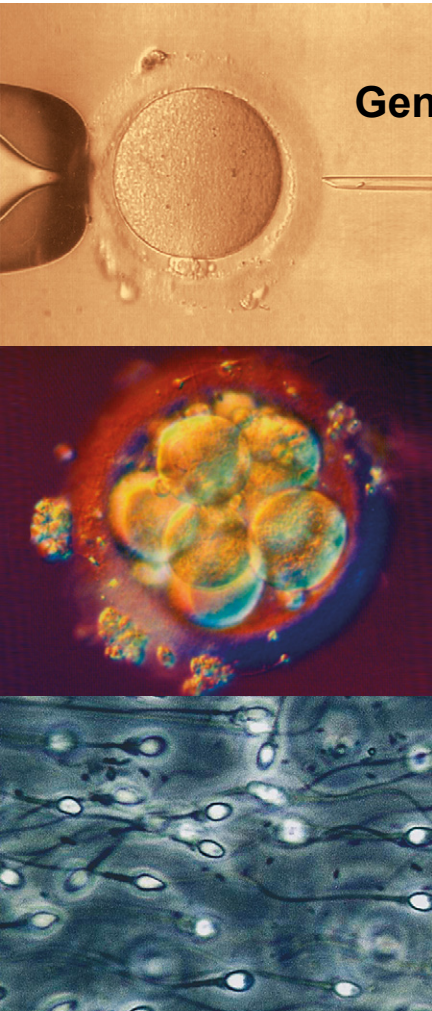


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Genetic Causes in Adrenal or Ovarian Hyperandrogenism in the Reproductive Years

M. Bals-Pratsch¹, B. Seifert¹, O. Ortmann²

Hyperandrogenism and androgenisation frequently occur within families so that a monogenic cause such as congenital adrenal hyperplasia (CAH) must be considered. For the most part, classical CAH is first diagnosed and treated on the basis of common sex development disorders in early childhood by pediatric endocrinologists. In contrast, the non-classic "late-onset CAH" is mostly symptomatic by androgenisation from the age of puberty. For both forms, the final diagnosis relies on the evidence of a CYP21 gene mutation. Even though the incidence of CAH in newborns with a ratio of 1:5000 is rare, the frequency of heterozygotes in central Europe is relatively prevalent with 1:50. In patients with hyperandrogenism of adrenal origin who desire children, a CYP21 mutation should therefore be excluded. In case of a known mutation carrier, the CYP21 gene diagnostic also should be applied on the partner. If both partners are genetic carriers, a dexamethasone (DEX) therapy of the pregnant woman should be considered very early in each case immediately after determining a pregnancy to prevent serious virilization of the external genitalia of female CAH fetuses. A common differential diagnosis is androgenisation through ovarian hyperandrogenism. For many years, candidate genes for the polycystic ovary syndrome (PCOS) have been investigated. The search focuses on genes involved in the regulation of insulin, follicle maturation as well as androgen secretion and regulation. Especially promising is a gene polymorphism on chromosome 19p13.2 in association with insulin resistance and disordered β -cell functions. Examinations of polymorphisms in FSH receptor genes make one expect that the effective gonadotropin dose in ovarian stimulation can be individually determined before treatment. Thus, severe hyperstimulation syndromes in PCOS patients possibly can be avoided. One might anticipate that new results in molecular genetic PCOS research in the upcoming years will lead to significant improvements in treatment strategies. **J Reproduktionsmed Endokrinol 2009; 6 (1): 19–23.**

Key words: PCOS, androgenisation, virilization, CAH, candidate genes, functional genetic polymorphisms, CYP21

■ Hyperandrogenism

The accumulation of hirsutism within families and balding in male family members suggests a joint genetic cause. Hirsutism, acne and loss of hair are clinical signs of hyperandrogenism in the reproductive years. These bodily symptoms also are described as androgenisation, which is to be distinguished from virilization with clitoral hypertrophy up to the point of disorders of sex development (DSD). A hypertrichosis on the other hand is not androgen-dependent but rather ethnically conditioned.

Hyperandrogenism affects not only skin and hair, but also leads to abnormal menstrual cycles and infertility as well as disorders in the metabolism of carbohydrates and lipids. Like hirsutism and balding, polycystic ovaries, insulin resistance and obesity also appear more frequently within affected families. Metabolic disorders are likely the common cause for abnormal menstrual cycles and hyperandrogenism. A raised sensitivity of target cells as well as increased or reduced local activity of enzyme systems in the target cells can cause hyperandrogenism.

Androgens are mainly produced in the adrenal glands and in the ovaries as well as in fatty tissue. The most important androgens are testosterone and DHEAS. The localization of **androgen-producing tumors** is signaled by DHEAS (Fig. 1) for adrenal tumors and by testosterone for ovarian tumors. Suspicion of

a tumor exists if values are $> 800 \mu\text{g/dl}$ for DHEAS and $> 200 \text{ ng/dl}$ for testosterone. In patients with androgenisation and hyperandrogenism with suspicion of neoplasms, imaging diagnostics of the adrenal glands and ovaries and, if indicated, of the pituitary gland are obligatory as well as diagnostics for internal

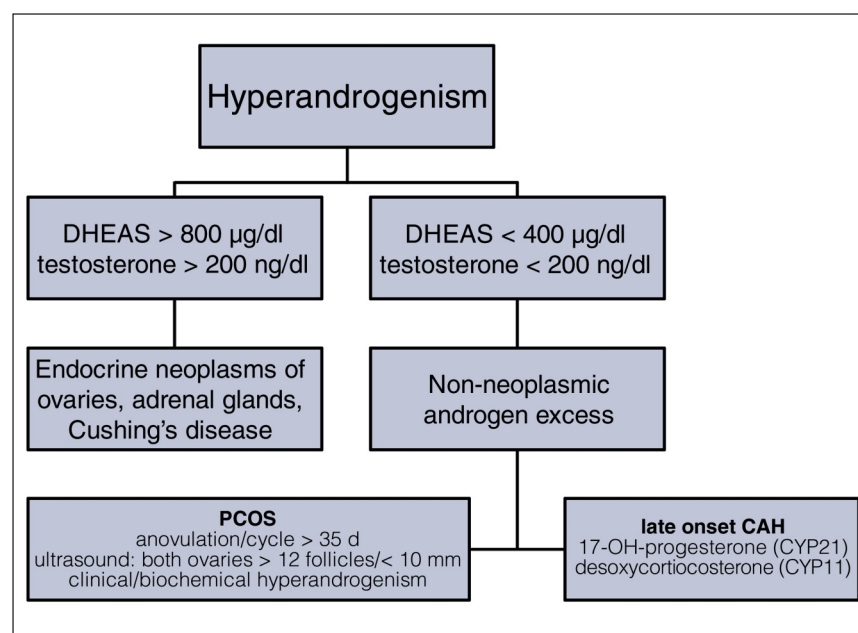


Figure 1. Clinical work-up of hyperandrogenism

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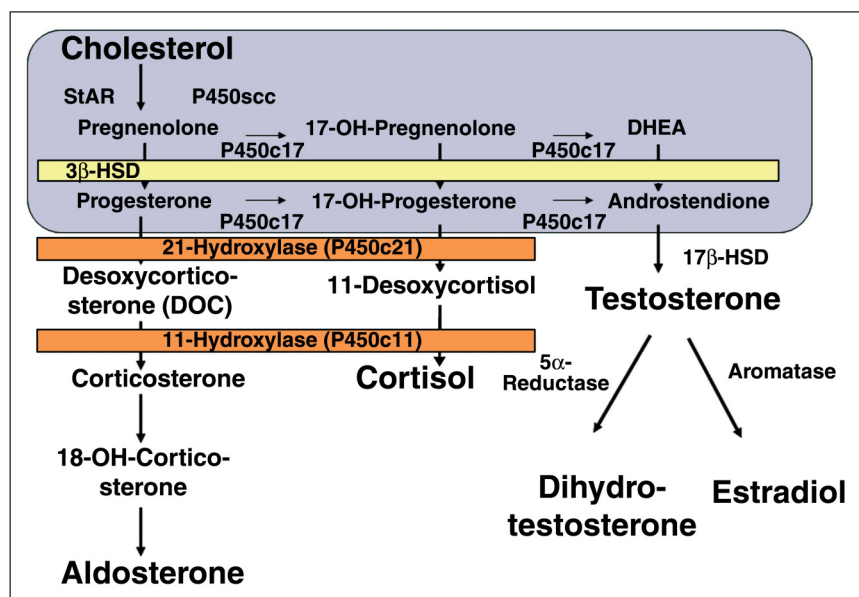


Figure 2. Simplified scheme for adrenal steroidogenesis

medicine and endocrinology, for example in suspicion of **Cushing's syndrome** (adrenal) or **Cushing's disease** (central). The diagnostics should be performed interdisciplinarily with gynecologists and internists specializing in endocrinology. If tumor occurrence is excluded, androgenisation either through medication containing androgens such as Gynodian® Depot or functional disorder can be considered for the differential diagnosis.

Functional Hyperandrogenism

The most common cause of androgenisation in the reproductive years is functional hyperandrogenism. Through hyperandrogenism, follicle atresia and anovulation frequently occur with the morphological correlative of polycystic ovaries. Mainly congenital hyperplasia of adrenals (CAH) in its various characteristics and polycystic ovary syndrome (PCOS) are to be distinguished from one another. However, CAH is seldom and PCOS frequent.

■ Congenital Adrenal Hyperplasia (CAH)

Inherited disorders of adrenal steroidogenesis result from a deficiency in one out of the five enzymatic steps necessary for normal cortisol synthesis (Fig. 2). Precursors of cortisol and aldosterone accumulate and DHEAS and testosterone production increase. The most com-

mon gene mutation CYP21 on chromosome 6p21.3 causes deficiency of 21-hydroxylase and accounts for 95 % of CAH cases. The incidence in newborns is 1:5,000–15,000. The precursor 17-OHP progesterone and androgen productions increase and cortisol and aldosterone biosynthesis are limited. 11β-hydroxylase deficiency is seldom and caused by CYP11B2 mutation (5 % of CAH cases). The gene is located on chromosome 8q24.3 and the incidence of the gene mutation in newborns is 1:100,000. The precursor desoxycortisol (DOC) is accumulated, thus affected patients suffer from hypertension. Other gene mutations in the adrenal steroidogenesis such as the 3β-HSD-II-gene mutation on chromosome 1p13.1 with deficiency of 3β-hydroxy-steroid-dehydrogenase [1] and accumulation of 17-OH-pregnenolone are rare (< 1 % of CAH cases).

The virilizing characteristic of **classic CAH** (with salt loss or simply virilization) is the most common cause of disorders of sex development. This diagnosis is made by pediatric endocrinologists based on symptoms mostly in newborn or infant stages. Nowadays elevated 17-OHP is detected regularly within the newborn screening in Germany and other Western countries. Prompt treatment with glucocorticoids in simple virilization CAH (ca 25 %) and also mineralocorticoids in CAH with salt loss (ca 75 %) has to be initiated to avoid life-

threatening events. The non-classic CAH (**late-onset CAH**) is mostly symptomatic beginning at puberty because these patients do not have genital abnormalities. Instead, these patients are mainly seen first by gynecologists because of menstrual disorders like secondary amenorrhea or oligomenorrhea, hirsutism and acne. In adrenal hyperandrogenism with increased DHEAS, high 17-OHP values in the follicular phase of the cycle indicate CYP21 mutations. 17-OHP values do not represent any reliable discriminating factors even in combination with the adrenocorticotrophic hormone (ACTH) test, unless the test results are generated in a highly specialized endocrine laboratory. Genetic counseling with molecular genetic diagnosis is mandatory in confirming the diagnostic of CAH. Patients with CAH should be regularly seen and treated with hydrocortisone by gynecologists and internists specialized in endocrinology [2].

CAH and the Desire to Have Children

CAH is a monogenic disorder with a frequency of 1:50 in heterozygous mutation carriers in central Europe. The expected ratio of homozygous affected, heterozygous or homozygous normal children in mutation carrier families according to the Mendelian rules of inheritance is 1:2:1. CAH homozygous females and males with a heterozygous partner even face a risk of 50 % for affected children. To improve fertility in CAH females with menstrual disorders the hydrocortisone substitution regimen should be changed to three to four single doses including a dose at 3 a. m. [3].

Genetic counseling should be offered to all couples at risk before getting pregnant. The possibility of **prenatal dexamethasone (DEX) treatment** as an experimental strategy to prevent unwanted virilization in affected female embryos should be discussed with pediatricians and gynecologists experienced in endocrinology and prenatal medicine. Treatment with DEX 20 µg/kg bodyweight in three divided doses based on prepregnancy weight (maximum 1.5 mg daily) is to be started at the time of diagnosing a pregnancy. DEX crosses the placenta from the mother to the embryo, suppresses ACTH secretion and prevents exaggerated adrenal androgen produc-

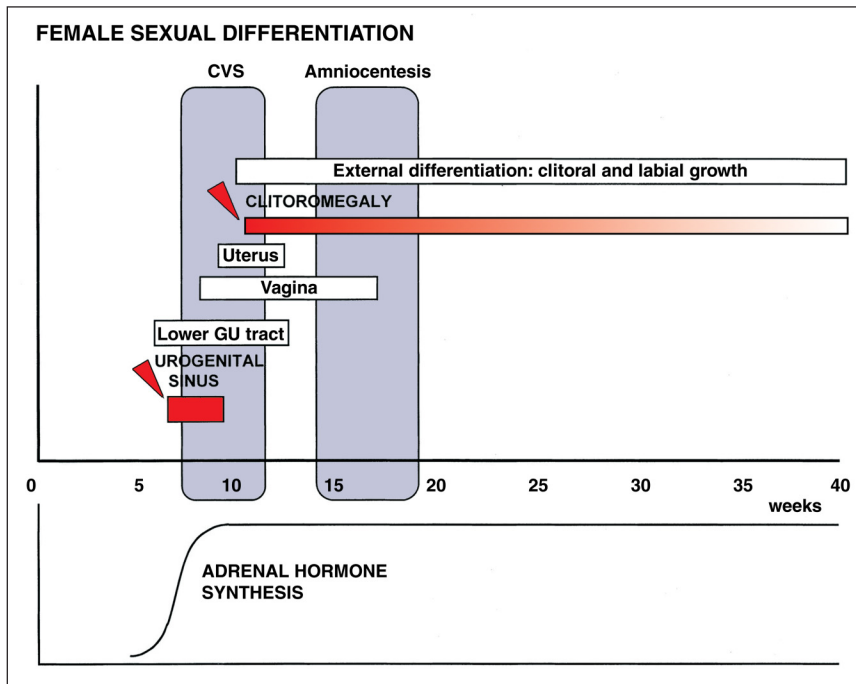


Figure 3. Female sexual differentiation. Reprint with permission from [4]. Copyright 2001, The Endocrine Society.

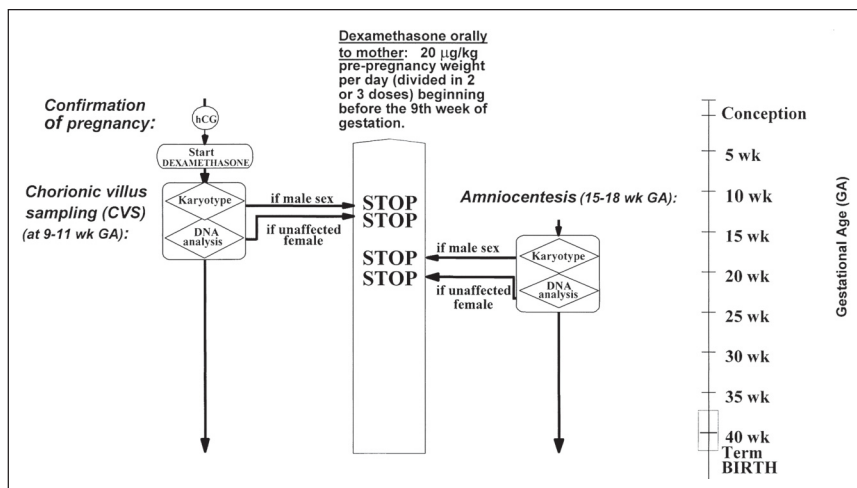


Figure 4. Prenatal dexamethasone-treatment to the mother in affected female and non-affected female and male fetuses. Reprint with permission from [4]. Copyright 2001, The Endocrine Society.

tion and thus fetal hyperandrogenism. If treatment is started as late as the ninth week of pregnancy, virilization of the affected female fetuses has already occurred (Fig. 3). Thus DEX treatment should be started in all pregnancies at risk, although seven of eight fetuses are treated without reason at least for a short term [4]. It can be stopped in male or unaffected female fetuses after karyotyping and DNA analysis by chorionic villus sampling (CVS) at 9–11 weeks of gestation or amniocentesis at 15–16 weeks of gestation (Fig. 4). Although it is undisputable today that DEX obviates the need for traumatizing genital surgery in affected females, potentially harmful

effects on cardiovascular, metabolic and neuroendocrine disorders in adult life cannot be excluded [5]. Recently long-term negative effects have been reported on verbal working memory and on certain aspects of self-perception even in short-term treated, CAH-unaffected children [6].

Thus, parents should be thoroughly informed about the potential risks and uncertainties as well as the benefits of the controversial aspects of prenatal treatment with DEX. It is important that all cases of prenatal treatment are reported to a CAH study center regarding the safety and future use of the treat-

ment. In Germany, the “Arbeitsgemeinschaft Pädiatrische Endokrinologie” (APE), a pediatric endocrinology association, has been collecting data centrally on the prenatal CAH therapy since 1990 at the University Children’s Medical Center of Erlangen (e-mail: Helmuth-Guenther.Doerr@uk-erlangen.de).

Prenatal CAH therapy in Germany still requires optimization. Some of the affected families are not adequately advised and diagnosed regarding endocrinology and genetics. Because interdisciplinary specialized pregnancy guidance is often missing, frequently initiation of DEX treatment is too late or with an inadequate dose of DEX or without treatment observation. Reporting to a central registration office only takes place partly (Download registration form: <http://www.repromedizin.de/files/downloads/aktueller-arztfragebogen-ags.pdf>).

Polycystic Ovary Syndrome (PCOS)

Functional hyperandrogenism often accompanies the sonographic image of polycystic ovaries (Fig. 5). The cardinal clinical symptoms are acne, hirsutism and an abnormal menstrual cycle. Stein and Leventhal [7] were the first to describe this syndrome. According to Geithövel et al [8] patients with polycystic ovaries can be divided into three groups: “ovarian form”, “adrenal form” or “metabolic syndrome”.

This complex grouping division, which corresponds to a category-parameter-cluster including a functional sonographic ovary score, has so far not been able to prevail. The classification of the American Association of Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) [9] is simple to use in clinical routine. PCOS, however, can only be diagnosed according to the current consensus from ASRM and ESHRE if at least two of the three PCOS criteria are fulfilled (ultrasound, hyperandrogenism, and anovulation or a cycle > 35 days [Fig. 1]). According to the ASRM/ESHRE consensus, other causes of hyperandrogenism, such as classic or non-classic CAH or Cushing’s syndrome, are exclusion criteria for PCOS.

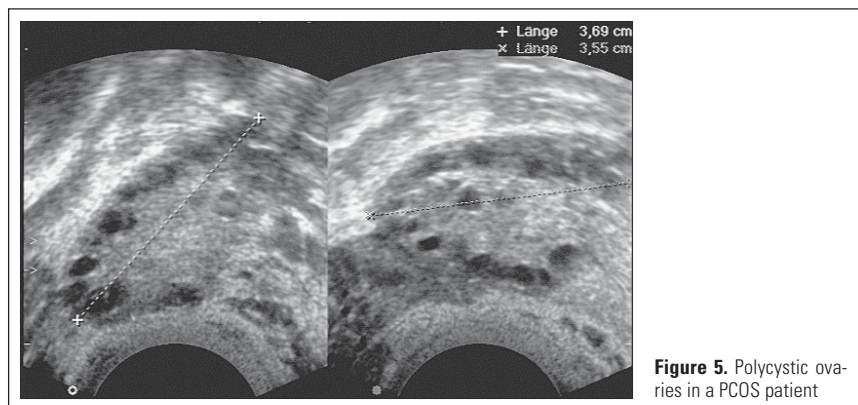


Figure 5. Polycystic ovaries in a PCOS patient

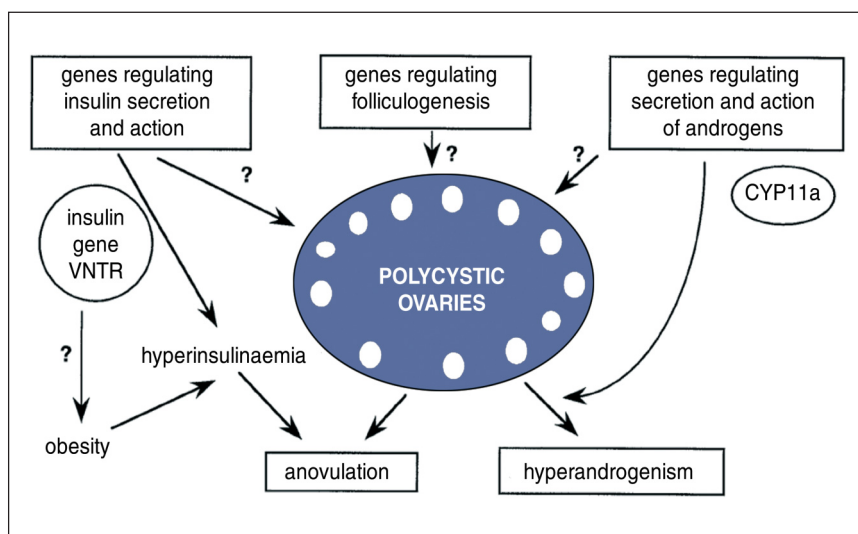


Figure 6. Suggested aetiological factors in PCOS. Reprint with permission from [10].

Candidate Genes

For many years, there has been a search for candidate genes for PCOS. In accordance with common clinical symptoms and findings like obesity, resistance to insulin, disorders in metabolizing lipids, hyperandrogenism, anovulation and tendency to miscarry, uncountable genes in correlation with these symptoms were examined (Fig. 6). Research particularly concentrates on genes in the regulation of insulin, the maturation of follicles and androgen secretion and effect [10]. The results are up to now inconsistent and contradictory because the areas of research are based on different definitions of PCOS as well as only on a small number of cases [11].

A potential candidate gene is the **insulin gene**, which influences the secretion and effect of insulin. The promoter of the insulin gene determines its expression. A VNTR (variable number of tandem repeats) polymorphism exists here. The number of repeats influences the expres-

sion of the insulin gene. Most women carry class-I alleles with an average of 40 repeats or class-III alleles with a mean of 157 repeats. An association between the existence of class-III alleles of the insulin gene and PCOS is probable. This would explain the risk for hyperinsulinism and type-II diabetes in PCOS patients [12].

A further candidate gene is the **insulin-like growth factor (IGF)**. The homozygotic mutation of the IGF2 gene with two G alleles of the ApaI variant is associated with PCOS [13]. The existence of the G allele possibly causes a raised IGF2 expression and secretion in the liver. IGF2 stimulates the production of androgens in the ovaries and adrenal glands and thus possibly explains an aspect of the pathomechanism in PCOS. On the other hand, our data showed no significant difference for the genome as well as for the allele distribution in the IGF2 gene among 219 PCOS patients and 152 healthy subjects [14].

The **CYP11a** gene codes the cytochrome 450scc as the key enzyme for the androgen biosynthesis and metabolism. It is localized on chromosome 15. While Gharani et al. [15] found an association between the 4R gene type polymorphism in the CYP11a gene and hyperandrogenism in PCOS patients, San Millán et al. [16] could not prove a correlation.

The examination of 37 candidate genes in 150 PCOS families showed an association with PCOS only for the **follicle-stimulating hormone receptor (FSHR)** gene [17]. As opposed to activin, follicle-stimulating hormone receptor inhibits follicular growth, increases ovarian androgen production, suppresses the endogenous FSH level and inhibits the release of insulin. These effects are characteristic of PCOS. Up to now, this data could not be confirmed [18].

In the meantime, with the D19S884 allele 8 (A8) within the intron 55 of **fibrillin 3 (FBN3)** gene on chromosome 19p13.2, a possible PCOS candidate gene has been identified by a workgroup from Chicago [19]. In this examination of 412 PCOS families, the D19S884 polymorphism was associated with resistance to insulin and a defective β -cell function of the pancreas.

From a clinical perspective, not only the pathogenesis of the PCOS is of significance but also the treatment options, particularly in infertility. The interaction between FSH and its receptor plays a key role in ovarian stimulation with gonadotropins. Polymorphisms in FSH receptor genes regarding the ovarian response were examined by several workgroups.

Looking at the genotype of the **FSH receptor** gene polymorphism p.N680S, patients with a slight or increased ovarian response to FSH stimulation can be identified before the beginning of the stimulation cycle [20]. Withdrawal from treatment and severe ovarian hyperstimulation syndrome therefore can possibly be avoided in the future.

The years to come will be exciting because genetic diagnostics will have increasing clinical significance in the clarification of PCOS, resulting in improved treatment strategies for internal medicine, endocrinology and reproductive medicine.

■ Practical Aspects

The most common cause of hyperandrogenism in the reproductive years is PCOS. For several years research has concentrated on identifying potential candidate genes for PCOS without a breakthrough yet. Although PCOS is frequent, rare cases of endocrine neoplasms and late onset CAH have to be distinguished from PCOS. Patients at risk of giving birth to CAH homozygous female fetuses should be offered prenatal dexamethasone treatment to prevent virilization in affected female embryos.

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