Endocrine characteristics of polycystic ovary syndrome (PCOS)

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Polycystic ovary syndrome (PCOS) is probably the most prevalent endocrinopathy in women and the most common cause of anovulatory infertility. Patients with PCOS have clinical and biochemical features consistent with the ultrasound diagnosis and they are likely to face the problems of hyperandrogenism, subfertility and recurrent miscarriage. The aim of the present review is to summarize our present knowledge on the hormonal background of this very prevalent syndrome and to give some clinical examples how the present knowledge can be applied to treat PCOS patients according to their current problem, such as menstrual cycle disorder, hirsutism, infertility or to prevent late consequences as diabetes mellitus. The etiology and pathogenesis of PCOS is still a matter of controversies, but it is apparent that inappropriate gonadotropin secretion, obesity, hyperinsulinism and insulin resistance are the major determining factors in the development of ovarian hyperandrogenism and chronic anovulation. Reversal of insulin resistance in PCOS constitutes the fundamental goal in the management of hyperandrogenic anovulatory infertility and in the prevention of long-term consequences. The value of the insulin sensitizer metformin therapy awaits further evaluation and should be integrated in the spectrum of therapeutic options that include the discussed surgical methods and GnRH analogues as well.

Keywords: Anovulatory infertility, Endocrinopathy, PCOS, Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is probably the most prevalent endocrinopathy in women and the most common cause of anovulatory infertility. More recent studies, although based on modified criteria of PCOS, also report high prevalence from 4% to 9% in the female population of fertile age1,2. Polycystic ovaries (PCO) seen by ultrasound is an even more frequent finding. It has been shown that one woman in five has polycystic ovaries that can be demonstrated on ultrasound examination1. According to some further large studies the prevalence of PCO in healthy volunteer populations may range up to 33%3. Women representing symptoms of oligo-amenorrhea with hyperandrogenism have polycystic ovaries in 87% of the cases1.

The aim of this review is to summarize our present knowledge on the hormonal background of this very prevalent syndrome and to give some clinical examples how the present knowledge can be applied to treat PCOS patients according to their current problem, e.g., menstrual cycle disorder, hirsutism, infertility or prevention of late consequences as diabetes mellitus.

Diagnosis

PCOS has been defined clinically, biochemically, and by ultrasound. The predominantly European diagnosis of PCOS is based on clinical signs of menstrual disturbance and/or hyperandrogenism (hirsutism, acne or alopecia) and established by transvaginal ultrasound examination of the ovaries characterizing the ovarian morphology. According to the criteria of Adams4, polycystic ovaries (PCO) should be diagnosed when more than eight discrete follicles of <10 mm diameter are seen in the ovary, usually peripherally arrayed around an enlarged, hyperechogenic, central stroma. Most of the patients with PCO have a clinical or biochemical feature consistent with the ultrasound diagnosis and they are likely to face the problems of hyperandrogenism, subfertility and recurrent miscarriage. As for the predominantly North American view, the 1990 National Institute of Health (NIH) conference on PCOS5 recommended that diagnostic criteria should include biochemical evidence of hyperandrogenism and ovarian dysfunction without regarding the morphological diagnosis of PCO by ultrasound as an essential part of the diagnosis. A recent proposal by Homburg6 attempts to bridge the gap between predominantly American biochemical marker-based diagnosis and predominantly European reliance on ultrasound as a sine qua non for diagnosis.

Pathophysiology

The pathophysiology of the disorder has been thoroughly investigated, but its etiology is still unsettled. There are theories supporting a primary
hypothalamic-pituitary defect, a primary ovarian steroidogenic defect, a primary adrenal steroidogenic defect and a primary defect of insulin resistance. Furthermore, the existing literature provides a strong basis for arguing that PCOS clusters in families. However, the mode of inheritance of the disorder is still uncertain. Several loci have been proposed as PCOS genes including CYPI1A, the insulin gene, and a region near the insulin receptor. Whatever the pathogenesis of PCOS, the endpoint is an ovary secreting excessive amount of androgens.

**Hormonal and biochemical characteristic**

Excessive ovarian androgen production is characteristic of most women with the typical ovarian morphology. PCOS patients have higher serum concentrations of testosterone, free testosterone and androstenedione. The source of the excessive ovarian androgen production is a key question. The rate limiting enzymes in androgen biosynthesis are 17-hydroxylase and 17/20 lyase activities that are disordered in PCOS. In response to a single dose of GnRH analogue, women with PCOS have an exaggerated increase in both 17-hydroxyprogesterone and androstendione. The 17-hydroxylase and 17/20 lyase belong to the enzyme complex cytochrome P450 17α, and the activity of this enzyme complex may be increased by several pathways in PCOS.

Among the candidates LH, insulin-like growth factor-1 (IGF-1) and insulin itself can be listed. LH is hypersecreted in 40-50% of PCOS patients. It is a unique feature of PCOS that the LH secretion is disproportionately increased over that of FSH, resulting in an elevated (>2:1) LH:FSH ratio. The increased mean LH level is due to the increased GnRH-LH pulse frequency that may be explained by the reduced opioidergic inhibition of GnRH in PCOS patients. Our previous studies suggest that central opioidergic and dopaminergic control of gonadotropin secretion is impaired in PCOS and remains unaffected by ovarian surgery, even when menstrual cyclicity is resumed. According to in vitro studies the androgen production by theca-stromal cells respond readily to LH stimulation with an increased expression of cytochrome P450 17α activity, with a synergistic effect occurring in the presence of IGF-1 or insulin. Furthermore, IGFBP-1, the binding globulin of IGF-1 is suppressed first of all in obese PCOS patients, and in this way the potential of IGF-1 is increased to act synergistically with LH to stimulate the theca and interstitial cells of the ovary to produce androgens.

It has been proven that hyperinsulinemia and insulin resistance play a key role in the pathophysiology of hyperandrogenism and probably the pathogenesis of PCOS. Insulin receptors are present in the ovary and insulin may also bind to IGF-1 receptors and acts as a gonadotrophic hormone, enhancing induction of ovarian LH receptors and LH binding capacity. Apart from the ovarian androgens, several observers have noted that a characteristic adrenal androgen, dehydroepiandrosterone sulfate (DHEAS), is found in high concentration in the blood of patients with PCOS and there is an enhanced responsiveness of adrenal androgens to stimulation. Furthermore, in many patients the entire syndrome can be corrected by partial adrenal suppression. We have also found elevated DHEAS level in PCOS that was reduced after ovarian wedge resection.

A further characteristic hormonal deviation in PCOS is hyperprolactinemia. It can be explained by estrogen priming at the pituitary level or by decreased central dopaminergic tone. Even in normal basal prolactin level, an exaggerated prolactin response to metoclopramide, or to thyroid releasing hormone (TRH) administration was observed in PCOS. According to our studies, the increased prolactin response to metoclopramide remains unaltered by ovarian surgical manipulations (wedge resection or laser vaporization) in PCOS indicating a persistent aberration in the dopaminergic control of prolactin secretion.

There are also characteristic features in the urinary steroid excretion of PCOS patients that can be profiled by gas chromatography. PCOS is characterized by increased 5α-reductase enzyme activity. This enzyme converts testosterone to the biologically active 5α-dihydrotestosterone in androgen-dependent target organs; increased activity of this enzyme in the skin causes hirsutism. Increased 5α-reductase enzyme activity increases the production of not only the 5α-androgen metabolites (androsterone), but enhances hepatic cortisol metabolism, too (increased 5α-tetrahydrocortisol-a-THF production). In this way ratios of 5α- to 5β-steroids (androsterone/etiocholanolone-An/Et and a-THF/THF) is characteristically increased in PCOS, as well as the increased ratio of androgene metabolites (AM) to cortisol metabolites (CM).

Capillary gas chromatographic profiling of urinary steroids may also be used to detect late onset steroid 21-hydroxylase deficiency, the most frequent enzyme deficiency that causes hirsutism, and that should be differentiated from PCOS.
Hormonal changes after therapeutic interventions

There is no single effective treatment for PCOS. Management of PCOS depends on the requirements of the patient. Infertility is treated with ovulation induction or by surgical ovarian manipulations (wedge resection or more recently laparoscopic electrocautery, laser vaporization of the ovaries). If the complaints focus on the hyperandrogenemic symptoms, first of all excessive hair growth, suppression of the ovarian androgen production should be achieved. Hyperinsulinemia, insulin resistance as a principal factor in the pathogenesis of PCOS has led to the use of insulin-lowering agents also called insulin sensitizers. The most extensively studied insulin-lowering agent in the treatment of PCOS is metformin: an oral antihyperglycemic agent used initially in the treatment of type 2 diabetes mellitus. Metformin can be used alone or in combination with agents administered for ovulation induction. Furthermore, metformin also appears to induce cardioprotective effects on serum lipids as well as plasminogen inhibitor (PAI)-1 and may decrease the risk of development of type 2 diabetes(1,3). The highly promising therapeutic profile of metformin deserves further studies and application.

In the following chapter of the review the author's data on the hormonal effects of ovarian surgery to achieve resumption of the menstrual cycle and infertility and the effects of long term GnRH analogue treatment on serum and urinary steroid hormones will be summarized. On one hand the clinical and hormonal effects of long term gonadotropin-releasing hormone (GnRH) analogue treatment was studied in hirsute PCOS patients and on the other hand infertile, clomiphene citrate resistant PCOS patients were surgically treated to achieve resumption of the menstrual cycle and fertility. Hormonal changes before and after surgery was evaluated, too.

GnRH analogue treatment of hyperandrogenemic PCOS patients

GnRH analogues exert a profound and prolonged suppression of pituitary gonadotropin secretion which accounts for the marked suppression of ovarian function(33). Short term studies performed on PCOS patients utilizing a short-acting GnRH agonist for 4 weeks proved marked suppression of ovarian steroidogenesis(34). Later on, it became evident that long term GnRH analogue treatment should be considered among the various therapeutic modalities offered in the context of hirsutism(35). Several studies have aimed to measure serum gonadotropin and androgen levels during GnRH analogue treatment in PCOS(36), but the efficacy of gas chromatographic profiling of urinary steroids in monitoring GnRH analogue therapy has not been studied yet, although the effect of GnRH analogue stimulation test on urinary steroid excretion was reported in a study(37).

Patients and methods

A long acting GnRH analogue (Decapeptyl Depot®-Ferring, Germany) was administered as monthly intramuscular injection for 6 months in 8 PCOS patients. Clinical and hormonal effects were measured. Serum LH, FSH, prolactin, testosterone, estradiol levels were determined monthly and profiling urinary steroids by column gas chromatography of 24 hr urine samples was performed before and in the third and sixth month of treatment according to Shackleton and Homoki(38,39). To evaluate 5α-reductase enzyme activity in the liver and skin of the patients, the ratios of androsterone (An) to etiocholanolone (Et) and 5α-tetrahydrocortisol (α-THF) to tetrahydrocortisol (THF) were calculated in urine samples before and after the GnRH analogue therapy. Changes in the ratio of androgen metabolites (AM) to cortisol metabolites (CM) during treatment were evaluated, too. Degree of hirsutism was assessed before and after treatment by Ferriman Gallwey score(40).

Results

LH has decreased significantly following the first injection of the GnRH analogue (from 11.9±2.9 to 1.05±0.5 U/l). FSH and prolactin levels have not changed during treatment. Testosterone levels were normalized (<3 nmol/l), estradiol was suppressed near to postmenopausal levels (50-100 pmol/l).

An/Et and α-THF/THF ratios in the urine samples have decreased significantly during therapy (An/Et from 2.1±0.25 to 1.6±0.2, α-THF/THF from 1.1±0.1 to 0.8±0.1), but they were still higher than that of in healthy females (normal ratios: An/Et 1, α-THF/THF 0.6). The elevated ratio of androgen metabolites to cortisol metabolites characteristic of PCOS has decreased during treatment to normal values (AM/CM from 0.8±0.2 to 0.5±0.1) Clinically, all the PCOS patients became amenorrhieic during GnRH agonist treatment, and 6 out of the 8 patients complained of mild hot flushes. Hirsutism assessed by Ferriman Gallwey score was diminished, but not significantly.
Conclusions of the chronic GnRH analogue treatment study:

Long acting GnRH analogue treatment in PCOS is effective in reducing serum LH, estradiol and androgen levels. Gas chromatographic profiling of urinary steroids by using specific ratios is a sensitive tool for monitoring changes in steroid hormone production during GnRH analogue administration. Use of specific ratios may help to avoid errors of urine collection. Increased 5α-reductase enzyme activity characteristic for PCOS is diminished during treatment, but it remains still higher than that of in healthy females. Production of androgen metabolites is reduced, too. The finding that 5α-reductase activity (ratios of An/Et and a-THF/THF) in our PCOS patients could be diminished, but not absolutely normalised raises the possibility that some disorders in PCOS are irremediable as it was found in a study concerning the inappropiate hypothalamic opioidergic and dopaminergic control of gonadotropin and prolactin secretion in PCOS patients.

Degree of hirsutism improves during GnRH analogue administration, but for a significant improvement probably a longer or combined treatment would be required. Our data on chronic GnRH analogue treatment in PCOS were published in details recently.

Surgical treatment of PCOS associated infertility

For the treatment of infertility associated with PCOS ovulation induction is the most appropriate treatment. Clomiphene citrate in doses of 50-200 mg/day from day 4 or 5 of the cycle for 5 days may be the simplest method to achieve ovulation in 80% of the cases, however, the overall pregnancy rate is only 30-40%. This discrepancy may partly be explained by the antiestrogenic effect of clomiphene citrate on the cervical mucus and endometrium, and the increased LH concentrations during clomiphene citrate action that may seriously compromise pregnancy rates in these patients. If clomiphene treatment fails to induce ovulation ("clomiphene failures") the next step may be stimulation of the ovaries with exogenous gonadotropins or surgical manipulation of the ovaries.

Surgical treatment, originally by bilateral wedge resection of the ovaries, or later by laparoscopic approaches (electrocautery, laser photodestruction, laser drilling) is found to be effective in restoring ovulation for at least 6 months, but the benefit of monopolar current may last for several years. As a consequence of profound changes in the gonadotropin secretion in response to ovarian surgery, resumption of normal menstrual cyclicity with subsequent ovulation has been observed. Although wedge resection by laparotomy has not been performed for 15-20 years, our data are available on the hormonal effects of this procedure. The aim of the study was to compare the hormonal and clinical effects of ovarian wedge resection, electrocoagulation and laser vaporisation in patients with polycystic ovary syndrome.

Patients and methods

The diagnosis of PCOS was based on the clinical manifestations of chronic hyperandrogenemia, such as menstrual disturbances (oligo- to amenorrhoea), hirsutism and infertility. Endocrinological features comprised elevated serum LH with normal or subnormal FSH concentrations and the finding of elevated serum testosterone, androstenedione and/or dehydroepiandrosterone sulfate (DHEAS) levels. The presence of enlarged ovaries with multiple subcapsular cysts was sonographically confirmed in all PCOS women. All patients had failed to ovulate in response to clomiphene citrate regimens (100 mg/day for 5 days) administered for at least 3 months.

Nine patients underwent classical wedge resection of the ovaries, 11 patients were treated by laparoscopic Nd:YAG laser vaporisation (contact approach for the laser beam, continuous wave mode), and in 56 patients laparoscopic multiple point electrocoagulation of the ovaries by monopolar current was performed.

Results

A significant decrease in serum LH five days after surgery could be achieved only after the laparoscopic approaches (laser or electrocoagulation). On the other hand, laparoscopic procedures induced an increase in serum FSH that may be favourable in initiating menstrual cyclicity.

Serum testosterone has decreased five days after surgery in some wedge resected patients, but a pronounced decrease could be achieved only by the laparoscopic methods.

Changes in the pulsatile pattern of LH and FSH were studied by multiple (every ten minutes for 6 hours) blood samplings before and after laser surgery. LH pulse amplitudes, but not pulse frequency have decreased significantly after laser surgery. Practically all the patients following the different surgical procedures had ovulatory cycles proved by basal body
temperature charts and progesterone determinations in the luteal phase. Pregnancy rates in the different study groups in one year after surgery were as follows: wedge resection 2/9, Nd:YAG laser 4/11, electrosurgery 15/56.

Conclusions of the ovarian surgical manipulation studies

All the surgical methods are effective in restoring menstrual cyclicity, but laparoscopic methods have higher pregnancy rates. The rapid recovery without adhesions following laparoscopic surgery is favourable. Laser surgery or electrosurgery are more effective in reducing circulating androgen and LH levels than wedge resection. Decrease in LH level after laser surgery is due to reduced pulse amplitudes.

Our results are in accordance with the literary data that laparoscopic surgical methods in clomiphene resistant PCOS patients are effective to restore fertility Interestingly, restoration of menstrual cyclicity and fertility in PCOS patients by normalized gonadotropin secretion is not accompanied by alterations in central dopaminergic and opioidergic control of gonadotropin and prolactin secretion. It may indicate that some central endocrine abnormalities in PCOS are inreminedial.

A further advantage of surgical therapy of PCOS related infertility is that stimulation with gonadotropins following ovarian surgery gives an enhanced ovarian response compared with the pre-surgery (pre-diathermy) response.

Summary and future perspectives

The etiology and pathogenesis of PCOS is still a matter of controversies, but it is apparent that inappropriate gonadotropin secretion, obesity, hyperinsulinism and insulin resistance are major determining factors in the development of ovarian hyperandrogenism and chronic anovulation. Follow up studies have also shown an increase in the incidence of diabetes in PCOS evaluated at perimenopausal age. Thus reversal of insulin resistance in PCOS constitutes the fundamental goal in the management of hyperandrogenic anovulatory infertility and in the prevention of long-term consequences. The value of the insulin sensitizer metformin therapy awaits further evaluation and it should be integrated in the spectrum of therapeutical options.

Finally, we may infer that our results support the notion that PCOS may successfully be managed depending on the goals of the treatment and the requirements of the patients. Hyperandrogenemia, hirsutism may effectively be treated by long acting GnRH analogues that according to literary data may be combined with oral contraceptives to enhance the therapeutic effect and to reduce the risk of bone loss during a prolonged treatment. On the other hand, surgical manipulations of the ovaries are not effective in reducing hirsutism. The laparoscopic ovarian surgery is indicated only in infertile patients if conventional ovulation induction fails to restore fertility.

The therapeutic interventions and their hormonal effects are in accordance with our knowledge on the endocrine background of PCOS. Our present knowledge on the pathophysiology of PCOS can be applied at the clinical level to help PCOS patients according to their requirements and to prevent long term consequences of this syndrome.

References


