Chapter 5
Aromatase Deficiency and Its Consequences

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Origin of scientific creativity: To know when to be astonished.
–Louis Pasteur

New developments have challenged long-held concepts of the role of estrogen in the human male and prenatally in the conceptus, have uncovered widespread effects of estrogen in diverse tissues in the male and female, and have emphasized the role of extraglandular estrogen synthesis and paracrine and intracrine actions. Three illuminating developments are mainly responsible for the challenge to conventional wisdom: (1) description of a man with a homozygous null mutation in the ERα (estrogen receptor α) gene that led to estrogen resistance (ERαR) and the detection of 7 men and an infant boy, and 11 prepubertal or pubertal age females with severe estrogen deficiency as a consequence of a variety of homozygous and compound heterozygous mutations in the CYP19 gene, the gene that encodes aromatase (P450 aromatase), the enzyme responsible for the last and irreversible step in estrogen synthesis from androgens by the gonads and extragonadal tissues, and which has a wide tissue distribution in the human; (2) the concurrent development of mice that lack the gene encoding ERα (αERKO mice) and the gene encoding aromatase (Arko mice); and (3) the discovery of a second widely distributed estrogen receptor ERβ and the development of ERβ knockout mice (βERKO), and later of mice in which the gene encoding each receptor has been disrupted (αβERKO). Estrogen deficiency or resistance in the men led to tall stature without a pubertal growth spurt, eunuchoid proportions, delayed skeletal maturation, and severe osteopenia despite high testosterone levels. In the aromatase-deficient men but not the ERαR man, low-dose E replacement induced within 6–7 months rapid epiphyseal fusion and cessation of growth and by 3 years of E Rx striking improvement in bone mass and repair of the osteoporosis without inducing gynecomastia. These observations highlight the critical role of estrogen but not androgen in the male as well as female on skeletal

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M.I. New, J.L. Simpson (eds.), *Hormonal and Genetic Basis of Sexual Differentiation Disorders and Hot Topics in Endocrinology*, Advances in Experimental Medicine and Biology 707, DOI 10.1007/978-1-4419-8002-1_5,

growth (including skeletal proportions) and maturation – an effect on growth plate chondrocytes on the one hand, and the role of estrogen sufficiency in the accrual and maintenance of bone mass and density which is regulated by osteoblasts and osteoclasts. In both sexes, estrogen deficiency leads to a dissociation between (1) skeletal growth (it continues at a steady rate without a pubertal growth spurt) and (2) skeletal maturation and accrual of bone density and mass. Prepubertal estrogen concentrations in the normal female are apparently important in the well-defined sex difference in the rate of skeletal maturation and possibly the age of pubertal onset.

P450 aromatase deficiency in the male leads to hypergonadotropism, macroorchidism, and increased serum testosterone concentration. It has an important effect on carbohydrate and lipid metabolism including the development of persistent insulin resistance and can be associated with premature onset of coronary atherosclerosis. Apparently, it does not have a critical effect in the male on psychosexual differentiation or behavior.

The clinical consequences of mutations in CYP19 on the fetal–placental unit have elucidated the critical role of placental aromatase in the protection of the female fetus from androgen excess, and the prevention of androgen-induced XX DSD (female pseudohermaphrodism) and of virilization of the mother (Table 5.1).

Table 5.1 46,XX DSD (female pseudohermaphrodism[a])

A. Androgen induced
  1. Fetal source
    a. Congenital virilizing adrenal hyperplasia (defective 21-hydroxylation, 11β-hydroxylation, 3β-hydroxysteroid dehydrogenase-2, P450 oxidoreductase (POR)
    b. Glucocorticoid receptor mutation
  2. **Feto-placental source**
    a. ***P450 aromatase deficiency***
    b. P450 oxidoreductase deficiency (affecting aromatase)
  3. Maternal source
    a. Iatrogenic
      (i) Testosterone and related steroids
      (ii) Certain synthetic oral progestagens
    b. Virilizing ovarian or adrenal tumor
    c. Virilizing luteoma of pregnancy
    d. Congenital virilizing adrenal hyperplasia in mother[b]

B. Non-androgen induced
  1. Disturbances in differentiation of urogenital structures associated with malformations of intestine and lower urinary tract (non-androgen-induced XX, DSD) (e.g. cloacal anomalies, müllerian agenesis (MURCS), vaginal atreasia, and labial adhesions)

[a]This term is previous terminology and is no longer recommended and should be abandoned. It is listed in parentheses during this transitional period

[b]In pregnant patient with CAH whose disorder is poorly controlled or who is non-compliant especially during the first trimester

Table 5.2 Aromatase deficiency and severe estrogen deficiency

In the mother
Virilization during pregnancy by an affected fetus, common
In the female
46,XX DSD (female pseudohermaphrodism)
Polycystic ovary syndrome
Virilization at puberty
In the male
Normal sex differentiation
Macroorchidism
In both sexes
Delayed sexual maturation
Tall stature
Osteopenia
Increased bone turnover
Insulin resistance
Abnormal plasma lipids
Psychosexual orientation appropriate for phenotypic sex
Role of placental aromatase
In the affected male and female fetus and pregnant mother
In the physiology of pregnancy

Virilization of the mother of an affected fetus due to increased placental androgen is a common feature of the disorder and a clue to the diagnosis. Fetal estrogen synthesis (or responsiveness through fetal ERα) is not essential for implantation, survival of the conceptus, or the timing of parturition. Nor is estrogen a mediator of fetal sex differentiation of the female genital tract (Table 5.2).

Table 5.3 Manifestations of aromatase deficiency in the female

Prenatal
Fetal: masculinization of urogenital sinus external genitalia: androgen-induced female pseudohermaphrodism; low plasma estrogen and very elevated androgen levels
Mother: Virilization, low plasma estrogen and elevated androgen levels
Infancy
Elevated plasma levels; undetectable plasma E_2 (±multicystic ovaries)
Puberty
No female secondary sex characteristics: severe estrogen deficiency
Tall stature
No pubertal growth spurt despite increased serum androgens
Delayed skeletal maturation
Virilization with progressive enlargement of the clitoris
Hypergonadotropic hypogonadism
Increased levels of plasma androgens
Polycystic ovaries
Osteopenia
Female psychosexual orientation

Aromatase deficiency syndrome in the female has distinct features in the fetus, during childhood, and at the age of puberty including androgen-induced XX DSD (female pseudohermaphrodism) virilization at puberty and without or incomplete feminization, polycystic ovaries, and hypergonadotropic hypogonadism (the phenotype may vary depending on the magnitude of the aromatase deficiency). The striking polycystic ovaries that occur in aromatase-deficient females during infancy, childhood, and adolescence appear to be a consequence of the increased intraovarian concentration of androgen and a high concentration of circulating FSH and do not require estrogen. Estrogen replacement therapy at puberty in both sexes arrests and corrects the functional changes and induces feminizing puberty in the female (Table 5.3).

The aromatase deficiency syndrome is most florid in nonsense mutations of the CYP19 gene. Aromatase deficiency varies clinically from florid to subtle depending on the magnitude of the aromatase deficiency.