Congenital adrenal hyperplasia – contemporary diagnostics and management during pregnancy

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Abstract
Congenital adrenal hyperplasia (CAH) is an autosomal recessive defect in steroidogenesis, mostly affecting 21-hydroxylase enzyme deficiency. Depending on the clinical level of 21-hydroxylase deficiency, three main types of CAH are differentiated: (1) classical salt-wasting (2) simple virilizing (classical non-salt-wasting) (3) non-classical. CAH prevalence is estimated at 1 : 14 000-1 : 10 000. Clinical picture varies considerably depending on the form. In the classical salt-wasting form, CAH may develop into shock. In simple virilizing CAH, virilization in girls and precocious puberty in boys are dominant. The non-classical form usually presents as hyperandrogenisation and fertility issues. CAH management is mainly based on the use of glucocorticoid therapy supplemented with mineralocorticoids if necessary. CAH requires special management during pregnancy and during labour. For accurate CAH treatment, a number of specialists must be involved, including endocrinology, gynecology, sexology, urology, genetics and psychology specialists.

Key words: congenital adrenal hyperplasia, glucocorticoids

Introduction
Congenital adrenal hyperplasia is an autosomal recessive disease related to steroidogenesis errors. In general, CAH decreases the availability of cortisol, and of aldosterone in its severe cases.

21-hydroxylase deficiency in zona fasciculata and zona glomerulosa of the adrenal cortex is the most common form of the disorder. It is caused by CYP21A2 gene mutation, which leads to excessive secretion of adrenal androgens [1].

Less frequent CAH forms include 11-beta-hydroxylase deficiency, 3-beta-hydroxysteroid dehydrogenase, 17-alpha-hydroxylase, 17,20-lyase and 11-beta-hydroxysteroid dehydrogenase type 1.

Depending on the degree of 21-hydroxylase deficiency, three main clinical types of CAH are differentiated [2]:
1) Classical salt-wasting (SW) form with a complete lack of enzyme activity causing cortisol deficiency and aldosterone deficiency.
2) Simple virilizing (SV) form, in which 1-2% enzyme activity without the symptoms of aldosterone deficiency in cortisol deficiency is preserved.
3) Non-classical (NC) form is a late onset adrenal hyperplasia manifesting itself through mild androgen excess during adolescence, with a 20%-50% 21-hydroxylase activity.

Epidemiology
The prevalence of CAH in its classical form reaches approximately 1 : 14 200 live births, based on newborn screening tests conducted in the United States and Great Britain. CAH prevalence is higher for certain ethnic groups, i.e. 1:280 for Alaskan Eskimo tribes [3].

In Poland, CAH is not included in standard newborn screening tests. Its prevalence is estimated at 1 : 14 000 to 1:10 000 live births.

Non-classical form of CAH is most frequent, with a prevalence of 1:1000 [4]. Of classical forms, the salt-wasting variety occurs more often. CAH is a relatively rare condition affecting approximately 1% of pregnant females.

Clinical picture
Although the classical salt-wasting form is already present during fetal life, symptoms of salt deficiency are manifested in infancy. If untreated, they lead to vomiting and diarrhoea. Lack of treatment may lead to death caused by hyponatremia, hyperkalemia, metabolic acidosis and shock, which may develop at that stage [5].

The severity of CAH in its simple virilizing form depends on the level of cortisol deficiency and the degree of adrenal androgen excess. In severe cases, simple virilizing CAH may lead to adrenal crisis, and in less severe ones to hypoglycaemia and hyperandrogeni-
sation, which takes the form of virilisation in girls, and precocious puberty in boys [6].

In non-classical form (NC) of CAH, symptoms are manifested relatively late and are non-specific. These include precocious puberty, accelerated growth and premature mineralisation of epiphyseal plates leading to growth suppression. Hirsutism, menstrual disorders, acne, and virilisation symptoms are typical of this type of CAH. Fertility issues developing with age are also common and affect approx. 13% of females with CAH [7].

In classical CAH, insufficient glandular development of the breasts is frequently recorded, which is probably caused by increased exposure to androgens during fetal life.

**Fertility issues**

Infertility affects approximately 40% of women suffering from the classical CAH form, and 20% of those suffering from the SV form [8]. Both conception and pregnancy cannot occur without a series of major changes in the body – without these, the blastocyst and the endometrium cannot interact successfully. During follicular phase, growth of endometrium is triggered by estrogen, with progesterone remaining at low concentration levels. Progesterone concentrations rise in the luteal phase and fall if there is no pregnancy.

In CAH females, concentration levels of progesterone are much higher than in normal population. Endometriotic milieu is affected by progesterone secretion during the luteal phase, therefore implantation must occur within a limited period of time.

In CAH females undergoing IVF, poor endometrium and recurring implantation failures are frequently observed. Even when managed by excessive glucocorticoid treatment, high concentrations of progesterone may still be detrimental to fertility, especially in terms of the quality of cervical mucus and sperm penetration. Both the oocyte and endometrial receptivity may be influenced by elevated progesterone levels.

CAH-related fertility issues are caused by a number of factors:

1) Intrauterine exposure to high doses of adrenal androgens affecting hypothalamus-pituitary-ovarian axis function.
2) High concentration of progesterone, 17-alpha-hydroxyprogesterone (17-OHP) and androgens which block gonadotropin secretion and ovulation.
3) A frequent co-occurrence of PCOS syndrome and insulin resistance increasing the risk of miscarriage and unovulatory cycles.
4) Intercourse difficulties caused by anatomical defects of external genital organs and the consequences of reconstructive surgical procedures.

Classical CAH patients are prone to developing metabolic syndrome, with excessive weight, obesity, higher concentration of insulin and insulin resistance being also more frequent. Factors causing metabolic issues include adrenaline deficiency causing hyperinsulinemia and insulin resistance via lack of the limiting effect of catecholamines on beta-3 receptors.

Adrenaline deficiency is related to hyperleptynemia, excessive weight and obesity, it also impedes thermogenesis and lipolysis. Hyperinsulinemia and insulin resistance, along with obesity and recurring hypercortisolemia may lead to arterial hypertension, dyslipidemia, carbohydrate metabolism disorders and endothelial cell damage.

**CAH diagnostics**

Laboratory diagnostics of classical CAH forms may involve the following criteria: evaluation of 17-OHP concentration level in serum, ACTH stimulation test, evaluation of steroids in urine, and CYP21A2 gene mutation analysis. In most patients suffering from the SW and SV varieties, 17-OHP concentration level in serum is higher than 35 ng/ml, with levels over 100 ng/ml being the average value. Increased excretion of 17-ketosteroids (17KS) in urine is also frequently recorded [9].

In the NC variety of CAH, laboratory diagnostics is based on evaluating the concentration levels of 17-OHP, and ACTH stimulation test. The tests should be carried out during follicular phase. If 17-OHP levels exceed 2.5 mg/ml (or 4 ng/ml, as suggested by some authors), ACTH stimulation test should be carried out. 17-OHP levels exceeding 10 ng/ml are treated as a definite marker of non-classical CAH.

ACTH stimulation test results are often treated as definitive in diagnosing NC CAH. In a test using synthetic ACTH, a positive CAH result ranges from 15 ng/ml to 100 ng/ml. Value ranges from 10 ng/ml and 15 ng/ml are often found in asymptomatic carriers (heterozygote) [10].

**CAH management during pregnancy**

Prenatal treatment and patient monitoring practices are similar to standard CAH practices recommended for non-pregnant patients [14]. However, the following guidelines should be observed:

1) As both the corpus luteum and adrenal glands secrete 17-OHP, CAH management during pregnancy cannot rely on monitoring the hormone.
2) Glucocorticoid dosage may need to be altered during pregnancy. The aim of the treatment is to keep concentration levels of testosterone and androstenedione in ranges typical of a normal pregnancy. During glucocorticoid treatment, caution should be taken in order to avoid inducing Cushingoid features.

3) As gestational diabetes is more frequent in pregnant women suffering from CAH, blood glucose should be monitored.

4) Medication which is metabolized (inactivated) by the placenta, such as hydrocortisone, prednisone and prednisolone should be selected, with hydrocortisone being the drug of choice for most practitioners. The dosage recommended depends on the medication selected: hydrocortisone daily dosage: 20-30 mg divided into two or three doses, prednisolone daily dosage: 4-7 mg divided into 2 doses. In non-classical CAH, glucocorticoid treatment is unnecessary if the patient has not received the therapy before pregnancy. However, the therapy should be continued with a glucocorticoid metabolized (inactivated) if the patient’s condition has been managed with glucocorticoids prior to the pregnancy.

5) Blood pressure, electrolytes, androgen concentration levels, and plasma renin activity should be monitored throughout the pregnancy.

6) Adrenal insufficiency may result in vomiting, nausea, insufficient weight gain and increased salt craving. Should any of these symptoms occur in pregnant women with CAH, additional evaluation is necessary.

Monitoring of mineralocorticoids treatment is based on plasma renin activity test results, which should not exceed the upper limit of normal. Mineralocorticoids may also be used – Cortinef is a recommended drug in CAH.

Prenatal treatment with dexamethasone crossing the placenta is only considered in the case of female fetuses with a risk of classical forms of CAH. The aim of the therapy is to reduce genital virilization of the fetus and prevent genitoplasty procedures usually performed in such cases. The treatment sparks controversy as it may be unsolicited in some cases due to the specifics of genetic diagnostics. As trophoblast biopsy and amniocentesis can be carried out long after the treatment should be started, some fetuses are at risk of unnecessary exposure to dexamethasone.

**CAH management during labor**

Children of CAH-positive mothers should be delivered in specialized medical centers, preferably through Cesarean section (depending on prior feminizing genitoplasty), with a simultaneous administration of stress dose glucocorticosteroids administered as soon as labor begins:

- 50-100 mg hydrocortisone sodium succinate administered intravenously every 6-8 hours.
- Adjustment of sodium deficiency: administering sodium with 10 ml 10% NaCl.
- Stress dose of glucocorticoid should be maintained until after delivery. Gradual discontinuation of increased hydrocortisone levels on the third day following delivery is recommended [16].

According to current recommendations, glucocorticoid and mineralocorticosteroid therapy is not a contraindication for breastfeeding.

Ambiguous genitalia of the infant warrant evaluation of 17-OHP values on/after day 3 of life. In the event of one CAH-positive parent with the other parent being heterozygous for CYP21A2 mutation, infant 17-OHP values on/after day 3 of life should also be evaluated.

**Conclusion**

CAH therapy depends on the form presented, symptom severity and the aim of treatment. As such, treatment aims to alleviate co-symptoms, improve sexual function and fertility, and prevent the development of metabolic syndrome. For accurate CAH treatment, a number of specialists must be involved, including endocrinology, gynecology, sexology, urology, genetics and psychology specialists.

**References**


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