic, suggesting a dominantly inherited trait controlling androgen levels (73). The probability of finding a metabolic disorder in the families of PCOS patients has been reported to be 2.7-fold higher than in families of the control group and metabolic disorders were more frequent in parents and grandparents of PCOS patients than in those of normal women (76). Increased total, low-density lipoprotein and triglyceride levels and an increased prevalence of MBS has been observed in affected sisters of women with PCOS compared with unaffected sisters, consistent with a heritable trait (76). Insulin resistance has also been demonstrated in brothers of women with PCO, comparable to that associated with a family history of type 2 DM and associated with elevations of blood pressure, abnormalities in serum lipid concentrations and impaired endothelial cell function (77).

Significant phenotypic and genetic heterogeneity have been observed both within and between families. However, the difficulties in classifying female family members as clearly affected or unaffected and lack of a definitive male phenotype complicate the use of linkage analysis to identify the PCOS genes. Each family is best considered on an individual basis to identify genetic markers that segregate with the clinical features of androgen excess (78).

2.3. Treatment

Women with polycystic ovary syndrome (PCOS) have a myriad of phenotypic and clinical features that may guide therapeutic options for metabolic protection and ovulation induction (79). Though the symptoms may be ameliorated by simply employing lifestyle measures, such as weight loss, medical treatments currently consist of the use of insulin sensitising agents, aromatase inhibitors and anti-androgens in conjunction with the oral contraceptive pill, or occasionally, the use of laparoscopic surgery (80). Several short-term trials of metformin therapy in adolescents have shown promising effects in lowering insulin secretion, improving insulin sensitivity, restoring normal menstrual cycles, correcting lipid abnormalities (7), reducing elevated androgen levels (81), improving cardiovascular risk factors, such as markers of subclinical inflammation and dyslipidemia (79), and in decreasing PAI-1

activity and reducing first trimester miscarriage. However, a large meta-analysis of 31 trials has reported no clinically significant beneficial effect of metformin in reproductive and biochemical parameters and concluded a paucity of data from randomized controlled trials (RCTs) to support the efficacy of insulin sensitising agents in treating the clinical and biochemical features of PCOS. Long-term prospective RCTs with larger sample sizes are needed before any recommendation can be made on the usefulness of these agents in the treatment of PCOS (82) and in the prevention of the metabolic syndrome (83). Despite promising findings in the safety and efficacy of metformin in preventing early pregnancy loss and decreasing the incidence of gestation, there are no clear data to suggest that metformin reduces pregnancy loss or improves pregnancy outcome in PCOS, and it is currently recommended that metformin be discontinued with the first positive pregnancy test result, unless there are other medical indications (e.g., type 2 DM) (79), and large-scale clinical research be undertaken to ensure the safety and efficacy of these drugs in pregnancy (84).

The management of infertility in women with PCOS centers on options for inducing ovulation. While weight loss, exercise, and metformin have proved effective in inducing ovulation in many insulin-resistant and obese women with PCOS according to an evidence-based review and recommended as the first-line treatment (85), a very recent Cochrane Database of Systematic Reviews, including 17 RCTs, 27 of them using metformin and involving 2150 women, concluded that though metformin is still of benefit in improving clinical pregnancy and ovulation rates compared to placebo or when metformin + CC is compared to CC, there is no evidence that metformin improves live-birth rates whether it is used alone or in combination with clomiphene, or when compared with clomiphene (86). Therefore, the use of metformin in improving reproductive outcomes in women with PCOS appears to be limited (86). On the basis of the currently available evidence and the consensus regarding the therapeutic challenges raised in PCOS women, the routine use of metformin in ovulation induction, is not recommended and it should be restricted to women with glucose intolerance. Clomiphene citrate is the recommended first-line treatment for ovulation induction, with a cumulative singleton live-birth rate of 72%, exogenous gonadotropins with intense monitoring of ovarian response or laparoscopic ovarian surgery with medication, the second-line intervention, should CC fail to result in pregnancy, and IVF, the third-line treatment. Insufficient evidence is currently available to recommend the clinical use of aromatase inhibitors for routine ovulation induction. However, before any intervention is initiated, preconception counseling should be provided, emphasizing the importance of lifestyle, especially weight reduction and exercise in overweight women (87). Despite the potential advantages and efficacy of laparoscopic ovarian surgery, such as repeated single ovulations, decreased adhesion formation, and lowered costs compared to gonadotropins, few RCTs comparing the success rates of surgery, with gonadotropins have been undertaken and long-term concerns with surgery, including adhesion formation and premature ovarian failure, remain (88).

Current evidence on lifestyle management (dietary, exercise or behavioral interventions) of obesity in women with PCOS, suggests that lifestyle management should be used as the primary therapy in overweight and obese women with PCOS for the treatment of metabolic complications and improvement in ovulatory function and pregnancy (89). A relatively small or modest (5–10%) weight loss results in improvements in insulin resistance, hyperandrogenism, menstrual function and fertility, thus reducing long-term risks (39). Hence, weight loss is the single best therapy for the treatment of individual components of the metabolic syndrome and should be considered as active medical therapy and not as an alternative to other medical interventions. However, further research is needed with regard to its role in improvement in pregnancy and live-birth rates (89). Primary prevention of metabolic sequelae, such as diabetes mellitus and cardiovascular disease, by lifestyle modifications is particularly important in adolescents, who have the opportunity to establish healthy habits before entering adulthood, and these measures may be more efficacious than pharmacological therapy (7).

Early diagnosis and treatment of PCOS in adolescents is essential in ensuring good health in adulthood and restoring self-esteem. Lifestyle interventions that prevent increased adiposity in adolescent daughters of PCOS mothers may also reduce their risk of acquiring many PCOS-related metabolic abnormalities in adulthood (65).

3. Conclusion

The deep-rooted origin and detrimental effects of PCOS on the on the biochemical, reproductive and metabolic functions of the body and its life-threatening consequences warrant the early recognition and management of this syndrome. Though it may be impossible to reverse the genetic programming of the syndrome, environmental factors, such as obesity, that may, with/without the interaction with genetic factors, play a key role in perturbing multiple organ system programming and the final manifestation of the syndrome, can largely be controlled. Despite the plethora of treatment options available, owing to a significant role of obesity in the developmental origin, etiology and pathophysiology of PCOS and amelioration of the symptoms by simple lifestyle measures, such as weight loss, pharmacological therapy should be employed only if lifestyle modifications fail. Evidence-based treatment practice with a patient-tailored approach should regulate the appropriate treatment option.

Clinical strategies to improve the fertility outcome in PCOS women and efforts to minimize transgenerational susceptibility to adult PCOS and its metabolic derangements should be the goal of future studies (68).

References

(1) Witchel SF. Puberty and polycystic ovary syndrome. Mol Cell Endocrinol 2006;254–255:146–53.
(2) Franks S, McCarthy MI, Hardy K. Development of polycystic ovary syndrome: involvement of genetic and environmental factors. Int J Androl 2006;29:278–85.
(3) Xita N, Georgiou I, Tsatsoulis A. The genetic basis of polycystic ovary syndrome. Eur J Endocrinol 2002;147:717–25.
(4) Mastorakos G, Lambrinoudaki I, Creatsas G. Polycystic ovary syndrome in adolescents: current and future treatment options. Paediatr Drugs 2006;8:311–8.
(5) Hassa H, Tanir HM, Yildiz Z. Comparison of clinical and laboratory characteristics of cases with polycystic ovarian syndrome based on Rotterdam's criteria and women whose only clinical signs are oligo/anovulation or hirsutism. Arch Gynecol Obstet 2006;274:227–32.

(6) Jakubowski L. Genetic aspects of polycystic ovary syndrome. Endokrynol Pol 2005;56:285–93 [in Polish].
(7) Kent SC, Legro RS. Polycystic ovary syndrome in adolescents. Adolesc Med 2002;13:73–88, vi.
(8) Xita N, Tsatsoulis A. Review: fetal programming of polycystic ovary syndrome by androgen excess: evidence from experimental, clinical, and genetic association studies. J Clin Endocrinol Metab 2006;91:1660–6.
(9) Isikoglu M, Berkkanoglu M, Cemal H, Ozgur K. Polycystic ovary syndrome: what is the role of obesity? In: Allahbadia GN, Agrawal R, editors. Polycystic ovary syndrome. UK: Anshan Publishers; 2006. p. 157–63.
(10) Balen A, Michelmore K. What is polycystic ovary syndrome? Are national views important? Hum Reprod 2002;17:2219–27.
(11) Barontini M, García-Rudaz MC, Veldhuis JD. Mechanisms of hypothalamic–pituitary–gonadal disruption in polycystic ovarian syndrome. Arch Med Res 2001;32:544–52.
(12) Borini A, Dal Prato L. The pathogenesis of infertility and early pregnancy loss in polycystic ovary syndrome. In: Allahbadia GN, Agrawal R, editors. Polycystic ovary syndrome. UK: Anshan Publishers; 2006. p. 221–32.
(13) Abdallah MA, Johnny A. The pathophysiology of polycystic ovary syndrome. In: Allahbadia GN, Agrawal R, editors. Polycystic ovary syndrome. UK: Anshan Publishers; 2006. p. 93–101.
(14) McCartney CR, Eagleson CA, Marshall JC. Regulation of gonadotropin secretion: implications for polycystic ovary syndrome. Semin Reprod Med 2002;20:317–36.
(15) Ropelato MG, Garcia-Rudaz MC, Castro-Fernandez C, Ulloa-Aguirre A, Escobar ME, Barontini M, et al.. A preponderance of basic luteinizing hormone (LH) isoforms accompanies inappropriate hypersecretion of both basal and pulsatile LH in adolescents with polycystic ovarian syndrome. J Clin Endocrinol Metab 1999;84:4629–36.
(16) Emperauger B, Kuttenn F. Polycystic ovarian dystrophies. Diagnostic criteria and treatment. Presse Med 1995;24:863–8 [in French].
(17) Cumming DC, Reid RL, Quigley ME, Rebar RW, Yen SS. Evidence for decreased endogenous dopamine and opioid inhibitory influences on LH secretion in polycystic ovary syndrome. Clin Endocrinol (Oxf) 1984;20:643–8.
(18) Spritzer PM, Poy M, Wiltgen D, Mylius LS, Capp E. Leptin concentrations in hirsute women with polycystic ovary syndrome or idiopathic hirsutism: influence on LH and relationship with hormonal, metabolic, and anthropometric measurements. Hum Reprod 2001;16:1340–6.
(19) ESHRE/ASRM. ESHRE/ASRM Rotterdam Consensus Meeting Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41–7.
(20) Marshall JC, Eagleson CA. Neuroendocrine aspects of polycystic ovary syndrome. Endocrinol Metab Clin North Am 1999;28:295–324.
(21) Legro RS, Driscoll D, Strauss III JF, Fox J, Dunaif A. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. PNAS 1998;95:14956–60.
(22) Barnes RB. The pathogenesis of polycystic ovary syndrome: lessons from ovarian stimulation studies. J Endocrinol Invest 1998;21:567–79.
(23) Nelson VL, Qin Kn KN, Rosenfield RL, Wood JR, Penning TM, Legro RS, et al.. The biochemical basis for increased testosterone production in theca cells propagated from patients with polycystic ovary syndrome. J Clin Endocrinol Metab 2001;86:5925–33.
(24) Nair S. Hirsutism and acne in polycystic ovary syndrome. In: Allahbadia GN, Agrawal R, editors. Polycystic ovary syndrome. UK: Anshan Publishers; 2006. p. 175–90.
(25) van der Spuy ZM, Dyer SJ. The pathogenesis of infertility and early pregnancy loss in polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol 2004;18:755–71.
(26) Charnvises K, Weerakiet S, Tingthanatikul Y, Wansumrith S, Chanprasertyothin S, Rojanasakul A. Acanthosis nigricans: clinical predictor of abnormal glucose tolerance in Asian women with polycystic ovary syndrome. Gynecol Endocrinol 2005;21:161–4.
(27) Kevenaar ME, Themmen AP, van Kerkwijk AJ, Valkenburg O, Uitterlinden AG, de Jong FH, et al.. Variants in the ACVR1 gene are associated with AMH levels in women with polycystic ovary syndrome. Hum Reprod 2009;24:241–9.
(28) Franks S, Mason H, Willis D. Follicular dynamics in the polycystic ovary syndrome. Mol Cell Endocrinol 2000;163:49–52.
(29) Goldzieher JW, Green JA. The polycystic ovary. I. Clinical and histologic features. J Clin Endocrinol Metab 1962;22:325–38.
(30) Webber LJ, Stubbs S, Stark J, Trew GH, Margara R, Hardy K, et al.. Formation and early development of follicles in the polycystic ovary. Lancet 2003;362:1017–21.
(31) MacDougall MJ, Tan SL, Jacobs HS. In-vitro fertilization and the ovarian hyperstimulation syndrome. Hum Reprod 1992;7:597–600.
(32) Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. Hum Reprod 2002;17:2858–64.
(33) Wood JR, Ho CK, Nelson-Degrave VL, McAllister JM, Strauss 3rd JF. The molecular signature of polycystic ovary syndrome (PCOS) theca cells defined by gene expression profiling. J Reprod Immunol 2004;63:51–60.
(34) Davies MJ. Evidence for effects of weight on reproduction in women. Reprod Biomed Online 2006;12:552–61.
(35) Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005;90:1929–35.
(36) Zeyneloglu HB, Esinler I. Chronic complications of polycystic ovary syndrome. In: Allahbadia GN, Agrawal R, editors. Polycystic ovary syndrome. UK: Anshan Publishers; 2006. p. 102–12.
(37) Glueck CJ, Papanna R, Wang P, Goldenberg N, Sieve-Smith L. Incidence and treatment of metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome. Metabolism 2003;52:908–15.
(38) Allahbadia GN, Merchant R. PCOS in the Indian subcontinent. Semin Reprod Med 2008;26:22–34.
(39) Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanisms and implication for pathogenesis. Endocr Rev 1997;18:774–800.
(40) Legro RS, Castracane VD, Kauffman RP. Detecting insulin resistance in polycystic ovary syndrome: purposes and pitfalls. Obstet Gynecol Surv 2004;59:141–54.
(41) Vignesh JP, Mohan V. Polycystic ovary syndrome: a component of metabolic syndrome? J Postgrad Med 2007;53:128–34.
(42) Dogan E, Gulekli B. The role of serum leptin elevation in obese women with polycystic ovary syndrome. In: Allahbadia GN, Agrawal R, editors. Polycystic ovary syndrome. UK: Anshan Publishers; 2006. p. 164–72.
(43) Waterworth DM, Bennett ST, Gharani N, McCarthy MI, Hague S, Batty S, et al.. Linkage and association of insulin gene VNTR regulatory polymorphism with polycystic ovary syndrome. Lancet 1997;349:986–90.
(44) Abbott DH, Dumesic DA, Franks S. Developmental origin of polycystic ovary syndrome – a hypothesis. J Endocrinol 2002;174:1–5.
(45) Witchel SF, Smith R, Tomboc M, Aston CE. Candidate gene analysis in premature pubarche and adolescent hyperandrogenism. Fertil Steril 2001;75:724–30.
(46) Bach LA. The insulin-like growth factor system: basic and clinical aspects. Aust N Z J Med 1999;29:355–61.
(47) Andersen PH, Kristensen K, Pedersen SB, Hjollund E, Schmitz O, Richelsen B. Effects of long-term total fasting and insulin on

ob gene expression in obese patients. Eur J Endocrinol 1997;137:229–33.
(48) Conn JJ, Jacobs HS, Conway GS. The prevalence of polycystic ovaries in women with type 2 diabetes mellitus. Clin Endocrinol (Oxf) 2000;52:81–6.
(49) Jamal K, Ozgur K. Predictors of dyslipidemia in women with polycystic ovary syndrome. In: Allahbadia GN, Agrawal R, editors. Polycystic ovary syndrome. UK: Anshan Publishers; 2006. p. 193–202.
(50) Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999;84:165–9.
(51) Dahlgren E, Janson PO, Johansson S, Lapidus L, Oden A. Polycystic ovary syndrome and risk for myocardial infarction. Evaluated from a risk factor model based on a prospective population study of women. Acta Obstet Gynecol Scand 1992;71:599–604.
(52) Agarwal SK, Vogel K, Weitsman SR, Magoffin DA. Leptin antagonizes the insulin-like growth factor-I augmentation of steroidogenesis in granulosa and theca cells of the human ovary. J Clin Endocrinol Metab 1999;84:1072–6.
(53) Machtinger R, Seidman D. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. In: Allahbadia GN, Agrawal R, editors. Polycystic ovary syndrome. UK: Anshan Publishers; 2006. p. 33–7.
(54) Ridker PM. Clinical application of C-reactive protein for cardiovascular disease: detection and prevention. Circulation 2003;107:363–9.
(55) Hahn S, Tan S, Elsenbruch S, Quadbeck B, Herrmann BL, Mann K, et al.. Clinical and biochemical characterization of women with polycystic ovary syndrome in North Rhine-Westphalia. Horm Metab Res 2005;37:438–44.
(56) Norman RJ, Masters L, Milner CR, Wang XJ, Davies MJ. Relative risk of conversion from normoglycemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. Hum Reprod 2001;16:1995–8.
(57) Wijeyaratne CN, Waduge R, Arandara D, Arasalingam A, Sivasuriam A, Dodampahala SH, et al.. Metabolic and polycystic ovary syndromes in indigenous South Asian women with previous gestational diabetes mellitus. BJOG 2006;113:1182–7.
(58) Gadducci A, Gargini A, Palla E, Fanucchi A, Genazzani AR. Polycystic ovary syndrome and gynecological cancers: is there a link? Gynecol Endocrinol 2005;20:200–8.
(59) Navaratnarajah R, Pillay OC, Hardiman P. Polycystic ovary syndrome and endometrial cancer. Semin Reprod Med 2008;26:62–71.
(60) Legro RS. Detection of insulin resistance and its treatment in adolescents with polycystic ovary syndrome. J Pediatr Endocrinol Metab 2002;15(Suppl. 5):1367–78.
(61) Arora S, Allahbadia GN. Early origins of polycystic ovary syndrome. In: Allahbadia GN, Agrawal R, editors. Polycystic ovary syndrome. UK: Anshan Publishers; 2006. p. 3–12.
(62) Ibáñez L, Díaz R, López-Bermejo A, Marcos MV. Clinical spectrum of premature pubarche: links to metabolic syndrome and ovarian hyperandrogenism. Rev Endocr Metab Disord 2009;10:63–76.
(63) Otto-Buczkowska E, Jarosz-Chobot P, Deja G. Early metabolic abnormalities–insulin resistance, hyperinsulinemia, impaired glucose tolerance and diabetes, in adolescent girls with polycystic ovarian syndrome. Przegl Lek 2006;63:234–8 [in Polish].
(64) Glueck CJ, Morrison JA, Wang P. Insulin resistance, obesity, hypofibrinolysis, hyperandrogenism, and coronary heart disease risk factors in 25 pre-perimenarchal girls age < or = 14 years, 13 with precocious puberty, 23 with a first-degree relative with polycystic ovary syndrome. J Pediatr Endocrinol Metab 2008;21:973–84.
(65) Abbott DH, Tarantal AF, Dumesic DA. Fetal, infant, adolescent and adult phenotypes of polycystic ovary syndrome in prenatally androgenized female rhesus monkeys. Am J Primatol 2009;71:776–84.
(66) Abbott DH, Barnett DK, Bruns CM, Dumesic DA. Androgen excess fetal programming of female reproduction: a developmental aetiology for polycystic ovary syndrome? Hum Reprod Update 2005;11:357–74.
(67) Schleussner E. Intrauterine programming of reproductive function – a valid concept? Gynakol Geburtshilfliche Rundsch 2009;49:2–7 [in German].
(68) Dumesic DA, Abbott DH, Padmanabhan V. Polycystic ovary syndrome and its developmental origins. Rev Endocr Metab Disord 2007;8:127–41.
(69) Wells JC, Chomtho S, Fewtrell MS. Programming of body composition by early growth and nutrition. Proc Nutr Soc 2007;66:423–34.
(70) Oken E, Gillman MW. Fetal origins of obesity. Obes Res 2003;11:496–506.
(71) Yajnik CS. Early life origins of insulin resistance and type 2 diabetes in India and other Asian countries. J Nutr 2004;134:205–10.
(72) Franks S, Gharani N, McCarthy M. Genetic abnormalities in polycystic ovary syndrome. Ann Endocrinol (Paris) 1999;60:131–3.
(73) Strauss 3rd JF. Some new thoughts on the pathophysiology and genetics of polycystic ovary syndrome. Ann NY Acad Sci 2003;997:42–8.
(74) Urbanek MT. He genetics of the polycystic ovary syndrome. Nat Clin Pract Endocrinol Metab 2007;3:103–11.
(75) Legro RS, Strauss JF. Molecular progress in infertility: polycystic ovary syndrome. Fertil Steril 2002;78:569–76.
(76) Arora S, Allahbadia GN. Familial associations in women with polycystic ovary syndrome. In: Allahbadia GN, Agrawal R, editors. Polycystic ovary syndrome. UK: Anshan Publishers; 2006. p. 85–90.
(77) Kaushal R, Parchure N, Bano G, Kaski JC, Nussey SS. Insulin resistance and endothelial dysfunction in the brothers of Indian subcontinent Asian women with polycystic ovaries. Clin Endocrinol (Oxf) 2004;60:322–8.
(78) Sanders EB, Aston CE, Ferrell RE, Witchel SF. Inter- and intrafamilial variability in premature pubarche and polycystic ovary syndrome. Fertil Steril 2002;78:473–8.
(79) Mathur R, Alexander CJ, Yano J, Trivax B, Azziz R. Use of metformin in polycystic ovary syndrome. Am J Obstet Gynecol 2008;199:596–609.
(80) Hart R. Definitions, prevalence and symptoms of polycystic ovaries and the polycystic ovary syndrome. In: Allahbadia GN, Agrawal R, editors. Polycystic ovary syndrome. UK: Anshan Publishers; 2006. p. 15–26.
(81) Arslanian SA, Lewy V, Danadian K, Saad R. Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. J Clin Endocrinol Metab 2002;87:1555–9.
(82) Pillai A, Bang H, Green C. Metformin and glitazones: do they really help PCOS patients? J Fam Pract 2007;56:444–53.
(83) Essah PA, Wickham EP, Nestler JE. The metabolic syndrome in polycystic ovary syndrome. Clin Obstet Gynecol 2007;50:205–25.
(84) Ho FL, Liew CF, Cunanan EC, Lee KO. Oral hypoglycaemic agents for diabetes in pregnancy – an appraisal of the current evidence for oral anti-diabetic drug use in pregnancy. Ann Acad Med Singapore 2007;36:672–8.
(85) Stadtmauer L, Oehninger S. Management of infertility in women with polycystic ovary syndrome: a practical guide. Treat Endocrinol 2005;4:279–92.
(86) Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-

inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev 2010;20(1):CD003053.
(87) Tarlatzis BC, Fauser BC, Legro RS, Norman RJ, Hoeger K, Pasquali R, et al.. Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril 2008;89:505–22.
(88) Farquhar CM. The role of ovarian surgery in polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol 2004;18:789–802.
(89) Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertil Steril 2009;92:1966–82.