Лекции / Lectures

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Polycystic ovary syndrome: pathogenetic mechanisms of the disease (part 1)

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Abstract. The article presents analysis of modern literature data on risk factors and pathogenesis of polycystic ovary syndrome (PCOS). Despite numerous studies, it has not been possible so far to formulate a unified concept of the pathogenesis and etiology of PCOS. This lecture considers mechanisms of PCOS development. The role of impaired steroidogenesis in the adrenal glands and ovaries in PCOS is observed. The focus is assigned to insulin resistance that is likely involved in the development of reproductive PCOS phenotype and might mediate on some of the changes in ovarian morphology seen in this disease. It has been shown that not only hereditary factors lead to the development of this syndrome, but also lifestyle, physical activity and concomitant somatic diseases.

Key words: polycystic ovary syndrome; pathogenesis; risk factors; insulin resistance; hyperandrogenis.

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The first reference to the picture of the disease, today known as PCOS, dates back to 1721 and was made by an Italian author A. Vallisneri. The author described a young married female peasant with moderate obesity and infertility who had two large cystic shiny ovaries with a white surface and the size of pigeon eggs [1].

Morphological changes in sclerocystic ovaries have been described in detail by A. Chereau: these data were published in Paris in 1844. In 1915, Ya.K. Hachkaruzov reported about significant (two or three times the size) ovarian enlargement in five women operated for suspected extrauterine pregnancy in Russia. Only seven years later, gynaecologists from Chicago I.F. Stein and M.L. Leventhal presented a documentation of seven females with hirsutism, infertility, amenorrhea or oligomenorrhea, and obesity with enlarged polycystic ovaries to the American College of Obstetricians and Gynaecologists [2]. It was then when this disease was distinguished as an independent nosological form and was given the name of "Stein-Leventhal syndrome", by the author's surnames.

PCOS amounts to 6-10% and, apparently, its prevalence grows significantly in obese patients. The diagnostic criteria for PCOS are based on consensuses outlining menstrual disorders (oligomenorrhea), clinical (hirsutism, acne, alopecia) or biochemical (increased serum androgen concentration) hyperandrogenism, and ultrasonic morphology of polycystic ovaries [3].

The polycystic ovary syndrome (PCOS) is a polygenetic endocrine disorder conditioned both by genetic and epigenetic factors. Depending on the female's stage of life, the clinical picture, diagnosis and treatment tactics of the disease vary. PCOS has a complex of reproductive, metabolic, and psychological peculiarities.

This disease impairing approximately 5-10% of females of reproductive age can be characterised by irregular periods, infertility and androgen excess, although it can be in different phenotypes [4].

Despite the numerous studies, no uniform concept of PCOS pathogenesis and aetiology has been formed to the date. Four different parts of the neuroendocrine system may be conventionally distinguished in its pathogenesis, each of which may claim the role of the disease onset factor. These are impairments at the levels of the hypothalamic-pituitary system, ovaries, adrenals, and peripheral insulin-sensitive tissues [5-7].

Specifically, these impairments include childhood infections/neuroinfections; craniocerebral trauma; psycho-emotional strain, stress; congenital ovarian enzyme defect (most often of 19-hydroxylase and 3β-ol-hydrogenase); extragenital endocrine pathology (Itsenko-Cushing disease/syndrome, obesity, adrenogenital syndrome).

Adrenal steroidogenesis:

The precursor of corticosteroid synthesis is cholesterol. The majority of cholesterol (80-90%) is bound to fatty acids and only 10% is accounted for free cholesterol. In adrenals, the latter is mainly contained in endoplasmic membranes and mitochondria, while cholesterol esters are concentrated in the cytoplasmic lipid droplets. Cholesterol enters adrenals from plasma and is synthesised from acetyl-CoA.

Cholesterol repletion is controlled by ACTH, the action of which accelerates the flow of free cholesterol from plasma, intensifies de novo intracellular cholesterol synthesis and stimulates intracellular hydrolysis of cholesterol esters in adrenals. ACTH regulates the speed of adrenal steroidogenesis through changing cholesterol metabolism and its redistribution both inside the cell and in mitochondria. Extracellular lipoproteins are an important regulator of cholesterol synthesis in the adrenals and a sufficient amount of extracellular cholesterol leads to suppression of it intracellular synthesis [8].

The processes of steroidogenesis are based on enzymes localised in mitochondria and smooth endoplasmic reticulum. Biosynthesis of corticosteroids begins in mitochondria, in which the action of $P450_{SCC}$ (20,22-desmolase) enables cholesterol side-chain cleavage in the inflowing cholesterol as well as formation of pregnenolone – the precursor for the majority of corticosteroids secreted in human adrenals [9].

Glucocorticoids are produced in smooth endoplasmic reticulum from pregnenolone with participation of the P450c17 enzyme through intermediates: 17α-hydroxypregnenolone and 17 "-hydroxyprogesterone. The subsequent

reaction with participation of P450c21 results in hydroxylation in the 21st position with production of 11-deoxycortisol which undergoes additional hydroxylation in the 11th position with participation of P450c11 in mitochondria. As a result of the two reactions, cortisol is produced that, as well as dehydroepiandrosterone, is present in the fascicular zone and partially in the reticulate zone of the adrenals. In these zones, the P450aldo enzyme (aldosterone synthase, P450c18) necessary for aldosterone production is absent [9, 10].

Mineralocorticoids (aldosterone) is produced in the cells of the glomerular zone, the functions of which are only partially under control.

ACTH. All three last stages of aldosterone synthesis – namely, production of corticosterone from 11-deoxycorticosterone, 18-hydroxycorticosterone and aldosterone – are regulated by the P450aldo enzyme.

Production of androgens in the adrenal cortex takes place in its reticular layer and partially in the fascicular zone through conversion of 17α-hydroxypregnenolone into C-19 steroids that include dehydroepiandrosterone and dehydroepiandrosterone sulphate. Androstenedione is produced from 17α-hydroxyprogesterone with participation of the 17,20-desmolase enzyme. Androstenedione may be converted into testosterone. In males, adrenal-origin testosterone is only a small part of the total testosterone circulating in the blood and excreted with urine [10].

The pattern of steroidogenesis is defined by enzymatic systems, the activity of which depends on ACTH [11]. Binding of ACTH to the receptor initiates a sequence of reactions and activation of cAMP-dependent protein kinase that, in turn, leads to phosphorylation of ribosomal proteins, production and increased activity of enzymes (cholesterol esterase, $P450_{SCC}$, etc.) defining the speed of steroidogenesis [12].

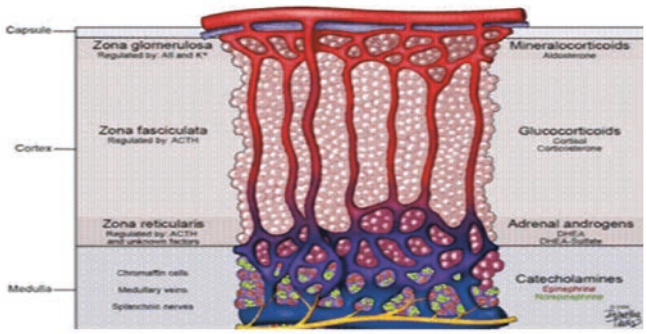

Figure 1. Histological structure of the ovary.

Ovarian steroidogenesis is conducted during the menstrual cycle in granulosa and theca cells. Before ovulation, theca cells separate from granulosa cells within one follicle using the basement membrane, i.e. granulosa cells of preovulatory follicles have no blood supply. However, at the peak level of LH, preovulatory follicles undergo luteinisation, during which the basement membrane disappears and capillaries grow into granulosa cells. Theca cells turn into theca lutein cells and granulosa cells are converted into granulosa lutein cells. If no pregnancy begins, the lifespan of the yellow body is 14 days. After 12-14 days, luteolysis and apoptosis processes are initiated, yellow body involution takes place and menstruation begins. Thereafter, ovarian steroidogenesis switches to another group of follicles with their granulosa and theca cells [12, 13].

The two-cell / two-gonadotropin theory. This theory of ovarian steroidogenesis stipulates that synthesis of estrogens and androgens in follicles is performed separately (i.e. compartmentalised). Ovarian theca cells synthesise androgens in response to LH action. In adequate stimulation with FSH, these androgens may convert into estrogens in granulosa cells through aromatisation. Receptors to FSH are only present on granulosa cells, while receptors to LH are only present on theca cells in the early follicular phase. The P450c17 (17-hydroxylase and 17,20-lyase) enzyme is only present in theca cells. Therefore, the conversion of 21-carbon steroids into 19-carbon steroids is only possible in these cells. On the other hand, aromatase is only present in granulosa cells. Thus, aromatisation of androgens into oestrogens is only possible in granulosa cells of the ovary. The validity of the two-cell / two-gonadotropin theory is confirmed by the fact that despite ovaries of females with hypogonadotropic hypogonadism may form follicles in response to introduction of FSH, the content of androgens and oestrogens not growing until LH is added to the stimulation scheme.

Blood serum AMH concentration in females with PCOS is 2-3 times higher in comparison to that in healthy women. Earlier, it was assumed that this is associated with a large number of small antral follicles. However, it was later demonstrated that AMH production is 75-fold higher in granulosa cells of anovulatory polycystic ovaries in comparison with normal ones. Additionally, AMH concentration was 5 times higher in follicular fluid of non-stimulated follicles in women with PCOS and anovulatory cycles as compared with that in females with ovulatory cycles [14, 15].

Further research showed a correlation between serum AMH concentration and symptom severity: it was reliably significantly lower in patients with PCOS and ovulatory cycles than in females with anovulatory cycles and compara-

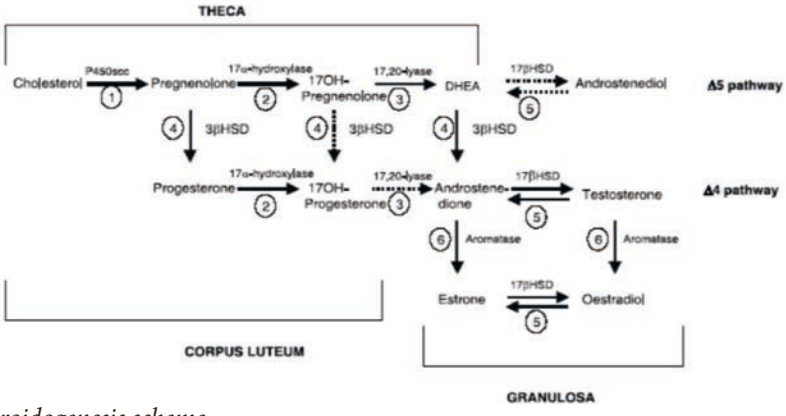

Figure 2. Ovarian steroidogenesis scheme.

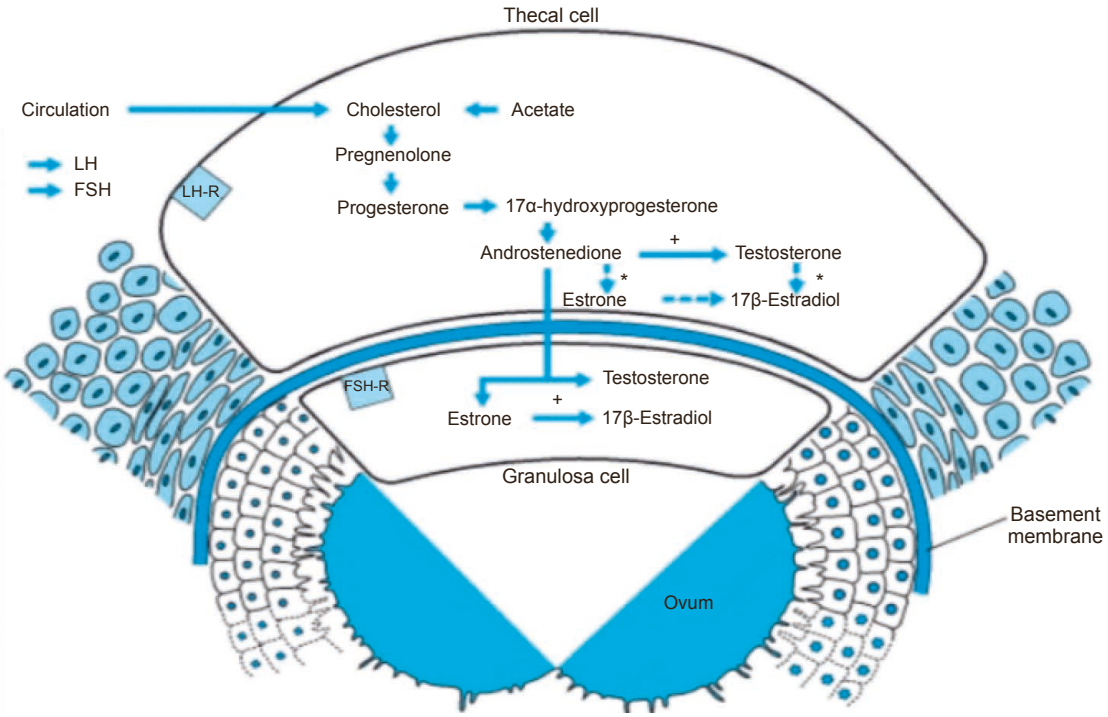

Figure 3. The two-cell / two-gonadotropin theory.

ble androgen levels. Therewith, it is worth noting that the contribution of such factor as the number of follicles did not exceed 5.3% from the overall contribution of all significant factors in AMH concentration. The aggregated data of these studies demonstrates that AMH concentration grows mainly due to the increase of its production in each follicle and not only through the buildup of their number. The fact that increased AMH production is characteristic to granulosa cells has been confirmed by data on the increase in the level of AMH mRNA in these cells obtained from follicles stimulated during IVF [15].

The reason for the increase in AMH production in females with PCOS is unknown. However, it may result from the effect of other factors changed in this disease, the most apparent among which is androgen excess. Thus, it has been demonstrated in a number of studies that the serum AMH level has positive correlation with the androgen level. T. Eldar-Geva et al. (2005) have shown that women with polycystic ovaries have higher blood serum AMH concentration in presence of hyperandrogenism [16]. It has been shown, that AMH levels decline during controlled ovarian hyperstimulation with a GnRH-antagonist short protocol in women with low and normal ovarian reserves. In contrast, in women with PCOS, an increase in AMH levels precedes this decline. These findings may support the hypothesis that androgens may play a role in AMH regulation in women [17].

Insulin resistance is defined as decreased glucose response to the present amount of insulin and is usually the result of impairments in insulin receptor and post-receptor signalling [18, 19, 20].

It is considered that a high level of circulating insulin in the ovary facilitates both androgen excess and anovulation.

What comes first, the hyperinsulinemia or the hyperandrogenism ?

We think IR comes first for the following reasons:

1- Insulin increases circulating androgen levels

2- Glucose increases the circulating levels of both insulin and androgen

3- Weight loss decreases the levels of both insulin and androgens

4- In vitro, insulin stimulates theca cell androgen productions

5- The experimental reduction of insulin levels in PCOS women reduces androgen levels

6- After normalisation of androgen with GnRH-a, the hyperinsulinism response to GTT remains abnormal in obese women with PCOS.

Unopposed E2

Anovulation - the progesterone levels are within suboptimal or absent effects over the endometrium – over-response to the proliferative effects of estrogen (E2) 21.

Insulin resistance and hyperinsulinemia especially in obese patients may trigger the development of PCOS in genetically predisposed individuals [4] .

Therefore, in PCOS, the prolonged unopposed estrogen, hyperinsulinemia, elevated free IGF-1 and androgens may further augment mitogenic activity within endometrial cells by activating mitogen-activated protein kinase (MAPK), leading to high prevalence of hyperplasia and possible transformation to endometrial cancer [22; 23].

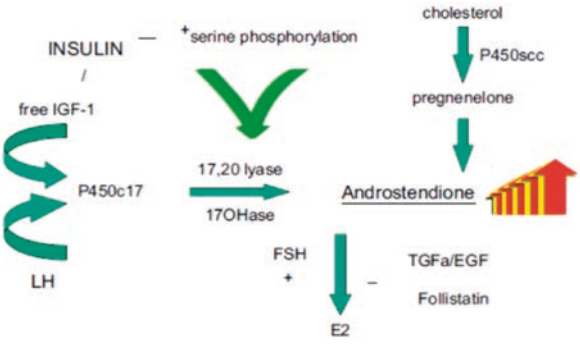

Figure 4. Insulin resistance development scheme.

Therefore, the pathogenesis of the polycystic ovarian syndrome is diverse and multidimensional. This syndrome develops not only due to the presence of hereditary PCOS factors; the lifestyle, physical activity, and concomitant somatic diseases of the patient are also of great significance [25].

Metabolic syndrome, obesity, and insulin resistance are observed in approximately one half of the PCOS patients; compensatory hyperinsulinemia features tissue-selective effects, which includes exacerbation of hyperandrogenism. PCOS apparently occurs as a complex pathogenetic process arising due to interaction between different genetic and environmental factors. Inherited factors include PCOS, hyperandrogenism, insulin resistance, and insulin secretion defects [26]. Further research on fundamentals of PCOS-associated impairments will be required for optimal correction of androgen levels, ovulation, and metabolic homeostasis.

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