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# Prenatal exposure to sex steroid hormones and behavioral/cognitive outcomes

JoAnn E. Manson*

*Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02215, USA*

**Abstract**

Experimental studies in animals indicate that androgen exposure in fetal or neonatal life largely accounts for known sex differences in brain structure and behavior. Clinical research in humans suggests similar influences of early androgen concentrations on some behaviors that show sex differences, including play behavior in childhood and sexual orientation in adulthood. Available research also suggests that sex steroid hormone exposure may contribute to sex differences in the risk of autism and affective disorders in schizophrenia. However, findings have been inconsistent for other characteristics that show sex differences, including aggression and spatial ability. Moreover, social and environmental factors may modulate some of the associations observed. This article reviews the evidence that early-life exposure to sex steroid hormones contributes to sexually dimorphic behavior and cognitive abilities in humans.


## 1. Introduction

Research in animals suggests that testosterone (T) accounts for most known sex differences in brain structure and behavior [1]. In rodents [2-4] and nonhuman primates [4-7], early administration of T to females increases male-typical behaviors; and removal of T in males by castration or administration of antiandrogens increases female-typical behaviors. Among the affected behaviors are juvenile play, grooming, aggression, sexual behavior, and spatial ability (maze performance). Behavioral changes have also been noted in female animals exposed to androgen from gestating next to male littermates [8,9].

In humans, sexually dimorphic (sex-typed) behaviors and cognitive abilities include childhood play patterns (playmate and toy preferences), spatial ability, aggression, sexual orientation, gender identity, and sociodevelopmental or psychiatric conditions such as autism, depression, and schizophrenia (Table 1) [3,10-13]. Testosterone surges occur at weeks 8 to 24 of gestation and 0 to 6 months after birth, suggesting that these may be critical periods of hormonal influence [10]. Investigators have typically used 2 broad approaches to examine the question of whether pre- or perinatal androgen exposure in humans affects sexually dimorphic outcomes. One approach is to study clinical samples, that is, individuals with endocrine disorders such as congenital adrenal hyperplasia (CAH) or those exposed in utero to androgenic progestins. The other approach is to study typical variations in pre- or perinatal hormone exposure in general populations, as assessed by T levels in umbilical cord blood, maternal serum, or amniotic fluid, or by other markers such as finger length ratio. These approaches each have unique strengths and limitations and, taken together, provide insight into the relationship between early-life T exposure and behavioral/cognitive outcomes.

## 2. Studies in clinical settings

### 2.1. Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency results in the overproduction of adrenal androgens starting at approximately 7 weeks' gestation and continuing until initiation of corticosteroid treatment, usually in the perinatal period [14]. The excess androgen results in varying degrees of virilization of the external genitalia in girls depending on the degree of enzyme deficiency and may possibly affect the fetal brain. Thus, CAH provides a human model for studying the effects of prenatal androgen exposure on behavior and cognition. Many small studies (the number of cases

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* Tel.: +1 617 278 0871; fax: +1 617 731 3843.
*E-mail address:* jmanson@rics.bwh.harvard.edu.

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Table 1
Sex differences in behavioral/cognitive outcomes

| | Male > female | Female > male |
|---|---|---|
| Cognitive abilities | Spatial ability (eg, mental rotation, targeting) | Verbal ability: memory and fluency<br>Perceptual speed and accuracy |
| Personality traits | Aggression<br>Sensation seeking | Nurturance |
| Gender-role behaviors | Male-typical activities | Female-typical activities |
| | Preference for boys as playmates | Preference for girls as playmates<br>Interest in babies |
| Gender identity | Sense of self as male | Sense of self as female |
| Sexual orientation | Arousal to females | Arousal to males |
| Sociodevelopmental/ psychiatric disorders | Autism<br>Asperger syndrome<br>Schizophrenia prevalence | Affective disorders<br>Affective disturbance in schizophrenia |

Adapted from Cohen-Bendahan et al [10]. See also Kessler et al [11], Aleman et al [12], and Goldstein [13].

typically ranges from 10 to 70) in North America, Europe, and Japan have examined gender-role behaviors in females with CAH. These studies have used diverse methods of behavioral assessment, including direct observation or self- or parent responses to semistructured interviews or standardized questionnaires. Compared with their sisters or other same-sex controls, females with CAH are more likely to engage in male-typical childhood play (ie, show a preference for boys' toys [eg, vehicles and construction sets] and for boys as playmates) [15-18]; show traits of autism [19], a condition that predominantly affects males, and score low on measures of empathy and need for intimacy [20]; exhibit male-typical interests as adolescents [21]; show little interest in infants [22], marriage, motherhood, and "feminine" appearance [18,23]; and report homosexual or bisexual behavior or fantasy (one third [10] are homosexual or bisexual) [24-27]. However, although a small percentage (3%-5%) indicate a desire to live as males [24-26,28], most girls and women with CAH have a core gender identity that is female [29].

Whether females with CAH differ from unaffected females with respect to other sexually dimorphic behavioral or cognitive variables is unclear. Studies of aggression have produced mixed results. A few studies have reported that females with CAH show enhanced spatial ability compared with healthy controls, but a greater number have not [30,31]. It should be noted that the sex difference in spatial ability is smaller than the sex difference in other traits, so detecting differences between CAH and control females might require larger samples than usually available.

In contrast to findings in females, males with CAH behaviorally resemble other males with respect to play patterns and interests in childhood and adolescence [15,21], aggression [32,33], and sexual orientation [26]. This similarity is not surprising, given that males with CAH tend to have fetal androgen levels that fall within the typical range for males. In males, feedback mechanisms appear to lower androgen production by the testes in response to the adrenal increase of CAH.

The behavioral profile observed in girls with CAH is usually attributed to prenatal androgen excess. However, such behaviors may also result from differential socialization by parents, postnatal rather than prenatal androgen excess, or other hormonal abnormalities characteristic of CAH [10]. There is little empirical support for these competing hypotheses, at least for childhood play patterns (data are more limited for other outcomes). Parents report that they do not treat their daughters with CAH in a more male-typical way [34], and a study in which parents were directly observed interacting with their children found that parents more strongly encouraged female-typical play patterns in daughters with CAH than in unaffected daughters [15]. Markers of elevated prenatal androgen (ie, degree of phenotypic and/or genotypic abnormality) correlate more strongly with male-typical behavior in females with CAH than do markers of elevated postnatal androgen (eg, accelerated bone aging) [16].

### 2.2. Other syndromes

Genetic males with complete androgen insensitivity syndrome (CAIS) lack functional androgen receptors and are phenotypically female; the condition is usually unrecognized until menstruation fails to occur at puberty. Persons with CAIS do not differ from genetic females with respect to sex-typed behavior, including gender identity and sexual orientation [35,36] (sexually dimorphic cognitive abilities have not been examined in individuals with CAIS). These results suggest that androgens are responsible for behavioral masculinization, although the relative contributions of prenatal and postnatal androgens and the role of socialization cannot be determined in these individuals. However, genetic males with congenital malformations of the external genitalia who are castrated and assigned to female sex at birth appear to have more male-typical play patterns and interests than control girls [37], suggesting that the sensitive period for some sex-typed behaviors may be confined to the prenatal period (because castration at birth eliminates the postnatal T surge). The evidence on gender identity is less clear, with 1 study showing (parent-reported) discordant gender identity in genetic males being reared as girls [38], but others not finding this effect [39].

### 2.3. Prenatal exposure to synthetic sex hormones

Girls born to mothers who were prescribed androgenic progestins during pregnancy may be more likely than unexposed siblings to exhibit male-typical childhood play behavior and interests [29] and to report use of physical aggression in conflict situations [40], but data are sparse and

inconsistent. In contrast to the data on CAH, Reinisch [40] found that prenatal exposure to androgenic progestins predicted increased physical aggression in boys as well as girls. Such exposure may lead to higher androgen levels in boys than does the presence of CAH, thus preventing compensation by decreases in testicular androgen.

## 3. Studies in general populations

Studies of normal variability in pre- or perinatal hormone levels also provide some support for the hypothesis that early-life T predicts certain sex-typed behaviors, but the amount of rigorous research on this topic is limited. Such studies have used indirect measures of fetal hormonal exposure, including T in umbilical cord blood, maternal serum during pregnancy, or amniotic fluid. Of these, amniotic T is generally considered to be the best reflection of fetal T exposure during the critical periods [10].

In the Avon Longitudinal Study of Parents and Children, mothers' serum T levels at a mean gestational age of 16 weeks (range, 5-36 weeks) were examined as predictors of their 31/2-year–old children's scores on the Preschool Activities Inventory, a standardized measure of involvement with sex-typical toys, games, and interests [41]. Mothers with high T in pregnancy were more likely to have daughters who preferred male-typical toys and activities, although the effect was modest and was not seen in sons. In the Child Health and Development Study, 163 pregnant women and their daughters were followed for 30 years. This study found that, consistent with the hypothesized critical period of weeks 8 to 24 of gestation, prenatal androgen exposure in the second trimester—but not the first or third trimester—was related to adult gendered behavior (measured by scores on a variety of sex-role inventories) [42,43]. As shown in the left panel of Fig. 1, adult daughters with low prenatal androgen exposure were more influenced by their mothers' efforts to encourage "femininity" than were adult daughters with high prenatal androgen. Furthermore, as shown in the right panel, the influence of prenatal androgen exposure on gendered behavior in adulthood was small for women who rated high on femininity in adolescence but large for women who rated low—those with high prenatal androgen exposure tended to exhibit less feminine behavior as adults.

To date, studies of amniotic T have tended to focus on autistic traits (see next section) or spatial ability. Similar to the CAH findings, studies of amniotic T do not suggest that higher prenatal exposures are associated with better spatial or mathematical ability; indeed, some investigators have found significant *inverse* relationships [44,45].

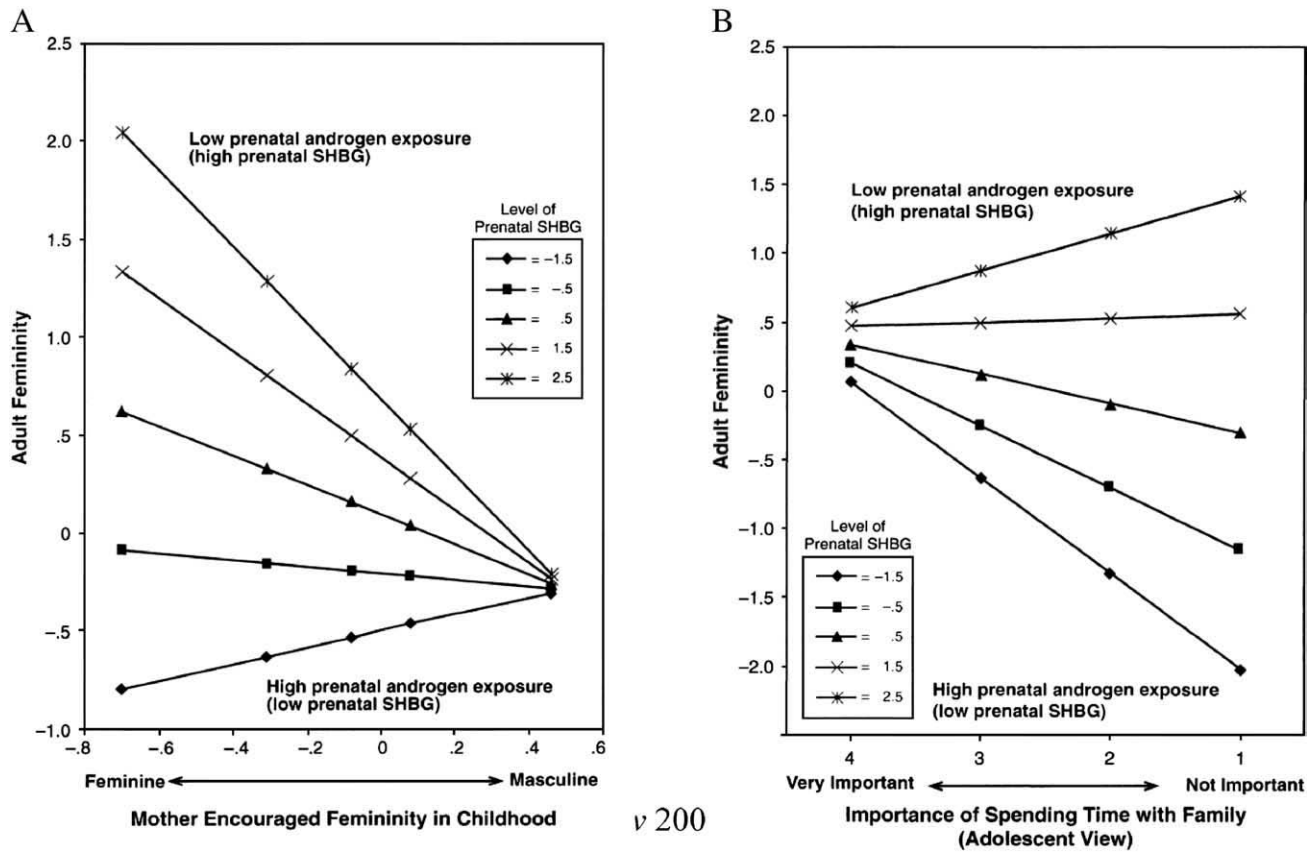


Fig. 1. Effect of (A) childhood gender socialization and (B) adolescent family attitudes on adult gendered behavior by level of prenatal androgen exposure, child health, and development study. Source: Udry [42].

## 4. Autism

The Cambridge Fetal Testosterone Project is an ongoing study of amniotic T and traits thought to be related to autism [46], a disorder that occurs far more frequently in males than females. Among approximately 100 children born in 1996 to 1997 who appeared healthy at birth, higher amniotic T significantly predicted amount of eye contact at age 12 months (quadratic relation in total sample and in boys) [47], vocabulary size at ages 18 and 24 months (inverse relation in total sample only) [48], restricted interests at age 4 years (inverse relation in total sample and in boys) [49], empathy at ages 4 and 8 years (inverse relation in total sample and in boys) [50,51], and tendency to *systematize* (defined as "the drive to analyze and construct systems") at ages 6 to 9 years (direct relation in total sample only) [52]. (Amniotic T was not associated with gender-typed play at ages 4-6 years [53].) In contrast to the pattern of findings for CAH, all of the within-sex associations that were found occurred in males rather than females. The findings provide some support for the hypothesis that T influences the neural mechanisms responsible for social and communicative behavior. The failure to find consistent within-sex associations may be due to a relatively narrow spectrum of T concentrations and/or low statistical power because of small sample sizes. An additional 400 children have been enrolled in this study, so future reports from this research group should be more informative.

The ratio of the second to fourth finger length is significantly lower in males than in females from childhood onward and has been hypothesized to be an indirect marker of prenatal T exposure during the first trimester of gestation. Finger ratio has been examined as a predictor of autism. A study of 95 families with children with autism or Asperger syndrome and control families found that finger ratio was highest in normal children, lower in children with Asperger syndrome, and lowest in children with autism. Furthermore, finger ratio was lower in relatives of autistic children than in relatives of control children [54]. Together with the amniotic T findings, this result may suggest a relation between prenatal T level and sociodevelopmental outcomes such as autism.

## 5. Affective disorders and schizophrenia

Depression and anxiety disorders are more common among women than men, and this sex difference is magnified among patients with schizophrenia [13]. Determining the etiology of sex differences in affective disturbances in schizophrenia may shed light on sex differences in affective disorders in general populations. Several lines of indirect evidence converge to suggest that prenatal factors, including sex steroid hormone levels, appear to affect vulnerability to schizophrenia and may also contribute to sex differences in affective disorders in this setting and possibly in other populations [13,55]. In healthy populations, brain regions involved in the regulation of emotional states contain sexually dimorphic structures; and functional magnetic resonance imaging studies find significant sex differences in brain activity in response to negatively valenced affective stimuli [56]. Furthermore, in healthy women, brain response to such stimuli varies according to the stage in the menstrual cycle, implicating hormonal factors [56]. Moreover, there is greater sexual dimorphism in those human brain structures involved in emotional processing that correspond to those found in animals to have high level of sex steroid receptors during critical periods of brain development [57]. In persons with schizophrenia, there are significant abnormalities in these sexually dimorphic brain regions [55]; and these abnormalities appear greater in female than in male patients [13]. Taken together, these data suggest a role for prenatal sex hormones in the origin of affective disorders and schizophrenia.

## 6. Summary and conclusions

Data from clinical samples and some studies in typical populations suggest that prenatal T influences sex-typed childhood play behavior; this effect is large and robust. Variation in prenatal T also appears to affect gender identity and sexual orientation. High prenatal T may be associated with increased tendencies toward aggression, but the data are mixed. There is scant evidence—from studies of CAH and studies of normal populations—that prenatal T influences spatial ability. Findings for a connection between prenatal T and indicators of autism appear stronger in boys than in girls, but research is limited. Recent research suggests that fetal hormones may affect vulnerability to affective disorders in schizophrenia and possibly general populations.

## 7. Directions for future research

Methodologically rigorous studies—that is, sufficiently large sample sizes, prospective designs, appropriate comparison groups, valid assessments of hormone exposures during critical periods, and adequate attention to socialization effects—are still needed to clarify the association between prenatal androgen exposure and sex-typed behaviors in childhood and adulthood. It is essential to establish that the study protocol elicits expected sex-related differences in the outcome of interest before examining the relationship between sex hormone levels and that outcome within each sex. Only then will research be able to address conclusively the key questions raised by Collaer and Hines [3] more than 10 years ago, including: How do prenatal hormone exposures, hormone exposures

after birth, and the social environment interact to influence sexually dimorphic behaviors?

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