# Clinical, hormonal, ovarian, and genetic aspects of 46,XX patients with congenital adrenal hyperplasia due to *CYP17A1* defects

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**Objective:** To perform a clinical, biochemical, and molecular evaluation of patients with *CYP17A1* defects, including ovarian imaging.
**Design:** Retrospective study.
**Setting:** Tertiary care center.
**Patient(s):** Sixteen patients with congenital adrenal hyperplasia due to *CYP17A1* defects with a median chronological age of 20 years and belonging to 10 unrelated families.
**Intervention(s):** None.
**Main Outcome Measure(s):** Clinical and biochemical parameters, molecular diagnosis, ovarian imaging, and therapeutic management.
**Result(s):** Seventy-one percent of patients presented with primary amenorrhea, 50% had no breast development, and pubic hair was absent or sparse in all patients; 88% had high blood pressure at diagnosis. Basal LH and P levels were high, and androgen levels were low in all patients. Ultrasound revealed ovarian enlargement in 68.7% and ovarian macrocysts in 62.5% of patients before treatment; three patients had a previous surgical correction of ovarian torsion or rupture. Molecular analysis revealed inactivating *CYP17A1* mutations in all patients. The most prevalent mutation was p.W406R, and one patient bore a novel p.G478S/p.I223Nfs*10 compound heterozygous mutation. Treatment with dexamethasone, estrogen, and P resulted in reduction of ovarian volume.

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**Conclusion(s):** Amenorrhea, absent/sparse pubic hair, hypertension, and ovarian macrocysts, whichincrease the risk of ovarian torsion, are important elements in the diagnosis of 46,XX patients with *CYP17A1* defects. High basal P levels in patients with hypergonadotropic hypogonadism point to the diagnosis of *CYP17A1* defects. Fertility can be achieved in these patients with novel reproductive techniques. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

**Key Words:** *CYP17A1*, congenital adrenal hyperplasia, ovarian cysts, P450c17 activity deficiency, hypergonadotropic hypogonadism

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Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder due to defects in the steroid biosynthetic pathway. Besides cortisol deficiency, and owing to the resulting ACTH excess, different types of CAH may involve increased or decreased production of mineralocorticoids and/or sex steroids (1).

Deficiency of adrenal 17-hydroxylation activity was first reported by Biglieri et al. (2). Most 46,XY patients with 17α-hydroxylase deficiency present with female-like or slightly virilized external genitalia with blind vaginal pouch, cryptorchidism, and high blood pressure, usually associated with hypokalemia. In addition, 46,XX individuals may also be affected, and while sex development is largely unaffected, resulting in normal internal and external genitalia at birth, hypergonadotropic hypogonadism and amenorrhea ensue at puberty (3–8). *CYP17A1* defects result in impaired production of cortisol with secondary elevation of ACTH and consequent high serum levels of 11-deoxycorticosterone, corticosterone, and 18-deoxycorticosterone, leading to a state of mineralocorticoid excess with clinical manifestation of high blood pressure, hypokalemia, low PRA, and low aldosterone levels.

Adrenal hormones are produced in the three zonae of the adrenal glands, namely, glomerulosa, fasciculata, and reticularis; ACTH physiologically stimulates steroidogenesis in zonae fasciculata and reticularis. Production of mineralocorticoids in zona glomerulosa does not involve 17α-hydroxylation, but the steroidogenic blockade in cortisol and androgen production due to *CYP17A1* defects results in increased precursors with mineralocorticoid activity (9). Steroidogenesis also occurs in the gonads stimulated by hCG, LH, and FSH, resulting in production of sex steroids.

The *CYP17A1* gene encodes a single microsomal enzyme, P450c17, which mediates both 17α-hydroxylase and 17, 20-lyase activities. These functions allow the adrenal glands and gonads to synthesize 17α-hydroxylated glucocorticoids and sex steroids, respectively (9–12). The electron donor flavoprotein cytochrome P450 oxidoreductase (POR) is necessary for P450c17, P450c21, and P450aro steroidogenic activity, and sex steroid biosynthesis depends on 17,20-lyase activity modulated by POR and the cofactor protein cytochrome $b_5$ (9).

Human *CYP17A1* is located at chromosome 10q24-q25 and comprises eight exons, spanning 8,673 bp (10). It is expressed in adrenal and gonadal tissue and in the central nervous system (13). Since *CYP17A1* cloning in 1987 (14), about 100 mutations have been described, including missense mutations, deletions, insertions, and splicing defects (15, 16).

The diagnosis of combined 17α-hydroxylase/17,20-lyase deficiency due to *CYP17A1* mutation in genetic females is generally made at puberty, when patients develop hypergonadotropic hypogonadism, usually associated with hypertension, hypokalemia, and reduced serum cortisol levels. In the literature, there are few reports of 46,XX patients with *CYP17A1* defects (3–5, 7, 15, 16). Here we describe detailed clinical and hormonal data of 46,XX patients with *CYP17A1* defects referred for molecular diagnosis and treatment in tertiary centers, with special regard to gonadal imaging and function.

## PATIENTS AND METHODS

This study was approved by the Institutional Review Board at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), Brazil, and all patients signed an informed written consent.

We evaluated 16 46,XX patients with combined 17α-hydroxylase/17,20 lyase deficiency from 10 unrelated families. Fourteen patients were followed at Universidade de Sao Paulo, Brazil (13 in HCFMUSP and one in FMRPUSP, Ribeirão Preto), one in Hospital de Niños Dr. Ricardo Gutiérrez, Buenos Aires, Argentina, and one in Unidad Médica Villa Country, Barranquilla, Colombia. All medical records were systematically revised to obtain accurate clinical and hormonal data.

### Psychiatric Assessment

Social and mental health assessment was performed by a trained psychologist and psychiatrist. The Hamilton rating scale questionnaire was applied for the diagnosis of depression; a score of 0–7 is considered to be normal (17).

### Laboratory Evaluation

Hormonal levels were measured by different methods such as radioimmunoassay, immunofluorometric, immunochemiluminescence, and electrochemiluminescence assays, and results were compared to the reference range for each methodology. Quality control parameters included intra- and interassay coefficients of variation less than 10% for manual methods and less than 7% for automated methods at multilevel (low, medium, and high) for commercial or in-house controls. Assay cross-reactivity with major interfering steroids was determined for 17 OHP (11-deoxycorticosterone = 0.035%; $P$=.7%; and cortisol = 0.008%), cortisol