FOETAL TESTOSTERONE – IMPLICATIONS IN AUTISM

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ABSTRACT

Pervasive developmental disorders are a heterogeneous group of conditions believed to arise from combinations of genetic and environmental influences. The androgen theory of autism suggests that autism spectrum conditions (ASC) are in part due to elevated levels of foetal testosterone (fT). Prenatal testosterone has important effects on brain organization and future behavior and this is positively correlated with a number of autistic traits. In this article we emphasize on the importance of hormonal influence and the lasting effects on neuropsycho development. Given the crucial role of prenatal exposure to hormones in the development of cognitive sex differences and traits associated with ASC, for future directions we consider it is important to detail the latest information on androgen hormone levels during pregnancy.

Keywords: prenatal testosterone, autism, prenatal exposure, risk factors

Several lines of evidence suggest a role for androgens in the etiology of autism, presumably exerted during prenatal brain development [1]. The prevalence of autism in men is three to four times higher than in women [2]. In a normal population, some of the characteristic features of autism — such as low empathizing and enhanced systemizing — are more common in males; in this respect, subjects with autism may hence be described as having an “extreme male brain” [1-3]. Elevated prenatal androgen levels have been associated with autism-related traits [4] and an indirect measure of fetal androgen exposure (assessment of the ratio between the second and fourth digit) [5] suggests elevated fetal testosterone levels to be associated with both autism and autism-related traits [6’7].

An ongoing longitudinal study has provided the most direct evidence for this hypothesis, showing that amniotic fluid testosterone levels predicted a range of autism-like behaviours in otherwise typically developing children, including reduced eye contact at 12 months of age [8-10], and the quality of social relationships and level of restricted interests at age 4 and 8 years [11].

PRENATAL RISK FACTORS FOR AUTISM

Autism etiology is unknown, although perinatal and neonatal exposures have been the focus of epidemiologic research for more than 40 years. Although studies show that obstetrical and neonatal complications may increase autism risk, the specific complications and magnitude of effect have been inconsistent. There is insufficient evidence to implicate any 1 perinatal or neonatal factor in autism etiology, although there is some evidence to suggest that exposure to a broad class of conditions reflecting general compromises to perinatal and neonatal health may increase the risk.
Gardener et al. [12] identified three prenatal risk factors which are associated with high maternal testosterone levels: gestational diabetes, obstetric suboptimality and primiparity. Four other risk factors will be considered here, two of which were identified as reliable risk factors for autism:

**Advanced parental age.** In James (2012) [13] it is speculated that advanced parental age might be associated with high intrauterine testosterone levels via maternal stress. However, it is thought that speculation may partially be reliable because it now seems that advanced paternal age might simply be associated with autism via the increased probability of de novo genetic or genomic anomalies arising more frequently as men age.

**Migration.** Gardener et al. identified maternal migration as a reliable risk factor for infant autism, and I suggested that the relationship might be mediated by high levels of maternal adrenal androgens occasioned by stressful condition in countries of origin, and by the stress of attempting to cope with a new and different society [13].

**Maternal smoking during pregnancy.** In recent years, it has been repeatedly reported that maternal smoking during pregnancy is associated with autism and related disorders, especially ADHD. High androgen levels have been reported in women who smoke [14-16] and this has specifically been reported in pregnant women [17].

**Interpregnancy interval.** Short interpregnancy intervals were associated with autism [18], two very large studies have reported that when the interpregnancy interval is less than 1 year, the second sibling is substantially and significantly more likely to suffer autism [19, 20]. It should be taken into account the fact that a short period between pregnancies generates anxiety when the mother takes a new assignment to lead to term a new pregnancy while she takes care of another young infant.

**FETAL ANDROGEN HORMONES**

Testosterone plays a critical organizational role in masculinization, both prenatally and at puberty. During puberty, testosterone exposure is essential for the suite of masculinizing effects associated with this developmental stage. Prenatal testosterone exposure influences fetal brain organization and future sexually differentiated behaviour [11, 21, 22]. This exposure also seems to reduce the growth of the second digit relative to the other fingers [4, 5]. As a result, the second-to fourth digit ratio (2D:4D) has been used as a proxy of both the exposure and sensitivity to prenatal testosterone [6, 23]. This association has spurred considerable interest in 2D:4D, which has been linked to an array of masculine traits including aggression [24], athletic ability, and perceived dominance [25]. Even among females, a lower 2D:4D tends to predict masculine behavioural traits [26, 27, 28].

For typical human males there seems to be a surge in fT levels at around weeks 8–24 of gestation [4, 29- 31]. During this period, male fetuses produce more than 2.5 times the levels observed in females [32]. Afterwards, there is a decline to barely detectable levels from the end of this period until birth. As a result, any effects of fT on development are most likely to take place during this period. For typical human females, levels are generally very low throughout pregnancy and childhood [30]. fT can be measured in amniotic fluid collected during midtrimester amniocentesis. fT is thought to enter the amniotic fluid via diffusion through the skin in early pregnancy and later from fetal urination [33,34]. Although the exact correlation between fT levels in the serum and the amniotic fluid is unknown, the maximal sex difference in amniotic fT occurs between weeks 12 and 18, closely paralleling peak serum levels [33].

There is now substantial literature on the effect of prenatal (fetal) testosterone on postnatal development. Due to the dangers of directly sampling fetal hormone levels, these studies generally measure fT levels through amniocentesis samples, obtained for clinical purposes (e.g. in order to detect genetic abnormalities in the fetus). Amniocentesis is typically performed during a relatively narrow time window which is thought to coincide with the hypothesized critical period for human sexual differentiation (between approximately weeks 8 and 24 of gestation) [30]. Males are exposed to testosterone from the fetal adrenals and testes. The female fetus is also exposed to androgens, but at lower levels. A small proportion may come from the fetal adrenals (a by-product of the production of corticosteroids).
and some comes from the maternal adrenals, ovaries and fat [35].

DIFFERENCES BETWEEN MALE AND FEMALE CASES OF AUTISM

In human beings, sex differences are apparent both in brain structures and cognitive skills [29, 36]. The psychological study of sex differences has traditionally focused on spatial, mathematical, and verbal ability [36]. However, there is increasing interest in potential sex differences in social cognition. Geary suggests three socio-cognitive abilities that should show a female superiority: the ability to read nonverbal communication signals (i.e. body posture and facial expressions), language, and theory of mind. Baron-Cohen proposes that females, on average, are better at ‘empathizing.’ This is defined as the drive to identify another’s mental states and respond to these with an appropriate emotion. This encompasses what is referred to as using a ‘theory of mind’ but includes an affective reaction as well. Both authors refer to evolutionary arguments to explain the female advantage in empathy or social cognition: First, because females historically migrated to the social group of their mate (while males remained in their birth group), females have been forced to form social alliances with non-kin. Arguably, being accepted into a new social group requires better social skills than staying within one’s kin group. Women’s role as primary care-giver for children may also have created selection pressures for greater empathy in order to read her infant’s mental states and needs rapidly, thus promoting the infant’s survival. Thirdly, women’s role in child care would have been significantly helped by the ability to form close relationships with other women to obtain social support. Fourthly, concern for others could have been disadvantageous for males as their reproductive success may have depended on dominating others, sometimes through physical aggression [4]. Finally, when females do compete with each other, they use indirect methods such as gossip and social exclusion in an attempt to damage the social networks crucial for female success and reduce their competitors’ desirability as mates. Although evolutionary explanations are not directly testable, these arguments give rise to the notion that the female advantage in social skills may not be solely due to cultural factors but may also be in part biological.

Sex differences are also seen in neurodevelopmental conditions involving social and communicative development. Thus, specific language delay, semantic–pragmatic disorder, and autism spectrum conditions are all more common in males [37, 38, 3]. Autism in particular has been described as an extreme form of some sexually dimorphic traits or an extreme of the male brain [8].

Four males are diagnosed with autism for every female, and AS males are nine times as common as AS females [3]. This sex difference suggests that there may be a male vulnerability to developing ASC, a hypothesis supported by multiple lines of evidence.

Autism is a spectrum of neurodevelopmental conditions characterized by difficulties in social development, abnormalities in communication, and the presence of repetitive behaviors/obsessive interests. Asperger Syndrome (AS) shares these features, but children with AS do not show the delay in language acquisition or general intellectual impairment of classic autism. It has been argued that autism and AS are essentially the same condition but with varied degrees of language development or IQ. Together they constitute two major subgroups of autism spectrum conditions.

PLASMATIC TESTOSTERONE AND AUTISTIC TRAITS

Some neuroanatomical studies comparing the brains of individuals with and without ASC reveal structural differences associated with high levels of ft, including hemispheric asymmetries. Finally, girls with abnormally high ft levels as a result of congenital adrenal hyperplasia (CAH) have a higher number of autistic traits than their unaffected sisters [4]. These findings have led to the androgen theory of ASC, which proposes that elevated ft contributes to differences in brain development that underlie the cognitive traits found in autism [4, 39].
At biological level, higher levels of fT, measured in amniotic fluid, are inversely correlated with the amount of eye contact at 12 months of age [9], vocabulary size at 18 and 24 months [10], and quality of social relationships at 4 years [4]. FT levels are correlated with number of autistic traits as measured against the Childhood Asperger Screening Test (CAST) and the Child Autism Spectrum Quotient (AQ-C) (Auyeung et al., submitted for publication), higher scores based on the Child Systemizing Quotient (SQ), and lower scores based on the Child Empathizing Quotient (EQ) [40]. Individuals with ASC also have lower-than expected 2nd to 4th digit (2D:4D) ratios [6], which is correlated with higher ratios of FT to fetal estrogen [4], as well as lower verbal and higher numerical intelligence.

FUTURE DIRECTIONS

There is converging evidence supporting a role of prenatal hormones in the development of sexually dimorphic behaviour. It is possible that genetic influences are responsible for, or interact with prenatal hormone levels that lead to the development of ASC. Considering the current support for a role of fT in the development of autistic traits, it would be beneficial for future studies to examine the relationships between FT levels, genetic variation and the development of autistic traits.

It would also be valuable to further establish the relationships between direct measures of hormones (e.g. amniotic fluid or serum measures) and physical characteristics (e.g. 2D:4D ratio or dermatoglyphics) which have been used as proxy measures of hormone exposure.

The benefit of using these types of measurements is that they are easy to obtain and have also been linked to multiple areas of human development. However, limited evidence exists for a relationship between these proxy measures and exposure to prenatal hormones. If such a link was confirmed using direct measures of hormones, it could simplify future investigations of hormone effects.

Sex differences in psychiatric disorders are common, which is particularly striking in autism spectrum disorders (ASDs) which are four times more prevalent in boys. High levels of testosterone during early development have been hypothesized to be a risk factor for ASDs, a fact supported by several studies showing fetal testosterone levels, as well as indirect measures of prenatal androgenization, are associated with ASDs and autistic-like traits.

REFERENCES


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