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Endocrine causes of infertility

Endokrynologiczne przyczyny niepłodności

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S u m m a r y

Impairment of fertility is a growing health problem. It should be always considered in relation to both partners, as it affects to a similar extent women and men. Proper development and function of male and female reproductive organs, the processes of egg cell and sperma formation and development as well as of conception and pregnancy maintenance depend on interaction of a number of factors, including hormones. Functioning of ovaries and testes is closely related to the activity of other endocrine glands. Therefore, infertility can be the result of a malfunction of the pituitary, thyroid or adrenals. The article discusses the most common causes of primary hypogonadism as well as hypothalamic and pituitary dysfunctions leading to hypogonadism, in particular gonadotropin deficiency and hyperprolactinemia. Special attention was paid to the endocrine effects of eating disorders, which result in impaired fertility. We also discussed the impact on fertility of the thyroid and adrenal diseases as well as hormonal disorders associated with polycystic ovary syndrome. Attention was paid to diagnosis and treatment of each disease in the context of optimization the patient's procreative capacity.

S t r e s z c z e n i e

Zaburzenia płodności stanowią narastający problem zdrowotny. Powinny być one rozważane zawsze w odniesieniu do obojga partnerów, gdyż dotyczą one w podobnym stopniu kobiet i mężczyzn. Prawidłowy rozwój i funkcjonowanie narządów rodnych kobiety i mężczyzny, procesy tworzenia i rozwoju komórek jajowych i plemników oraz poczęcia dziecka i utrzymania ciąży zależą od współdziałania szeregu czynników, w tym hormonów. Działanie jajników i jąder jest ściśle związane z czynnością innych gruczołów wydzielania wewnętrznego. Dlatego też niepłodność może być skutkiem nieprawidłowego funkcjonowania przysadki, tarczycy czy nadnerczy. W artykule omówiono najczęstsze przyczyny pierwotnej niedoczynności gonad oraz zaburzenia czynności podwzgórza i przysadki prowadzące do hipogonadyzmu, ze szczególnym uwzględnieniem niedoboru gonadotropin i hiperprolaktynemii. Szczególną uwagę zwrócono na endokrynne skutki zaburzeń odżywiania prowadzące do upośledzenia płodności. Omówiono także wpływ na płodność chorób tarczycy i nadnerczy oraz zaburzeń hormonalnych związanych z zespołem policystycznych jajników. Zwrócono uwagę na diagnostykę poszczególnych jednostek chorobowych i ich leczenie w kontekście optymalizacji zdolności prokreacyjnych pacjenta.

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INTRODUCTION

According to World Health Organization infertility is a disease (ICD-10 code for female infertility is N97 and for male infertility – N46). It can be diagnosed when there is "the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse" (1). Therefore, the diagnostic procedures should start after 12 months of unsuccessful efforts to bear a child. From the beginning, it should concern both partners. From the beginning, it should concern both partners, as of infertility cases:

- 30% are due to a problem in the woman,
- 30% – in the man,
- 20% – both in the woman and in the man,
- and 20% remain unexplained (idiopathic).

To conceive and maintain a pregnancy, there is needed not only healthy sperm and healthy egg, properly built and functioning female and male genital organs, but also correct functioning of a number of factors, including hormones, to allow the embryo to nest in the uterine cavity, to be properly nourished, oxygenated, and tolerated by the maternal immune system.

It is crucial to differentiate inability to get pregnant (sterilitas) from inability to maintain pregnancy (infertilitas), usually manifested by recurrent miscarriages.

Recurrent miscarriages are defined as consecutive two or more spontaneous abortions (i.e., terminations of pregnancies prior to 20 weeks). They are mainly due to woman's health problems. The most common causes are chromosomal abnormalities of egg, sperm or embryo. The probability of an egg cell aneuploidy increases with maternal age. Recurrent miscarriages may be also caused by endocrinopathies (thyroid diseases, PCOS, diabetes, corpus luteum insufficiency), as well as anatomical defects of the uterus, infections (especially *Mycoplasma*, *Ureaplasma*, *Chlamydia*), immunological (systemic lupus erythematosus, antiphospholipid syndrome) or hematologic disorders (thrombophilia). The relationship was also shown between recurrent miscarriages and excessive consumption of caffeine, alcohol and cigarette smoking (2, 3).

Nowadays more and more often the state of reduced fertility (subfertility) is observed, caused mainly by aging. Postponing parenthood "for later" further increases the risk of occurrence of chronic diseases, that affect fertility, and often masks them when potential parents are not aware of them.

The article discusses some causes of infertility and miscarriages, focusing on endocrine disorders.

HYPERGONADOTROPIC HYPOGONADISM

The most important factor affecting woman's fertility is her age. It is an increasing problem (also a social problem), as the percentage of older women trying to conceive, rises. The function of ovaries is usually preserved until age of 40, afterward more and more cycles are anovulatory, the endocrine function of the ovary decreases and estradiol concentration in the luteal phase lowers. The symptoms of approaching menopause begin at about 47 years of age and last for about 4 years. The last period is usually between the age of 44 and 56, in Poland, statistically at 51.25 years of age (4). In men testosterone concentration may also decrease with age (late onset hypogonadism – LOH), but spermatogenesis remains preserved until senility. Reduced levels of estrogen in women and testosterone in men lead to increased pituitary gonadotropin secretion in a negative feedback mechanism (hypergonadotropic hypogonadism).

Premature ovarian failure, testicular failure

Premature ovarian failure (POF) can be diagnosed when, in a woman under 40 years of age, the concentration of FSH is above 40 IU/L twice at an interval of at least 4-6 weeks at low estradiol concentration and normal TSH and prolactin (PRL) levels. Ovarian reserve is reduced or falling to zero (low AMH – anti-Müllerian hormone level).

The cause of POF is unknown in 90% of cases. The ovarian injury may be the result of viral infections, smoking, and autoimmunity (5-9). POF may be a part of the autoimmune poliglandular syndrome (APS). Therefore, there is recommended screening for other potential autoimmune co-morbidities (Hashimoto's thyroiditis, Addison's disease, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, diabetes, celiac disease), including the determination of anti-ovarian antibodies, anti-thyroid peroxidase antibodies (a-TPO), anti-nuclear antibodies (ANA), rheumatoid factor (RF), anti-tissue transglutaminase antibodies, or if need performing a colonoscopy (10, 11).

POF may be also the result of radio- or chemotherapy (tab. 1) as well as surgical treatment of ovaries or testes. In the case of radiotherapy, ovarian failure occurs at doses > 0.06 Gy, and spermatogenesis depletion at doses > 1.20 Gy (12, 13). Irreversible damage to the ovaries occurs at a dose of > 8 Gy, and to testicular Leydig cells at a dose of > 20 Gy (12, 13). There were no reports indicating an increase in the percentage of congenital malformations, perinatal disorders or cancer in naturally conceived children of fathers previously treated for cancer by chemo- or radiotherapy, however the risk may be greater using IVF and ICSI because of a possible damage to the DNA of germ cells and lack of selection of sperm with normal DNA. To reduce the risk, it is recommended a delay of at least 12-18 months from the cessation of treatment to attempt of pregnancy.

Tab. 1. Drugs used in chemotherapy and the probability of fertility impairment

Probability of fertility impairment	Drugs
high	cyclophosphamide, melphalan, dacarbazine, busulfan, chlormethine (e.g. MOPP protocol)
middle	cisplatin, carboplatin, doxorubicin, BEP, ABVD
low	vincristine, methotrexate, bleomycin, mercaptopurine, vinblastine

Premature ovarian failure occurs in several genetic disorders, such as Turner syndrome (45X0), fragile X syndrome (*FMR1* gene), pseudohypoparathyroidism type 1a (*GNAS1* gene), galactosemia, Fanconi anemia, Bloom syndrome, Werner syndrome. There were also described rare cases of POF of genetic cause (POF1-7) (14, 15). When POF occurs in a woman under 30 years of age, cytogenetic testing with karyotype analysis is recommended (16).

The chances of getting pregnant in these cases are negligible. For people undergoing chemotherapy or radiotherapy, cryopreservation of ovarian cortex in women and sperm in men is proposed prior to the oncologic treatment. Causal treatment should be applied, if possible. There were case reports of restoring of gonadal function after applying of gluten-free diet in women with celiac disease. There were also trials of dehydroandrostenedione (DHEA) supplementation in women with POF. It was shown, that DHEA therapy in some patients with POF increases the chances of getting pregnant, reduces the risk of miscarriage and improves the results of IVF in women with POF (9, 10).

Therefore, it is recommended determine DHEA-S concentration in patients with POF. The use of melatonin in women with POF may be also considered, as it was shown, that this hormone regulates menstruation and gonadotropin concentrations in the perimenopausal period (19-24).

To prevent other health consequences of hypogonadism, hormone replacement therapy is used.

Hypergonadotropic hypogonadism in men should always be an indication to determine the karyotype, because the most frequent (often undiagnosed!) cause of it is Klinefelter syndrome. Subsequently, there should be done screening for causes of secondary testicular failure (tumor, inflammation, toxic damage of the testes, metabolic disorders).

HYPOGONADOTROPIC HYPOGONADISM

Deficiency of pituitary gonadotropins (FSH and LH) leads to secondary ovaries/testes failure, manifested by menstrual disorders in women, erectile dysfunction in men, low libido, lack or loss of tertiary sexual characteristics with thinning or even lack of pubic and axillary hair as well as facial hair in men (19).

Hypogonadotropic hypogonadism (HH) may be caused by tumor, granulomatous or inflammatory diseases, as well as injuries or damage caused by ischemia, radiotherapy or chemotherapy of the area of hypothalamus or pituitary. Gonadotropin deficiency may also be genetically determined (e.g. Kallmann syndrome – an isolated GnRH deficiency, Pasqualini syndrome, GnRH-R mutations) or be the result of developmental disorders (e.g. empty sella syndrome, pituitary hypoplasia).

If the causal treatment is impossible, hormonal replacement therapy is used: sequential estrogen and progestins in women, and testosterone in men. It allows also to achieve normally developed sexual organs. To induce ovulation, a selective estrogen receptor modulator – clomiphene is used, and when this treatment is inefficient, gonadotropins or pulsatile gonadotropin-releasing hormone (GnRH) therapy are administered.

Spermatogenesis can be induced in men by clomiphene, gonadotropins or pulsatile GnRH treatment, however, it may require a long period of time (even up to 2 years).

Dysfunction of the hypothalamic-pituitary-gonadal axis

Impaired activation of the hypothalamic-pituitary-gonadal axis results in alterations of pulsatile GnRH secretion (usually reduced frequency and amplitude of GnRH pulses). In men, the effect is gonadotropin deficiency, which leads to reduction of testosterone secretion and disorders of spermatogenesis. In women, there is no gonadotropin surge, without which ovulation does not occur, or too low FSH and LH concentrations, which result in disturbances in maturation of Graafian follicles or luteal phase insufficiency.

Functional hypothalamic amenorrhea can be diagnosed when, in the absence of organic or anatomical disorders of the hypothalamic-pituitary-ovarian axis, LH and FSH values are within normal limits or are slightly reduced, and there are reduced estrogen concentrations in the second phase of the ovarian cycle (19). The GnRH test is useful in diagnosis. Functional HH is usually the result of negative energy balance, caused by excessive physical effort or significant weight loss, or mental stress (low leptin and kisspeptin concentrations lead to disturbances in GnRH secretion).

HH may be also secondary to chronic diseases: cancer, chronic gastrointestinal diseases causing malnutrition, liver diseases leading to its failure or chronic kidney disease.

Stress, excessive exercise

These factors increase the secretion of corticotropin releasing hormone (CRH) from the hypothalamus, which leads to increased concentrations of ACTH and cortisol. Hypercortisolism reduces the frequency of GnRH pulses. In females under the influence of prolonged stress (businesswomen) or excessive exercise (sportswomen) luteal phase insufficiency, anovulatory cycles, menstrual disorders, amenorrhea and infertility are often observed. In competitive athletes reduced leptin concentrations were also found, which is associated with a small amount of fat and severe energy consumption. The most predisposed to these disorders are women practicing synchronized swimming, artistic gymnastics, ballet and long-distance running.

Emaciation, intensive weight loss

Impairment of gonadotropin secretion is often seen in cachectic and intensely weight-losing persons. An important role in it is probably played by leptin – a hormone secreted by adipose tissue, which stimulates pulsatile release of GnRH from the hypothalamus and secretion of LH and FSH from the pituitary. It is considered that the achievement of adequate body weight, i.e. an appropriate amount of fat, is a signal for the hypothalamus to initiate release of GnRH (onset of puberty). This mechanism is impaired in underweighted patients. The only effective way to restore normal function of the hypothalamic-pituitary-gonadal axis is to increase body weight. Hypothalamic amenorrhea caused by long-term eating disorders can be difficult to reversible or even irreversible (25). In women with normal body weight and persistent hypothalamic-pituitary failure, gonadotropins are used to stimulate ovulation.

There are trials to treat with kisspeptin (26).

Obesity

Obesity impairs fertility in various mechanisms, including:

- increased aromatization of androgens to estrogens in adipose tissue,
- decrease of SHBG concentration and the consequent increase of free estradiol and testosterone,

– increase of insulin level, which stimulates ovarian stromal cells to androgen production,
– increase of leptin concentration.

Elevated estradiol concentration in the early follicular phase reduces FSH concentration in the negative feedback mechanism (FSH < LH). Therefore, concentrations of estradiol and FSH on the third day of the cycle are good predictors of recruitment of the dominant follicle. In obese subjects, because of higher estradiol levels, FSH concentration is more reduced, but not very low, so that the new follicle is growing, but does not reach full maturity and the ability to ovulate (27). The follicles achieve the diameter of 2-10 mm, often undergo luteinization under the influence of high LH concentrations and atresia, becoming a part of the stroma, which secretes androstenedione and testosterone (28-30). These hormonal disorders result in oligoovulation or anovulation. It has been shown, that ovulation disorders are about 32% more frequent in women with a BMI of 25-30 kg/m^2 (31, 32). They may be reversible through weight loss – even a 5% weight reduction increases the chances for pregnancy (33). Metformin is effective in insulin resistance and abnormal glucose tolerance treatment (OGTT necessary).

In men, estrogen excess inhibits LH, and consequently testosterone secretion. It manifests with gynecomastia, decrease in libido and impaired spermatogenesis. Leptin excess may impair sensitivity of Leydig cells to gonadotropins and directly inhibit testosterone secretion by the testes (34).

HYPERPROLACTINEMIA

Hyperprolactinemia impairs pulsatile secretion of GnRH by the hypothalamus, and thus pulsatile LH and FSH release from the pituitary. It also inhibits gonadotropin receptors in gonads. The result in women is reduction of estradiol and progesterone concentrations and inhibition of follicular maturation (hence the picture polycystic ovaries in ultrasound), in men – lowering of testosterone levels and inhibition of spermatogenesis. High PRL concentrations in females may lead to amenorrhea-galactorrhea syndrome, while in males to lower libido, erectile dysfunction, and gynecomastia.

The diagnostic evaluation of hyperprolactinemia in women first requires exclusion of pregnancy. PRL physiologically increases with stress, sleep, sexual intercourse, exercise and teasing nipples. The drug-induced hyperprolactinemia is also often. PRL-enhancing drugs include: neuroleptics, antidepressants, metoclopramide, H_2-blockers, methyldopa, verapamil, reserpine, morphine, methadone, cocaine and oral contraceptives.

Serum PRL concentration > 150 ug/l is highly indicative of a prolactinoma. Prolactinoma is a pituitary adenoma arising from lactotroph cells that secrete PRL. Tumors > 1 cm (macroadenoma) may be accompanied by neurological symptoms: impaired vision, headaches, and hypopituitarism. In the treatment dopamine D_2 receptor agonists are used (bromocriptine, cabergoline, or quinagolide). The goal of treatment is to normalize hypothalamic-pituitary function and to reduce the tumor size, which often results in restoration of fertility.

Functional hyperprolactinemia, i.e. excessive secretion of PRL in response to physiological stimuli, can also cause ovulation disorders. Small dose of bromocriptine (e.g. half a tablet per night) normalizes the menstrual cycle.

To determine the cause of hyperprolactinemia metoclopramide stimulation test may be helpful. In healthy subjects, following oral administration of 10 mg Metoclopramide, a physiological 2-6-fold increase in the PRL concentration is observed. Lower than 2-fold increase supports the diagnosis of prolactinoma and is an indication for magnetic resonance imaging of the pituitary gland, while an increase of > 6-fold suggests functional hyperprolactinemia (35).

If high PRL levels are not accompanied by clinical symptoms, macroprolactinemia should be excluded. Macroprolactin (big-big prolactin – BB-PRL) is a biologically inactive molecule, which is, however, detected by the immunoassays and may lead to overestimation of PRL results.

Dopamine agonist treatment is not recommended in unexplained infertility, or when excessive secretion of PRL in response to metoclopramide is observed whereas basal serum PRL concentration is within normal range.

HYPOTHYROIDISM

Thyroid hormone deficiency leads to a decrease in levels of SHBG, an abnormal synthesis and metabolism of estrogens and a dysfunctional secretion of gonadotropins in response to GnRH. An increased production of thyroliberin (TRH) that stimulates the release of thyrotropin (TSH) and prolactin (PRL) results in the development of hyperprolactinaemia.

Both clinical and subclinical hypothyroidism may be associated with menstrual disorders (short cycles, heavy periods) as well as with miscarriage and preterm birth. Women with hypothyroidism who become pregnant are more likely to be hypertensive and develop placental abruption (36). Severe hypothyroidism results in low birth weight and worse health of newborn children, furthermore, school children with TSH levels > 2.5 mIU/ml exhibit an decreased IQ (37, 38).

The normal functioning of the thyroid gland should be restored at least 3 months before planned pregnancy. The optimal TSH level for a woman trying to get pregnant is 1-1.5 mIU/ml, and should not be higher than 2.5 mIU/ml.

The expectant mother and the developing fetus must receive the optimal amount of iodine for their thyroids to function properly. During pregnancy, women are recommended to maintain a daily intake of 150 μg of iodine (max. 500 μg per day). This is also recommended for women with Hashimoto's thyroiditis, those treated for thyroid hormone deficiency with levothyroxine,

as well as those with Graves' disease and with a euthyroid goiter (39).

Men with hypothyroidism may develop hypogonadotropic hypogonadism, which may also be characterised by swelling and then by a fibrosis of the intertubular space, which leads to testicular atrophy. Clinically, patients present with a diminished libido and erection problems (in up to 80% of cases), and those with severe hypothyroidism may develop testicular hydroceles. Semen tests reveal abnormal sperm morphology and a reduced number of sperm cells.

If thyroid hormone deficiency is present before puberty, this delays the whole process. Precocious pseudopuberty without symptomatic adrenarche is a very rare condition. Girls develop breasts, and may have galactorrhea and precocious menstruation. In boys, the maturation of Sertoli cells is delayed, with the proliferation lasting longer, resulting in the number of Sertoli cells being larger. Clinically, macroorchidism (large testes) and an increased number of sperm cells are observed.

Hyperthyroidism

Hyperthyroidism is characterised by shorter cycles than usual and light menstrual periods. However, in most women, ovulation occurs and fertility is preserved. Women with gestational thyrotoxicosis are at a higher risk of preterm delivery, preeclampsia, pregnancy-induced hypertension and congestive circulatory failure. In the perinatal period, thyroid storm may occur. Newborn children have lower birth weight, congenital disorders are more common and the risk of perinatal death is higher.

In men, thyrotoxicosis results in elevated secretion of SHBG in the liver, which leads to higher levels of estrogens than androgens. This translates into erectile dysfunction, decreased libido, gynecomastia, and reduced number and mobility of sperm cells.

Prepubertal hyperthyroidism may lead to delayed puberty. In boys, puberty is precocious, the proliferation of Sertoli cells is hindered and their number is reduced, which results in small testes and oligozoospermia.

Autoimmune thyroid diseases

Autoimmune thyroid diseases greatly influence fertility. Recurrent miscarriages are 2.73-5 times more common in women with chronic lymphocytic thyroiditis (Hashimoto's thyroiditis) than in the total population (40). Women with anti-thyroid antibodies have also been reported to fail IVF more frequently. The mechanism of these miscarriages remains unknown. During pregnancy, anti-thyroid antibodies may activate the immune system and induce an immune reaction against the fetal-placental unit or they may be only a peripheral marker of the autoimmune processes associated with the reproductive system which are responsible for pregnancy loss. Women who have had recurrent miscarriages are recommended to have the levels of anti-thyroid antibodies (a-TPO) measured (39). Some researchers suggest that miscarriages associated with thyroid autoimmunity in euthyroid women might be prevented by administering small doses of levothyroxine. However, this treatment has not been proven to be a reliably effective means of reducing the number of miscarriages or preterm deliveries in women with anti-thyroid antibodies and TSH level less than 2.5 mIU/ml (41-43).

Also, TSH receptor antibodies (TRAb), which are typical of Graves' disease but are also present in about 30% of individuals with Hashimoto's thyroiditis, may be associated with difficulties in fertilisation, implantation and placental development. The cross-reactivity of TSH receptor antibodies may inhibit the support of hCG to the corpus luteum. In pregnant women with autoimmune thyroiditis, the rate of increase in hCG levels is slower. For this reason, the levels of progesterone must be monitored in early pregnancy.

HYPERCORTISOLEMIA

Disorders of gonadal function are found in most patients with Cushing's disease/syndrome (a pituitary/adrenal tumour resulting in hypercortisolemia). The presence of an elevated amount of cortisol inhibits the secretion of gonadotropins, leading to hypogonadism. Also, this inhibits the secretion of SHBG. Furthermore, high levels of ACTH in Cushing's disease stimulate the production of androgens by the adrenal glands. Apart from the typical clinical picture of hypercortisolemia, men present with decreased libido, impotence and infertility, whereas women face menstruation problems and infertility. Moreover, if ACTH is produced in excessive amounts, women have concomitant symptoms of hyperandrogenisation, i.e. hirsutism and acne, which ought to be differentiated from polycystic ovary syndrome.

NON-CLASSICAL CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia (CAH) results from a gene-dependent (inherited in an autosomal recessive manner) deficiency of enzymes involved in cortisol synthesis. The cortisol deficiency leads to an increased secretion of ACTH, which stimulates the synthesis of adrenal androgens and leads to secondary adrenocortical hyperplasia. 21α-hydroxylase deficiency occurs in 95% of cases whereas deficiency of other enzymes (e.g. 11β-hydroxylase, 17α- hydroxylase) is less common.

The incidence of classical CAH is between 1:10 000 and 1:20 000, with the disease becoming apparent short after birth and the usually dramatic clinical symptoms resulting from the deficiency of cortisol and sometimes of mineralocorticoids (salt-wasting syndrome). In girls, the condition is characterised by masculinisation and virilisation of genitals, precocious adrenarche (development of axillary and pubic hair), and primary or secondary lack of menstruation,

whereas boys have precocious puberty. The incidence of non-classical CAH is between 1:30 and 1:1000. In this case, salt-wasting does not occur and the degrees of androgenisation are variable. The condition may result in precocious puberty with faster skeletal growth and maturation rate and low final height as well as severe acne. Non-classical CAH that becomes apparent in adults is diagnosed in women who present with acne, hirsutism, temporal alopecia, seborrhoea, macroclitoris, menstrual disorders, sometimes secondary lack of menstruation, and infertility. Cycles are anovulatory (in about 30% of women), and in the follicular phase the levels of progesterone are elevated, which may lead to implantation failure (in this group, the early pregnancy loss rate is more than 20%). Ultrasound images reveal microfollicular ovaries. In men, non-classical CAH leads to oligozoospermia, and testicular adrenal rest tumours (TART) are more common. Male fertility is reduced because adrenal androgens suppress the secretion of gonadotropins. Since the incidence of non-classical CAH is high, each male patient with oligozoospermia ought to have the concentrations of 17OH-progesterone measured. Laboratory tests reveal elevated levels of testosterone, DHEA-S, androstenedione and 17OH-progesterone as well as increased urinary excretion of androgen metabolites. After administering 250 μg of synthetic $^{1\text{-}24}$ACTH, the concentration of 17OH-progesterone increases and is > 10 ng/ml after 60 minutes and the levels of androgens increase simultaneously. The definitive diagnosis is based on genetic testing (*CYP21* gene mutation).

Treatment for CAH includes hydrocortisone, dexamethasone or prednisone in order to suppress ACTH, minimize the symptoms of androgenisation and adrenal hyperplasia, as well as in order to compensate for any cortisol deficiency. Apart from this, salt-wasting patients with classical CAH are treated with fludrocortisone.

POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS) is found in about 5-10% of women in child-bearing age. The primary cause of the condition remains unclear. However, possible causes include impaired secretion of gonadotropins, steroidogenesis disorders and impaired insulin function. PCOS is characterised by impaired ovarian morphology and function. Patients present with hyperandrogenism (hirsutism, acne, androgenic alopecia), irregular cycles or lack of menstruation and anovulatory cycles, which makes pregnancy difficult or even impossible (44). Women with PCOS are often obese, insulin-resistant and have metabolic syndrome, which puts them at a higher risk of developing cardio-vascular diseases, impaired glucose tolerance and diabetes (30). Insulin-resistant women with PCOS are more likely to have miscarriages. The number of miscarriages increases in women with higher BMI (29). PCOS has been shown to be more prevalent in patients with autoimmune thyroid disease and subclinical hypothyroidism, which may also contribute to infertility.

PCOS should be diagnosed after other causes of PCOS-like symptoms on ultrasound images have been excluded. These are non-classical congenital adrenal hyperplasia, hyperprolactinaemia and Cushing's syndrome.

Hormone tests reveal elevated concentrations of LH, distorted balance between LH and FSH hormones (usually > 2:1 whereas the correct ratio is about 1:1), hyperandrogenaemia (elevated concentrations of testosterone and androstenedione), decreased concentrations of SHBG, insulin resistance and hyperinsulinaemia. The elevated levels of androgens are due to the stimulation of the cells in the wall of the Graafian follicle by LH. Also, insulin uses IGF-1 receptors to increase the activity of 17α-hydroxylase in the ovary, which stimulates the synthesis of androgens. As a result of hyperinsulinism, the synthesis of insulin-like growth factor-binding protein 1 (IGF-BP 1) is decreased, which increases the synergistic activity of IGF-1 with insulin. Consequently, the ovaries are enlarged and the tunica albuginea is thickened, which additionally hinders ovulation. Women with PCOS are more likely to miscarriage (30-50%). It is accepted that this is due to hyperinsulinaemia and high activity of plasminogen activator inhibitor (PAI).

In order to induce ovulation, patients with PCOS and infertility are treated with clomifene, which is a selective estrogen receptor modulator (SERM), and if this fails, gonadotropin preparations are administered. Recently, aromatase inhibitors (letrozole) have also been used and are now under registration process.

Obese women should definitely reduce their body weight, as this either restores ovulation cycles or augments the effect of pharmacological stimulation. According to the literature, good results have also been achieved in patients treated with metformin. It has been shown that metformin increases the frequency of ovulation up to 46% (as compared with placebo – up to 24%), and combined with clomifene – up to 76% (45). It has also been demonstrated that it decreases insulin resistance, reduces the activity of PAI and diminishes the miscarriage rate from 20 to 9.1%. It has been suggested that treatment with metformin prior to and during pregnancy is the only way of reducing pregnancy losses in women with PCOS (46, 47). No teratogenic effect of metformin has been evidenced so far. However, randomised studies in large patient populations have not confirmed the association between metformin use and a greater chance to get pregnant and carry to term. For this reason, according to the newest recommendations, infertility treatment should not be an indication for its use. However, treatment with metformin is fully justified in women with PCOS and insulin resistance.

CONCLUSIONS

Infertility is a multifactorial disease. Hormonal disorders are a common cause of infertility. Endocrine diagnostics should be a necessary part of evaluation of infertile couple. Endocrinologist can help infertile couple not only in getting pregnant, but also contribute to the birth of a healthy baby by a healthy mother.

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