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Polycystic Ovary Syndrome

Ingrid Dravecká and Ivica Lazúrová
Department of Internal Medicine, Medical Faculty, University Košice
Slovakia

1. Introduction

1.1 Definition

Polycystic ovary syndrome (PCOS) is a remarkably common disorder of premenopausal women with a prevalence of 5-10%. Besides reproductive endocrine abnormalities, including amenorrhea or oligomenorrhea, hyperandrogenism and infertility, patients with PCOS often show an insulin resistance and beta-cell dysfunction (1).

1.2 Diagnostic criteria

The condition was described by Stein and Leventhal in 1935. There is a considerable controversy on the optimal criteria for PCOS. Although the **NIH** (National Institute of Health) **criteria** as hyperandrogenic anovulatory PCOS were proposed in 1992, these have now expanded to **non NIH criteria** including hyperandrogenic ovulatory to non-hyperandrogenic anovulatory PCOS (2). After a meeting between ESHRE (European Society for Human Reproduction and Embryology) and ASRM (American Society for Reproductive Medicine) in Rotterdam in 2003, a new set of criteria for PCOS was proposed, commonly refered to as **Rotterdam criteria**: 1. irregular/no ovulations, 2. clinical/paraclinical hyperandrogenemia and 3. polycystic ovaries. Two out of the three criteria need to be fulfilled and other causes of hyperandrogenemia should by excluded. The Rotterdam criteria are curently debated because they introduced two new fenotypes (3). It is known that the metabolic disturbances of PCOS are more pronounced in hyperandrogen patients compared to patients with no hyperandrogenemia in genetic studies. In 2006 AES (Androgen Excess Society) published a position statement which suggested that androgen excess is the key component of PCOS related to clinical symptoms and long–term morbidity. According to **AES**, diagnostic **criteria** should be modified to include only those with hyperandrogenism and polycystic ovary or ovarian dysfunction (2). This definition excluded the phenotype subset of polycystic ovary and ovarian dysfunction without hyperandrogenism.

NIH criteria covered first two phenotypes: A and B, Rotterdam criteria covered all four phenotypes (including non hyperandrogenic anovulatory polycystic ovary) and finally AES criteria excluded non-hyperandrogenic phenotype Table 1 (2).

These criteria recognize that PCOS is a functional disorder in which ovarian hyperandrogenism can occur in the presence or absence of ovarian morphologic changes. However, according to Rotterdam criteria or AES criteria, polycystic ovaries need not to be

present to make a diagnosis of PCOS and controversely their presence alone does not establish the diagnosis of PCOS (2).

Features	Phenotypes						
	A	B	C	D	E	F	G
Hyperandrogenism (biochemical/clinical)	+	+	+	-	+	-	-
Oligo - or anovulation	+	+	-	+	-	-	+
Polycystic ovaries	+	-	+	+	-	+	-
NIH criteria	√	√					
ESHRE/ASRM criteria	√	√	√	√			
AES criteria	√	√	√				

Table 1. Comparison of the different reproductive diagnostic criteria for PCOS resulting in potentially different phenotypes (2)

1.3 Ethiopathogenesis

Although exact pathogenic mechanisms of PCOS are still not completely rocognised, most of factors involved in the development of PCOS can be devided into following groups:

- Aberration of gonadotropic secretion
- Genetics
- Environmental factors
- Hyperinsulinemia and insulin resistance

1.4 Aberration of gonadotropic secretion

It is well known, that gonadotropin-releasing hormone (GnRH) pulse frequency is accelerated in PCOS. However, it is not clear whether this accelerated pulse frequency is primarily or secondarily to the relatively low levels of progesterone resulting in rare ovulatory events. Both situations lead to an increase luteinizing hormone (LH) levels resulting in increased ovarian androgen production (4).

1.5 Genetics

Lines of evidence suggest that PCOS is a heritable disorder. Various approaches have been undertaken to try to define a specific genetic etiology. While a number of candidate genes appear to make modest contributions to the clinical expression of PCOS, no single gene has been confidentaly identified to play a predominant role in the pathogenesis of PCOS.

Family studies showed a PCOS prevalence of 25-50% in first degree relatives of patients with PCOS, suggesting a strong inheritance of PCOS. PCOS is a heterogenous disease and the genetic profile of different phenotypes may differ (5). In the study of Franks et al. authors compared metabolic and hormonal parametres of probands with PCOS and oligoamenorrhea with affected sisters with ultrasound findings of polycystic ovary. Although affected sisters had fewer symptoms that probands, serum testosterone, LH and insulin sensitivity index were similar in both groups. Affected sisters had also the higher frequency of oligomenorrhea, hirsutism and other hyperandrogenic symptoms. Thus authors demostrated a moderate to high heritability for all traits studied in affected pairs Figure 1, Figure 2 (6).

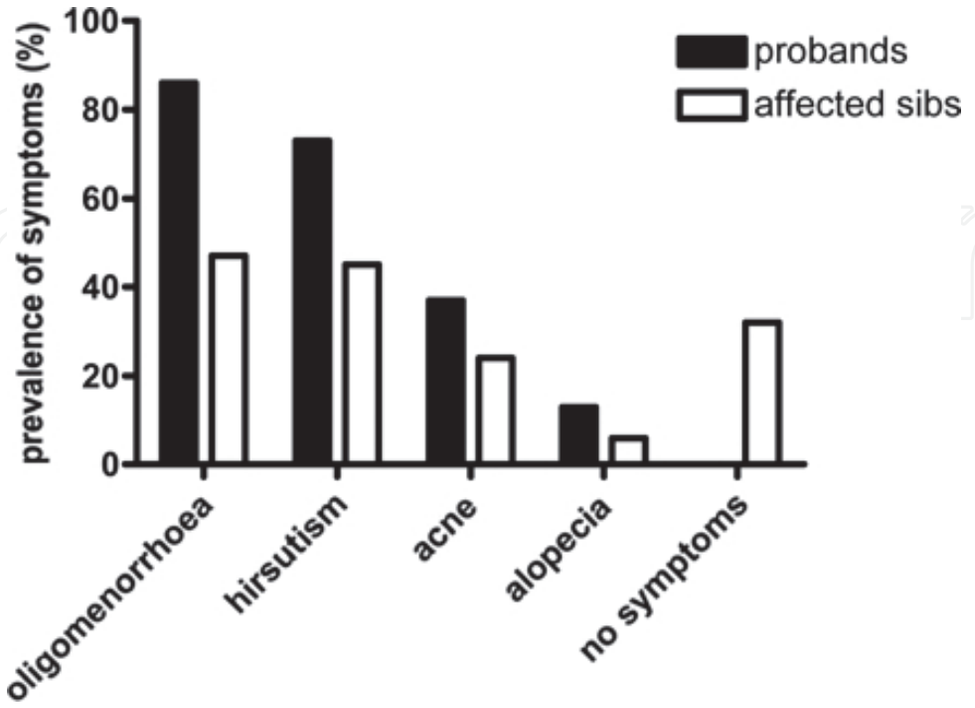

Fig. 1. Distribution of symptoms in probands with PCOS and affected sisters (6).

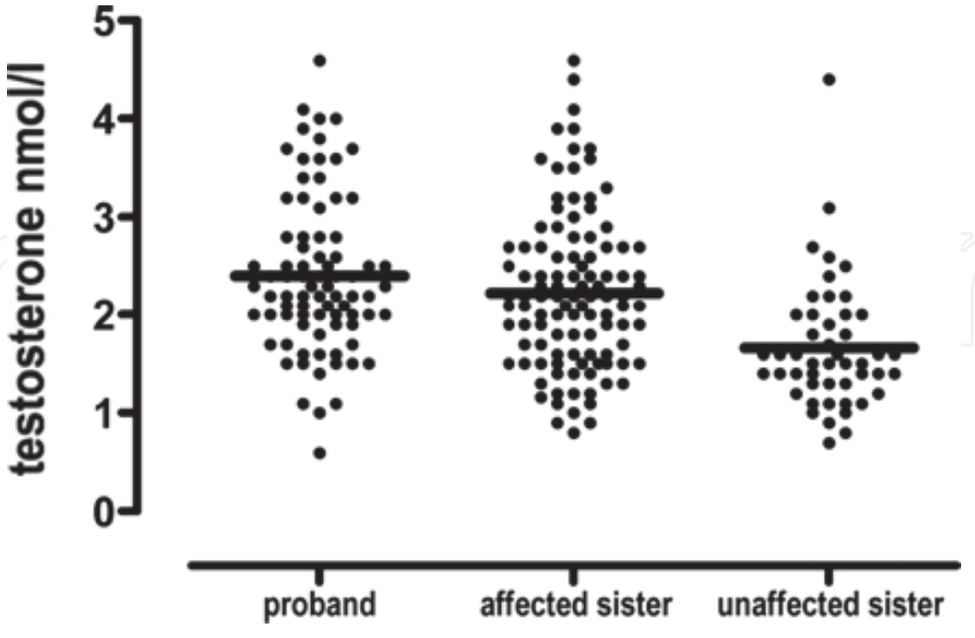

Fig. 2. Serum testosterone concentrations in individual probands, affected sisters, and unaffected sisters (6).

The most commonly used method for evaluation of the genetic profile in PCOS has been the candidate gene approach. Using this approach, severel genes involved in androgen synthesis, secretion, metabolism and regulation have been evaluated along with group of genes affecting insulin resistance, insulin secretion and inflammation. Candidate genes studies however brought only few informations. Genome wide association studies are likely to be more informative. Recent sudies therefore applied DNA microarrays to evaluate differences in gene expresion in different tissues between PCOS patients and controls. Results of these studies may be used to achieve new knowledge of the pathogenesis of PCOS which is still unknown. Like other common dissease such as diabetes mellitus type 2, PCOS is most likely a multigenetic dissease with several genes having small and additive effect.
Locus on chromosome 19p13 2 appears to be most promissing candidate gene locus. Genes involved in the serin phosphorylation of the insulin receptor (INS VNTR, CYP 11), PPAR-gamma, calpain 10 (CAPN10) and genes coding for sex hormone binding globuline (SHBG), androgen receptor and insulin receptor substrate play an important role in the PCOS susceptibility (1). PCOS is a heterogenous disease and the genetic profile of different fenotypes may differ (5).

1.6 Environmental factors

Low birth weight is associated with an icreased risk of insulin resistance and diabetes mellitus type 2. Given the association between insulin resistance and hyperandrogenemia in patients with PCOS, low birth weight may therefore be associated with an increased risk for PCOS. Studies by Prof. Ibanez documented that girls that later developed PCOS had significantly lower birth weight than controls (7). However, in population studies low birth weight was associated with insulin resistance but not with hyperandrogenemia or with adrenal acitivity. These studies support that PCOS is not caused by low birth weight alone, but is more likely the result of interaction between genetic and environmental factors. There are speculations about influence of androgen exposure to development of fetal hyperandrogenic state (8). It is well known that lifestyle can modify PCOS phenotype. Environmental factors can be devided into the exogenous i.e. food, vitamin D deficiency, exposure to bisphenol A (PBA) – for example in study of Diamanti – Kadarakis PCOS women had significantly higher levels of PBA as compared to normal women (9). Among endogenous factors the most important are ethnicity, age, glycemia, insulin sennsitivity and many others.

1.7 Hyperinsulinemia and insulin resistance

The link between PCOS and insulin resistance was first described in 1980 and has later been confirmed in many studies. The exact mechanism of insulin resistance in patients with metabolic syndrome is however still unknown. Some patients have increased serine phosphorylation of beta subunit of insulin receptor but also distant parts of the insulin receptor cascade are affected (10). Some authors documented impaired glycogen synthase activity which was confirmed by studies on muscle biopsies from patients with PCOS. Impaired glucose metabolism in PCOS represents probably primary not secondary mechanism. Hyperinsulinaemia is frequently seen in obese PCOS but also in some lean PCOS women. Insulin sensitivity has been described to be reduced by 50% in lean PCOS patients which was statisticaly significant (11). Insulin stimulates p450c17 activity in

ovaries and adrenals leading to increased androgen production. In addition, hyperinsulinemia decreases the hepatic SHBG production and through this mechanism free testosterone levels increases. Low SHBG is a good predictor of PCOS and is associated with impaired insulin sensitivity. The pathogenesis of PCOS may be looked as a vicious cycle involving both hyperandrogenaemia and insulin resistance/ hyperinsulinemia. Insulin resistance induces hyperinsulinemia and subsequently stimulates the ovarian and adrenal hormonal production, inhibits SHBG production and testosterone activity increases Figure3 (5).

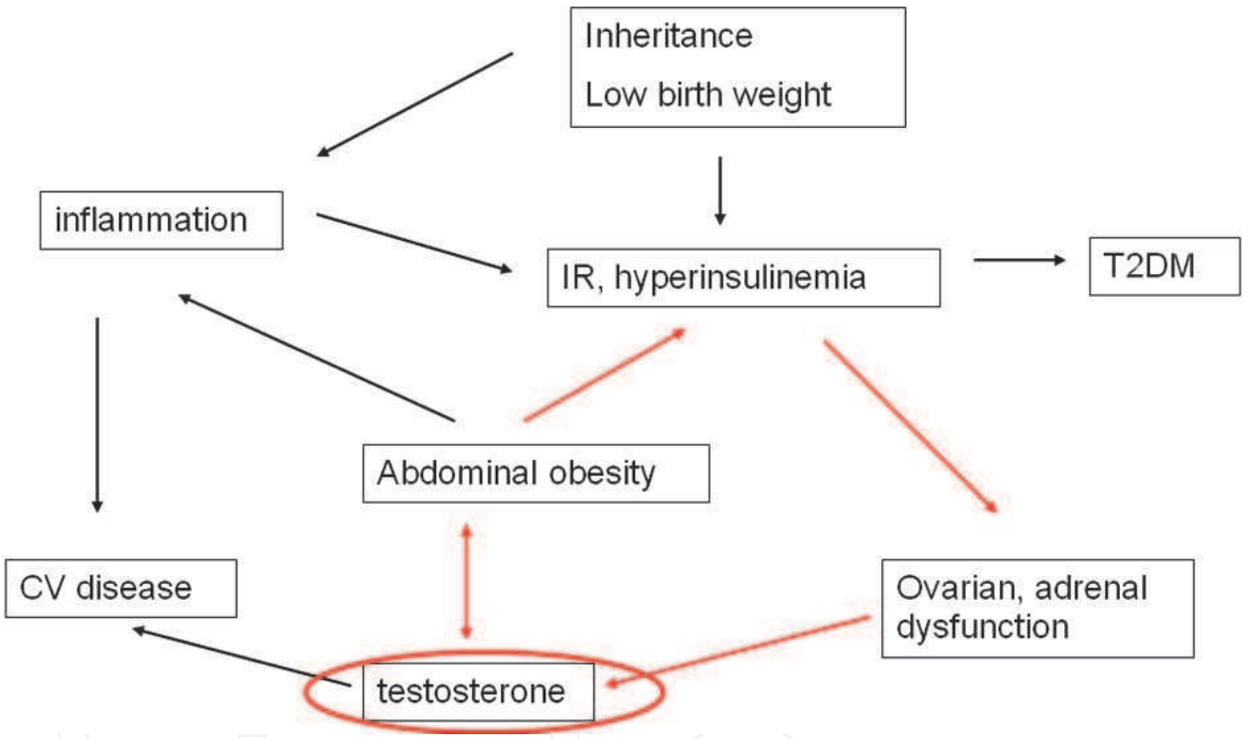

Fig. 3. Hyperinsulinemia and hyperandrogenemia as a vicious cycle in PCOS (5) CV-cardiovascular, IR insulin resistance, T2M – type 2 diabetes mellitus

Obesity and body fat distribution have an important influence on insulin sensitivity**.** Although 50% of PCOS women are not obese, obesity could potentially contribute to insulin resistance in PCOS. Lean PCOS women seem to have an insulin resistance that intrinsic to the syndrome, while in obese PCOS patients obesity additionally contributes to the impairment of the glucose metabolism (1). Elucidating the pathogenesis of insulin resistance in PCOS will provide insight into an important cause of type 2 diabetes (39).

Body composition and fat metabolism in PCOS

Approximately 75% patients with PCOS are overweight, but a high waist-to-hip ratio (WHR) indicating increased abdominal fat mass is seen in both normal and overweight

patients with PCOS (5). There are only few studies concerning the correlations between phenotypic expression, body composition and PCOS, and relationship with the processes of growth and sexual maturation and various environmental factors (nutrition, physical activity, stress, and other factors). Variation in human body composition and shape ranges considerably: many body size and shape indices (height, weight, body composition, and proportions) are the result of long evolution process and adaptation to environment. Obviously, the morphological body parameters, physiological and biochemical indices are complex and compound the interdependent system. If waist circumference and WHR of women with PCOS increase, reproductive function and metabolic state of a woman is altered more than in cases when there are no changes in these parameters. The investigations of the strongest sexual dimorphism sign – the subcutaneous and visceral fat topography – showed that women with PCOS have greater adipose tissue mass in the areas of the abdomen, waist, and upper arms than control women (12).

Ghrelin and cholecystokinin secretion following meals are impaired in PCOS, suggesting changed appetite regulation. In a study of Glintborg et al. the prevalence of eating disorder was 36,3% in women presenting hirsutism, and controversely, PCOS was overrepresented in bulimic women (5). The genetic property of subclinical eating behaviour and the link between subclinical eating behaviour and PCOS has been studied before but the role of leptin within this connection has never been investigated. In the study of Jahanfar et al., serum leptin level correlated significantly with bulimia score. The genetic property of subclinical eating disorder was not confirmed. Leptin was linked with both subclinical eating disorder and PCOS (13).

In the study of Puder et al., PCOS women had significantly higher trunk to fat ratio (T/E fat) as compared with body mass index matched women, they also had higher values of inflammatory markers such as highly sensitive C-reactive protein (hsCRP), procalcitonin, tumor necrosis factor alpha (TNF-alpha). Additional adjusting to T/E fat eliminated the effect of PCOS on insulin resistance and inflammatory markers. They conclude that the increase in inflamatory markers in PCOS women is primarly associated with increased central fat excess rather than PCOS per se (14). Among other considerations, anomalies of plasma growth hormone (GH) secretion and/or altered insulin growth factor I (IGF-I) concentrations may play role in the pathogenesis of PCOS. Abdominal obesity, which can exacerbate the insulin resistance and reproductive features of the syndrome, is associated with profoundly reduced and disorderly GH secretion. A stimulatory role of GH in early and later stages of folliculogenesis and ovulation, hyposomatotropism may contribute to impaired follicular development and anovulation in PCOS (15). Increased intra-abdominal fat is of central importance in PCOS as it affects GH secretion, insulin resistance, lipid metabolism, and inflammatory status. Life style modification and weight loss improves ovulation rate and fertility and testosterone levels are decreased (5).

Inflammation

PCOS is a proinflamatory state as evidenced by elevated plasma concentrations of hsCRP. In obesity-related diabetic syndrome, TNF alpha is overexpressed in adipose tissue and induces insulin resistance through acute and chronic effects on insulin sensitive tissues. Chronic exposure to TNF-alfa decreases the expression of glucose transporter 4 (GLUT4), the insulin-sensitive glucose transport protein. Because decreased GLUT4 expression has been identified in PCOS, it is possible that TNFalpha contributes to this postreceptor defect.

The source of excess circulating TNFalpha in PCOS is likely to be adipose tissue in the obese. In lean women with PCOS increased visceral adiposity has been proposed as a source of excess TNFalpha (16).
Systemic review and metaanalysis of relevant studies suggest that adiponectin is lower in women with PCOS compared with non-PCOS controls of similar body mass index (BMI). Lower adiponectin levels are associated with the insulin resistance observed in women with PCOS compared with controls. It has been demonstrated that the more insulin resistant women with PCOS recruited, the lower serum adiponectin levels were found (17).
In PCOS previous studies showed positive associations between leptin and BMI, waist circumference and insulin resistance, indicating that fat mass in PCOS is the most important predictor of leptin secretion in PCOS and this data do not support a pathogenic role of leptin in PCOS. Chemokines such as migration inhibitor factor (MIF), monocyte chomatractant protein (MCP-1) and macrophage inflammatory protein (MIP) are increased and in some studies and well correlated with testosterone levels in PCOS patients (5, 16).

Cardiovascular risk factors in PCOS

High percentage of patients with PCOS have abnormal lipid profiles including increased total cholesterol (TC), low densitiy lipoprotein cholesterol (LDL-C), whereas high density cholesterol (HDL-C) levels are decreased. Patients with PCOS have increased prevalence of coronary atherosclerosis and echocardiography abnormalities but no prospective studies exist in PCOS populations. Retrospective studies found significantly increased risk of hypertension and cardiovascular disseases and current estimated risk for cardiovascular disseases is 4-11 fold increased in PCOS. Patients with PCOS have 5-7 fold higher risk for acute myocardial infarction, however no prospective studies exist until this time. There is increased CD36 which is expressed on the surface of monocytes and macrophages. In addition increased CD36, plasminogene activator inhibitor (PAI-1), homocystein were reported to be higher in women with PCOS. Previous studies did not found any differences in interleukin 6 (IL-6) between patients with PCOS and controls and no effect of metformin or glitazone treatment (1, 5). HsCRP is secreted in response to cytokines including IL-6. Despite the fact that data are inconsistent, increased levels of hsCRP in patients with PCOS were reported in some previous studies. HsCRP positively correlated with DEXA scan whereas no correlation was observed with testosterone levels. Pioglitazone-mediated improvement of insulin sensitivity was accompanied by decreased hsCRP levels (5, 18). Young women with PCOS mostly have a normal blood pressure, while especially older, obese patienst with PCOS suffer from an elevated blood pressure. In contrast to adolescent with PCOS who mostly have still normal lipid profiles, women with PCOS often have a dyslipidemia (1).

Risk of type 2 diabetes mellitus

PCOS is powerful risk factor for impaired glucose tolerance and type 2 diabetes mellitus. Insulin-resistant patients with PCOS maintain normal glucose levels by an insulin hypersecretion. These patients are at an icreased risk of beta cell exhaustion and development of type 2 diabetes mellitus (19). In study of women with PCOS the prevalance of diabetes mellitus was up to 7,5% and impaired glucose tolerance was 31% (1,20). Metaanalysis of clinical studies has been performed by Moran et al. Totaly 2 192 studies were reviewed and 35 were selected for final analysis. Results showed an increased

prevalence of impaired glucose tolerance and type 2 diabetes mellitus and metabolic syndrome in both BMI and non BMI-matched studies Table 2 (21).

	OR non BMI	BMI-matched
IGT	2,48	2,58
DMt2	4,43	4,0
MS	2,88	2,2

Table 2. Prevalence of impaired glucose tolerance (IGT) and type 2 diabetes mellitus (DMt2) and metabolic syndrome (MS) in BMI and non BMI-matched studies (21)

Other risks of PCOS

Among risks related to pregnancy there was documented a higher prevalence of gestational diabetes mellitus, which was significantly higher than that in control group of women. Moreover, patients with PCOS have significantly higher risk of pregnancy-induced hypertension, preeclampsia, neonatal complications and higher abortrtion rate. Women with PCOS seem to expierence increased risk of cesarean delivery and perinatal morbidity and mortality (22). There is also increased risk of breast cancer as well as endometrial cancer (33).

Bone mineral density (BMD) in PCOS

Several factors may contribute to the conserved BMD in PCOS. Patients with PCOS have relatively high levels of estradiol and are characterized by abdominal obesity and insulin resistance. Abdominal obesity and increased visceral fat mass are seen in overweight and normal-weight patients with PCOS. Adiposity is known to be positively associated with BMD. Furthermore, more than 50% of patients with PCOS are insulin resistant, and previous studies suggested that hyperinsulinemia, independent of BMI, may protect against the development of osteoporosis. Only few studies found positive associations between testosterone and BMD in PCOS, but this may in part be explained by the use of imprecise testosterone assays in most studies (23). In the study of Glintborg, treatment with pioglitazone of insulin-resistant premenopausal patients with PCOS was followed by significantly decreased BMD at the hip and lumbar spine and decreased markers of bone mineral turnover. These findings suggest that pioglitazone may have adverse effects on BMD even in a study population relatively protected from bone mineral loss (23).

Vitamin D and PCOS

Recent studies clearly documented that obesity is associated with decreased 25OH vitamin D levels. Patients with PCOS and metabolic syndrome had significantly lower levels of vitamin D2 being in negative correlation with fasting insulin and insulin sensitivity. Supporting the relative vitamin D insuficiency in PCOS some studies found a higher levels of parathormone (PTH) in these patients. Association between vitamin D receptor (VDR) gene polymorphisms (Apal) and insulin resistance, PTH, 25OH vitamin D is speculated. Some authors documented efficacy of vitamin D replacement on insulin resistance and in the treatmend of anovulation (24, 25, 26). Low serum 25OH vitamin D concentrations result from the presence of obesity and insulin resistance (24).

In the study of Wehr et al., the prevalance of vit D deficiency in 206 women affected by PCOS was 72.8%. PCOS women with metabolic syndrome had lower vit D levels than PCOS women without metabolic symptoms. In multivariate regression analysis 250HD and BMI were independent predictors of homeostatic model assessment-insulin resistance index (HOMA), vitamin D was also independent predictor of metabolic syndrome in PCOS. There was significant positive correlation of vitamin D levels SHBG and quantitative insulin sensitivity check index (QUICKI) and a negative one found with BMI, WHR, waist circumference, blood pressure, glucose, isnulin, HOMA-IR and triglycerides. Nevertheless large intervetion trial are needed to evaluate the effect of vit D supplementation on metabolic distubances in PCOS Table 3 (27).

Positive correlation of 25OHD

SHBG	0,009

Negative correlations of 25OHD

Waist circumference	0,001
Hip circumference	0,001
Blood pressure	0,05
Fasting glucose	0,001
Fasting insulin	0,001
HOMA IR	0,001
Triglycerides	0,002
CRP	0,005

Table 3. Correlations of vitamin 25OHD (27)

Autoimmunity and PCOS

There are some reports regarding the relationship between PCOS and autoimmune disorders. However, the data are controversial and some studies documented a higher prevalence of antihistone and anti ds-DNA antibodies in PCOS (28). Concerning organ-specific antibodies, one study clearly demonstrated a high prevalence of antibodies against thyroid specific components, higher prevalence of autoimmune thyroiditis and higher thyrotropin levels as well (29). There are so far no reports about antiovarian antibodies in patients with PCOS. There are speculations about the presence of antivorian simulating antibodies analogically to thyroid simulating antibodies (28). As was documented by the study of Janssen and colleagues, patients with PCOS had significantly higher frequency of antihyroid antibodies and ultrasound picture hypoechogenic thyroid gland (29).

2. Diagnosis of PCOS

Diagnostic approach in PCOS includes:
1. History taking and physical examination
2. Laboratory and hormonal evaluations
3. Ovarian ultrasonography

Physical examination includes: assessment of hirsutism using scoring scale of Feriman and Gallwey, measurment of blood pressure, waist and hip ratio.

Transvaginal ultrasonography is necessary to confirm polycystic ovaries.
Laboratory investigations include: total and free testosterone, SHGB, LH, FSH, prolactin, 17hydroxy-progesterone, dehydroepiandrosterone sulfate (DHEAS), fasting plasma glucose and lipids, TSH.
Secondary evaluation includes exclusion of suspected Cushing syndrome: 24 hours UFC, Dexamethasone supression test (overnight, 2 mg 2 days), oral glucose tolerance test if fasting blood glucose is between 5,6 - 7,0 mmol/l and magnetic resonance (computer tomography) of adrenal glands – if suspected virillizing tumor.

3. Treatment of PCOS

Various intervetions have been proposed ranging from life-style modifications, administration of pharmaceutical agents (such as clomiphene citrate, insulin sensitizing agents, gonadotropins and gonadotropin-releasing hormone analogues), the use of laparoscopic ovarian drilling and the application of assisted reproduction techniques (30).
Treatment is related to the preference of patient and includes:
1. Treatment of hirsutism or acne
2. Treatment of oligo/amenorrhea and infertility
3. Treatment of insulin resistance and metabolic syndrome

1. Treatment of hirsutism or acne

Combination of estrogene-progestin therapy in the form of ***oral contraceptives*** is the first line of endocrine treatment for hirsutism and acne. The estrogenic component is responsible for the supression of LH and thus serum androgen levels. It also results in increase of SHBG lowering the free fraction of testosterone. Assessment of adequacy of ovarian suppression can be made at the end of the third week after starting treatment. The effect on acne can be expected to be maximal in 1-2 months. However, the effect on hair growth may not be evident for 6 months and the maximum effect requires 9-12 months (31). ***Cyproterone acetate*** acts by competitive inhibition of the binding of testosterone and dihydrotestosterone to the androgen receptors. ***Spironolactone*** appears to be as effective an antiandrogen as cyproterone actetate in doses 100-200 mg daily. ***Flutamide*** is a potent nonsteroidal antiandrogen without progestational, estrogenic, corticoid, antigonadotropic effect (32, 33). ***Finasteride*** is a competitive inhibitor of type 2 5alpha-reductase and for this reason can be useful for the treatment of hirsutism (33, 34).
Gonadotropin-releasing hormone agonists *(GnRH agonists)* have been reported to be effective in the treatment of hirsutism. Their chronic administration supresses pituitary-ovarian function thus inhibiting both ovarian androgen and estrogen secretion. Addition of dexamethasone to leuprolide has been reported to further improve the response in some women with PCOS (33).
Recent randomized, prospecitve trial comparing low dose flutamide, finasteride, ketoconazole and combination cyproterone-acetate-ethinyl estradiol demonstrated relative superiority of flutamide and cyproterone acetate-ethinyl estradiol in the treatment of hirsutism (33).
Aims of treatment hirsutism or acne include:
- suppression of adrenal or ovarian androgen production
- alteration of binding of androgens to their plasma proteins
- impairment of the peripheral conversion of androgen precursors to active androgen
- inhibition of androgen action in peripheral tissues

2. Treatment of oligo/amenorrhea and infertility

Chronic oligoanovulation results in persistent stimulation of endometrial tissue by estrogen increasing the risk of endometrial cancer. A three-fold increased risk of endometrial cancer has been reported. Thus anovulatory women with PCOS are recommended to take progestins to reduce the risk of endometrial hyperplasia or carcinoma. The combined estrogene-progestin therapy is also beneficial in women with PCOS because in both inhibits endometrial proliferation and reduces ovarian androgen production (33). In some studies insulin sensitizing agents such as metformin and glitazone improved menstrual cycle irregularities, however their indication in case when patient does not wish to be pregnant is controversial and generally not recommended (30).

Clomiphene citrate remains still the first line therapy for induction of ovulation in women with PCOS. The usual regimen is 50 mg per day for 5 days beginning on cycle day 3 mg daily for 5 days, ovulation can be induced in about 80% of women (33). There are many reports about combined clomiphene citrate and metformin therapy, unfortunately with controversial results. In higher doses metformin together with clomiphene citrate significantly improved ovulation rate and pregnancy rate, however did not improved live birth rate. Those patients who fail clomiphene therapy will usually require either low dose human recombinant FSH or human menoapusal gonadotropin for ovulation induction. Pregnancy rate is similar to clomiphene citrate, but live birth rate is lower when compared with clomiphene citrate (30, 35, 36).

There has been renewed interest in surgically inducing ovulation in women with PCOS using laparoscopy and electrocautery or laser. Laparoscopic ovarian diathermy (LOD) is associated with lower multiple gestation rates than gonadotropins, because LOD can achieve unifollicular ovulation. There was no evidence of difference in live birth rate and miscarriage in women with clomiphene-resistant PCOS undergoing LOD versus gonadotropin treatment. LOD is an alternative to gonadotropin therapy for clomiphene-citrate resistant anovulatory PCOS. LOD restores menstrual regularity in 63%-85% of women, and the benefitial effects on reproductive outcomes seem to last for several years in many women (30, 37).

Progestins: reduce risk of endometrial cancer
Estrogene-progestin: inhibits endometrial proliferation, reduces androgen production
Clomiphene citrate: first line therapy (80% ovulation rate)
Human recombinant FSH: if clomiphene failed
Human menopausal gonadotropin
Aromatase inhibitors
Surgically induced ovulation: laparoscopy, electrocautery, laser (80% pregnancy rate, 80% conceptions within first 8 months)
In vitro fertilization

3. Treatment of insulin resistance and metabolic syndrome

Insulin resistance in women with PCOS appears more common than in the general population. Many studies show the common coexistence of obesity with insulin resistance, particulary in the presence of abdominal phenotype, although this disorder may be present even in those with normal weight. PCOS-related insulin resistance is partly independent of the presence of obesity, and that obesity in PCOS women simply adds and additional deterious effects on insulin sensitivity, by mechanisms that have still not been defined and could be different between obese and non-obese PCOS women (38). In women with PCOS,

basal insulin secretion is increased and hepatic insulin clearance is reduced, resulting in hyperinsulinemia. Obesity and PCOS have a synergistic negative impact on insulin senzitivity. In both obese and non-obese PCOS women , insulin secretion is inappropriately low for their degree od insulin resistance, suggesting the presence of pancreatic beta-cell dysfunction. There is a positive association between insulin and androgen levels in their PCOS subjects (39). Insulin resistance also appears to play a pathogenic role in the metabolic syndrome. Metabolic syndrome and its components are common in women with PCOS, placing them at increased risk for cardiovascular disease (40). Women with PCOS have 11-fold increase in the prevalence of metabolic syndrome compared with age-matched controls (41).

As noted, lowering insulin levels with weight reduction or drugs may induce ovulation in obese, hyperinsulinemic women with PCOS. Weight loss prior to improves live birth rate in obese women with or without PCOS. Multiple observation studies have noted that weight loss is associated with improved spontaneous ovulation rates in women with PCOS, while pregnancies have been reported after losing as little as 5% of initial body weight. However weight loss is recommended for those who are overweight with a body mass index over 25-27 kg/m2 (30, 33).

Insulin resistance is regarded as a major pathophysiological feature of the syndrome. Therefore, agents that improve insulin sensitivity, that is, metformin ant thiazolidinediones (TZDs), have been extensively trialled in PCOS patients with encouraging results (42).

Metformin treatment and PCOS

Metformin is a biguanide agent used in the treatment of type 2 diabetes mellitus. In women with PCOS, metformin was sparked by the recognition of its pleiotropic actions on several tissues. It lowers serum insulin levels and improves insulin sensitivity not only by its glucose lowering effect but also by increasing peripheral glucose utilization. Apart from its action on classic insulin-sensitive tissues, it has been clearly demonstrated that metformin has a positive effect in the treatment of reproductive abberations in women with PCOS, which indirectly suggests a potential direct effect at the ovarian level. Metformin treatment increases ovulation rate, improves menstrual cyclicity, and reduces serum androgen levels in these patients (38). Metformin appears to affect ovarian function in a dual mode through the elevation of insulin excess acting upon the ovary and through direct ovarian effects. Regarding the action of metformin on theca cells, data demonstrate reduced CYP17 activity in women with PCOS. In rat granulosa cells, metformin treatment was shown to reduce basal and FSH-stimulated progesterone and estradiol production (43). Metformin may exert a direct effect on granulosa cells through activation of 5´-adenosine monophosphate activated protein kinase (AMPK) and subsequent reduction of steroid production (44). Stimulation of AMPK appears to be a key mediator of metformin´s action on hepatic gluconeogenesis and lipogenesis (43). The analysis of follicular fluid seemed to confirm that metformin acts directly on the ovary improving local levels of androgens, ovarian insulin resistance and the levels of several growth factors, Figure 4 (52).

Metformin restores ovulation in a significant proportion of patients with PCOS and has resulted in pregnancy. Metformin pretreatment improves the efficacy of clomiphene-citrate on PCOS patients with clomiphene-citrate resistance (19, 33). The target dose is 1500-2550 mg/day. Clinical response is usually seen at the dose of 1000 mg daily (33). Recent small studies also suggest that metformin continued during pregnancy reduces the high rates of gestational diabetes and first-trimester spontaneous abortion characteristic of PCOS (19, 43). Some studies have reported a decrease in TC, LDL-C and triglyceride levels and increase in

HDL-C concentration whereas others have not. Another study in its metaanalysis found only LDL-C levels to be significantly reduced following metformin treatment, with TC, HDL-C a triglyceride remaining unchanged (44). Metformin has been shown to exert antiatheroslerotic, anti-inflmatory and antithrombotic properties by reducing carotic intima-media thickness, endothelin, hsCRP, PAI-1 and leptin and increasing adiponectin levels in PCOS patients (42). Metformin treatment has been associated with decreased androgen (total and free testosterone, androstendione) and LH levels and increased SHBG and DHEAS concentrations (42).

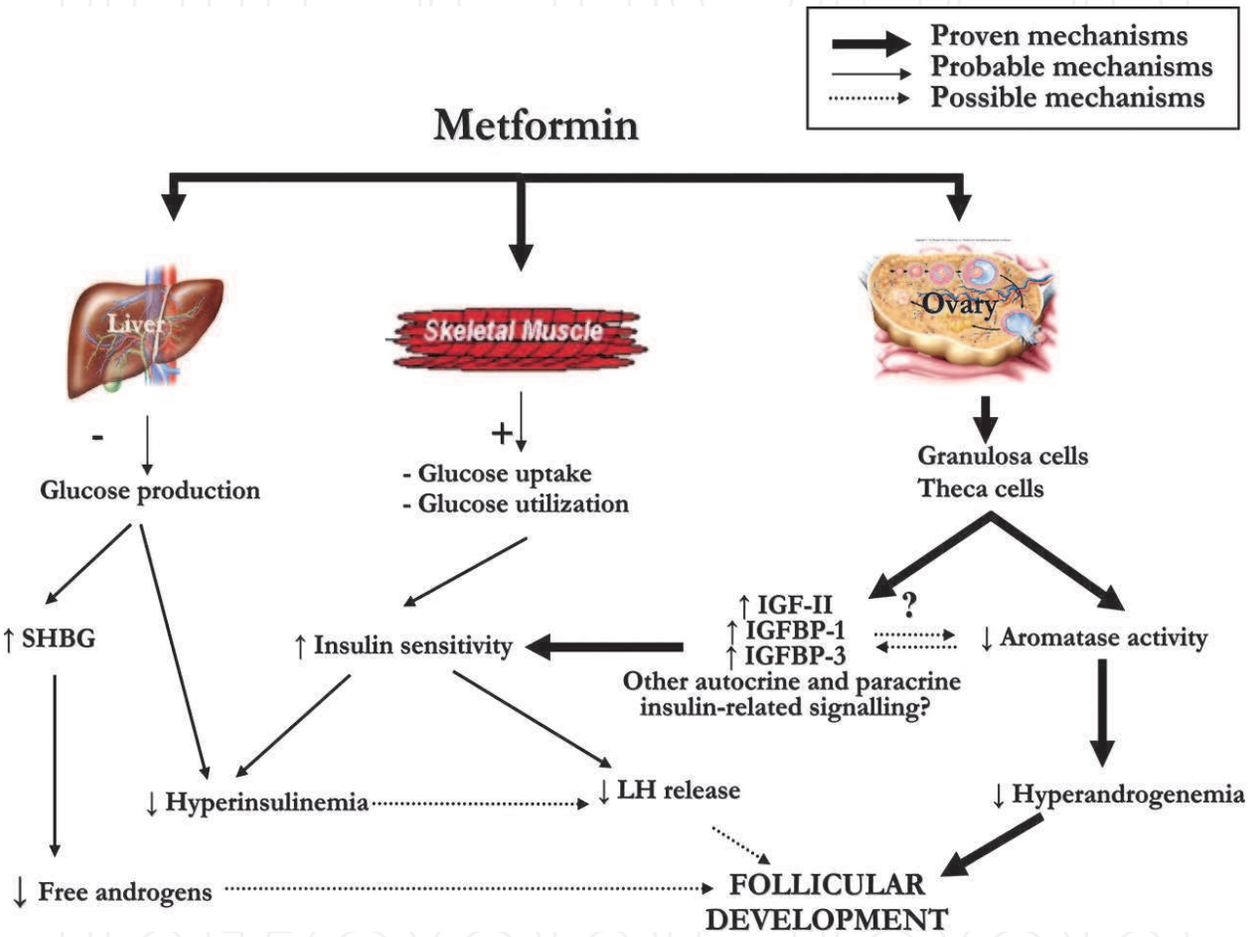

Fig. 4. Hypothesis for metformin effects on follicular development (52)

Knowledge regarding the predictors for metformin response is crucial. Some studies demonstrated that metformin appears to benefit to PCOS subjects irrespective of their weight or degree of insulin resistance. Metformin may be more effective in insulin-resistance PCOS patients with low BMI. There have been examinated genetic factors. Polymorphism of serine-threonine kinase gene STK11 was associated with a significantly decreased chance of ovulation in PCOS subjects treated with metformin (38). It is commonly expierence that obese women, particulary those with morbid obesity, are refractory to metformin therapy. Insulin resistant PCOS patients with low BMI were reported to be more likely to respond to metformin. However, previous studies did not confirm the predictive value of insulin resistance indices for ovulation induction by metformin. Metformin may be able to directly affect ovarian steroidogenesis. This drug could affect the central regulation of ovulation by

modulating GnRH release through the activation of the hypothalamic AMPK (43). The study of Palomba et al. demonstrates that the efficacy of metformin in inducing ovulation in patients with polycystic ovary syndrome is probably due to a direct action of the drug on the ovary, and that the ovulatory response to the drug seems to be related more to local drug sensitivity or resistance than to improvements in the systemic hormonal and/or metabolic pattern (52). Treating insulin resistance with metformin may improve fertility, facilitate weight loss, improve the lipid profile, reduce the incidence of diabetes, and prevent atherosclerosis, myocardial infarction, and stroke (19). It is very difficult to conclude regarding the efficacy of metformin in PCOS, since the published data are incosistent due to various study designs concerning patients characteristics, weight change, dose regimen and outcome meassures.

TZDs are ligands of the peroxisome proliferator-activator receptor-gamma, a nuclear transcription factor. TZDs lower fasting and postprandial glucose levels by increasing glucose utilization in skeletal muscle and decreasing hepatic gluconeogenesis and ameliorate hypertiglyceridemia (38, 42). In PCOS patients, rosiglitazone treatment improved insulin resistance and normalized the menstrual cycle (45). It had beneficial effect on serum levels of adipinectin and resistin (46). Rosiglitazone decreased fastig glucose and insulin levels, increase HDL-C and reduced TC and LDL-C and triglyceride concentration (42). Tarkun et al. observed that rosiglitazone treatment decreased androgen production and it had benefecial effects on endothelian dysfunction and low-grade chronic inflammation in normal weight women with PCOS (47). In another study, rosiglitazone therapy decreased androgen levels (DHEAS, total and free testosterone), increase SHBG levels, reduced estradiol production and restored menstrual cycles, induced ovulation rate and improved hirsutism score (42). Rosiglitazone has been shown to enhance both sponateneous and clomiphene-induced ovulation in overweight and obese women with PCOS (37,48). However, due to its side effect, it has been withdrawn from the market. The efficacy of rosiglitazone and pioglitazone in PCOS has not been compared in any study (42).

Administration of pioglitazone in women with PCOS resulted in remarkable decline in fasting serum insulin levels, improvement of insulin sensitivity. Pioglitazone increased serum SHBG concentrations, resulting in significant decrease in the free androgen index. Treatment was also associated with higher ovulation rates (49). In women with PCOS who failed to respond optimally to meformin, when pioglitazone was added, insulin, glucose, insulin resistance, insulin secretion, and DHEAS fell, HDL-C, TC and SHBG rose, and menstrual regularity improved (50). Application of insulin sensitizers showed favorable influence on the basic hormonal deviations in PCOS – the hyperandrogenemia and insulin resistance. In cases with PCOS, metformin treatment influences better hyperandrogenemia, while rosiglitazone affects more pronouncedly insulin resistance and hyperinsulinemia (51). The study of Li et al. included meta-analysis of 10 trials. TZDs were found to be superior to metformin in reducing serum levels of free testosterone and DHEAS after 3-month treatment. Decreases in triglyceride levels were more pronounced with metformin after 6 months. Decreases in BMI are greater with metformin treatment as assessed at 3 and 6 months. The findings do not indicate that metformin is superior to TZDs for the treatment of PCOS or vice versa. Between studies, heterogeneity was a major confounder (53).

TZDs should be used in substitution of or in adition to metformin in insulin-resistant or obese PCOS women who do not tolerate or do not respond to metformin therapy. For menstrual

disorders, oral contraceptives are considered the primary treatment, with intermittent progesterone therapy and insulin-sensitizing agents as alternative therapies (38, 42).

4. Conclusions

PCOS is a common disorder which affects 5%-10% of women of reproductive age (1). PCOS can be described as a multiorgan disease affecting most endocrine organs including ovaries, adrenals, pituitary, fat cells, bones, and endocrine pancreas (5). However, the diagnosis of PCOS comprises more than reproductive or cosmetics problems Table 4. PCOS constitutes major health issue for young women. Insulin resistance, dyslipidemia and hypertension contribute to an enhanced cardiovascular and diabetes risk (1).

Adolescents	Reproductive phase	Postmenopause
Oligomenorrhea	Infertility	Impaired glucose tolerance
Hirsutism	Hirsutism	Type 2 diabetes
Acne	Obesity	Dyslipidemia
Obesity	Impaired glucose tolerance	Hypertension
		Cardiovaskular risk factors

Table 4. PCOS throughout the life cycle (1)

The risk of diabetes is greater in anovulatory women with polycystic ovaries, in obese subjects and those with a family history of type 2 diabetes (3). Women with PCOS are at significantly increased risk for impaired glucose tolerance and type 2 diabetes (31,1% impaired glucose tolerance, 7,5% undiagnosed diabetes) (20, 21). Legro et al. found that not only obese but also nonobese PCOS women may also have glucose intolerance (10,3% impaired glucose tolerance, 1,5% diabetes) (20). Abdominal obesity appears to be the primary determinant of metabolic abnormalities in PCOS (2). Abdominal obesity and increased activation of the inflammatory system are seen in both normal weight and obese patients with PCOS. (5). Subclinical inflammation and insulin resistance are important predictors of cardiovaslular disease. Patients with PCOS have an excess of central fat independent of total fat mass. Central fat excess is usually associated with an increase in serum inflammatory markers and insulin resistance. On the other hand, sex hormones affect body fat distribution and thereby might in part explain the genderspecific differences in body fat distribution (14). Insulin resistance and hyperandrogenism may also, either directly or indirectly, influence metabolic abnormalities and potentially contribute to abdominal obesity (2). Abdominal obesity and insulin resistance stimulate ovarian and adrenal androgen production, whereas SHBG levels are decreased (5). Women with PCOS should be informed of their long-term risk of type 2 diabetes and likely cardiovascualr disease. There is need for a comperhensive screening and education program for women of all ages with PCOS (41). While hyperandrogenemia and concomitant hirsutism, acne, or infertility are certainly troublesome to a woman, an incereased risk of developing diabetes and atherosclerosis has the potential to shorten her lifespan (19).

PCOS is a unique, natural model for the study of influence of androgen excess on bone mass among women. The deleterious effect on bone of amenorrhea is balanced by androgen overproduction. Obesity and insulin resistance aggravate hyperandrogenism. Serum vitamin D is significantly lower in obese than in non-obese women individuals and may

contribute to lower serum 25OH vitamin D in obesity. Hypovitaminosis D results from the presence of obesity but is independent of the presence of PCOS. Vitamin D supplementation can be useful in the treatment of obese women with PCOS (24). Wehr et al. are the first to describe an inverse association of low 25OH vitamin D levels with impaired beta-cell function, impaired glucose tolerance, and metabolic syndrome in women with PCOS (27).

The treatment of infertile women with PCOS is surrounded by many controversies. Before any intervention is initiated, the improvement of life-style, especially weigh reduction is recomended. Clomiphene-citrate, an anti-estrogen remains the first-line of treatment for ovulation induction. Recomended second-line of intervetion is eihter exogenous gonadotropins or laparoscopic ovarian surgery. Recomended third-line treatment is *in vitro* fertilization (30). Treating of insulin resistance, when present, with metformin may improve fertility, facilitate weight loss, improve the lipid profile, reduce the incidence of diabetes, and prevent atherosclerosis, myoacrdial infarction, and stroke (19). The use of metformin alone or in combination with life-style modifications has produced a list of metabolic and clinical benefits in both obese and non-obese women with PCOS which has allowed an indiscriminate use of this compound worldwide (38). On the other hand, according to ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group metformin use in PCOS should be restricted to women with glucose intolerance (30). According to Nestler metformin remains an important therapeutic option in the pharmacologic treatment of infertility in PCOS, and its use should not be restricted to women with glucose intolerance, as recomended by the ESHRE/ASRM Consensus statement (35).

Because of the high prevalence of PCOS and the long-term implications on metabolic risk factors, fertility, and quality of life, doctors need to be aware of the syndrome in daily practise (5). In conclusion, it is clear that PCOS is an anigma. Its underlying pathophysiology is not fully understood. No treatment is a panacea, because treatments, so far, have been directed at the symptoms but not at the syndrome itself (33).

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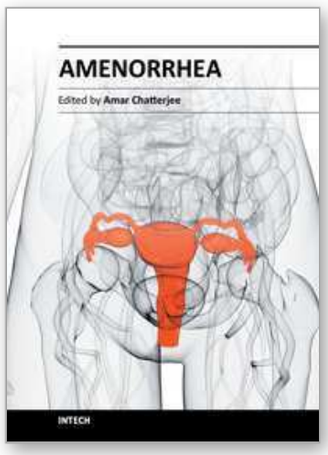

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InTech Europe
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Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821