Aromatase and estrogen receptor α deficiency

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Studies on the phenotypes of women and men with mutations disrupting estrogen biosynthesis and action have significantly advanced our knowledge of the physiologic roles of estrogen in humans. Aromatase deficiency results from autosomal recessive inheritance of mutations in the *CYP19A1* gene. It gives rise to ambiguous genitalia in 46,XX fetuses. At puberty, affected girls have hypergonadotropic hypogonadism, do not develop secondary sexual characteristics, and exhibit progressive virilization. The affected 46,XY men have normal male sexual differentiation and pubertal maturation. These men, however, are extremely tall and have eunucoid proportions with continued linear growth into adulthood, severely delayed epiphyseal closure, and osteoporosis due to estrogen deficiency. Although estrogen has been shown to be essential for normal sperm production and function in mice, its role in fertility is not clear in men. Thus far, one man and an unrelated woman with estrogen resistance due to mutations in the estrogen receptor α (*ESR1*) gene have been described. Their clinical presentations are similar to that of aromatase-deficient men and women. (Fertil Steril® 2014;101:323–9. ©2014 by American Society for Reproductive Medicine.)

Key Words: Aromatase deficiency, estrogen resistance, estrogen receptor-alpha, mutation

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The physiologic roles of estrogens in women include development of secondary sexual characteristics, regulation of gonadotropin secretion for ovulation, preparation of the uterine, breast, and possibly other tissues for progesterone response, maintenance of bone mass, regulation of lipoprotein synthesis, prevention of urogenital atrophy, and possibly regulation of insulin responsiveness and maintenance of cognitive function (1). The key physiologic roles of estrogens in men were largely unanticipated until 1994 when estrogen was found to be necessary for fusion of epiphyses and prevention of bone loss (2, 3). Since 1994, our understanding of the physiologic roles of estrogen in mice and humans has improved drastically with the discovery of men and women with mutations in the *CYP19A1* (aromatase) and *ESR1* (estrogen receptor α[ERα]) genes and generation of knockout mice with selective disruptions of these genes (3–10). Consequences of the mutations in the aromatase gene in many adults and children and a mutant ERα gene in a man and a woman will be discussed in this review.

Until the early 1990s, aromatase deficiency was considered to be incompatible with life. Following the first description in 1991 of a Japanese newborn girl with an aromatase gene defect, there have been numerous reports in the world literature describing aromatase deficiency (4, 5). Thus far, a number of newborn girls and boys, older children including adolescents, and adults with aromatase gene defects have been described in detail (4, 6, 7, 11–15). Convincingly, estrogen formation in these patients was virtually absent, giving rise to a number of anticipated as well as previously unanticipated symptoms. We know now that aromatase deficiency is an autosomal recessive condition manifest in 46,XX fetuses by female pseudohermaphroditism and, in the case of adult men, tall stature with eunocoid proportions due to unfused epiphyses. In fact, the essential role of estrogen as a determinant of height and bone mass was understood for the first time after the description of estrogen-resistant or aromatase-deficient men (7, 15). In the majority of aromatase-deficient patients, transient maternal virilization during pregnancy was reported or documented. In fact, maternal virilization during the pregnancy was the key clue that led to the genetic diagnosis of aromatase deficiency in one asymptomatic newborn boy (13). In utero virilization of 46,XX spotted hyenas constitute a natural animal model to explain some but not all of the mechanisms giving rise to genital ambiguity in newborn girls who are affected by aromatase deficiency (16).

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Intriguingly, studying aromatase-deficient men confirmed and extended the conclusions drawn from an estrogen-resistant man regarding the role of estrogen action in men (2, 3, 7, 15).

In addition to the physiologic roles of estrogen summarized above, this steroid is important in regulating glucose metabolism and libido, at least in men. An estrogen-resistant man and aromatase-deficient men were reported to have glucose intolerance (2, 17). Estrogen replacement in aromatase-deficient men improved insulin resistance (17, 18). An aromatase deficient man had low sexual desire that was improved by low doses of estrogen replacement (19).

It would not be an exaggeration to state that the studies on aromatase-deficient or estrogen-resistant individuals have provided a fuller picture of the physiology of estrogen and uncovered previously unanticipated roles of estrogen in men. These observations and studies on humans were complemented by mechanism-based studies using mouse knockout models. I provide herein a summary of these developments over the past two decades.

CONSEQUENCES OF AROMATASE DEFICIENCY DURING PREGNANCY

The earliest clinical signs of aromatase deficiency become manifest during pregnancy. A woman carrying an aromatase-deficient fetus becomes severely virilized. An elaborate mechanism, which involves the fetal adrenal androgen production, altered placental steroid metabolism, maternal virilization, and masculinization of a 46,XX fetus, accounts for these clinical signs. The pregnant mother has male levels of circulating testosterone and develops cystic acne, hirsutism, and clitoromegaly, whereas the 46,XX fetus is born with severely masculinized external genitalia.

The placenta develops from trophectoderm of the blastocyst and is genetically fetal tissue. Among mammals, the human placenta is uniquely capable of aromatizing massive quantities of androgens into estrogens most efficiently. In pregnant women at or near term, there is a daily production of 70 μmol (20 mg) E_2 and 300–450 μmol (80–120 mg) estriol (20). During the third trimester of gestation, it is very common to detect maternal serum E_2 levels >100,000 pmol/L (27,000 pg/mL) and estriol levels >55,000 pmol/L (20). The physiologic role of this massive placental estrogen production during pregnancy is not understood. However, when the aromatization capacity of the placenta is exceeded by the overproduction of androgenic steroids of maternal origin, e.g., by luteomas, during early pregnancy, virilization of the female fetus and the mother has been noted (21). In contrast, serum E_2 (1,053–1,900 pmol/L or 287–518 pg/mL) or estriol (134–2,200 pmol/L or 37–608 pg/mL) levels in the third trimester were extremely low in the pregnant mothers of the infants with aromatase deficiency (4, 14). Placental tissue from such a newborn with aromatase deficiency failed to convert precursor steroids into estrogens (4). As a result, the androgen and estrogen precursor DHEAS, derived primarily from the fetal adrenal, is converted in the placenta to androstenedione and testosterone. Thus, both the female fetus and the mother become virilized. Severe genital ambiguity noted in the female fetuses implies exposure of external genitalia to testosterone and dihydrotestosterone much earlier than 12th week of gestation (4, 6, 11, 12, 14, 15, 22).

MUTATIONS AND PHENOTYPES

Estrogen biosynthesis is catalyzed by an enzyme located in the endoplasmic reticulum of estrogen-producing cells. This enzyme, aromatase, is a member of the cytochrome P450 superfamily and the product of the *CYP19A1* gene (23). Aromatase catalyzes the three precursors—androstenedione, testosterone, and 16α-hydroxydehydroepiandrosterone sulfate (after conversion to 16α-hydroxyandrostenedione)—into estrone, estradiol and estriol, respectively (24). In humans, the *CYP19A1* gene and its product aromatase are expressed in the ovary, testis, placenta, adipose tissue, skin, and brain (25). Estrogen levels in the circulation are primarily maintained by aromatase activity in the ovarian granulosa cells of ovulatory women and the adipose tissue of men and postmenopausal women (25).

The size of the aromatase gene is >123 kb, and its tissue-specific expression is regulated by the use of tissue-specific promoters involving alternative splicing (25, 26). Despite the size and complexity of the aromatase gene, only a limited number of definitively characterized humans with aromatase deficiency have been reported, as indicated above, although deficiencies of most other steroidogenic P450s (17α-hydroxylase, 11β-hydroxylase, 21β-hydroxylase) have already been well characterized. Examination of genomic DNA from the Japanese newborn girl, who represented the first reported case of aromatase deficiency, revealed that a consensus splice acceptor site between the coding exon VI and intron VI was mutated, resulting in the use of a cryptic acceptor site further downstream in intron VI (4, 5). This homozygous mutation added an insert of 87 bp to the aromatase mRNA, resulting in translation of an abnormal protein with 29 extra amino acids (5). This infant was born with severely virilized external genitalia.

The first case of female adolescent aromatase deficiency was described in an 18-year-old girl with primary amenorrhea and female pseudohermaphroditism (6). She was found to be compound heterozygous for two different missense mutations in the heme-binding region of the aromatase gene (23). The first adult diagnosed with aromatase deficiency was a 24-year-old man (15). He and his 28-year-old sister, both affected by aromatase deficiency, were found to have the same homozygous missense mutation in a highly conserved region of the aromatase gene thought to guard the substrate access channel (15). In this same region, another homozygous mutation was found in a 38-year-old Italian man (7). These initial reports were followed by a number of publications describing aromatase deficiency in virilized newborn girls or unremarkable boys and/or their virilized mothers as a result of homozygous or compound heterozygous point mutations yielding frameshifts, nonsense codons, or stop codons in the aromatase gene (11, 13, 14). In vitro transient expression of aromatase cDNAs with missense mutations gave rise to only trace amounts of aromatase activity. These mutations in the aromatase gene in females have given rise to certain common phenotypic features,