

# Neonatal free testosterone and decreased head circumference in females: evidence of reduced inactivation of testosterone in the brain

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doi: 10.1111/dmcn.12115

SIR—Whitehouse et al. reported that an inverse association was found between free testosterone levels in umbilical cord blood at birth and head circumference growth at 1 year of age.<sup>1</sup> In a recent study, Auyeung et al. found no sex differences in postnatal salivary testosterone at 3 to 4 months of age,<sup>2</sup> which is the peak of the postnatal testosterone surge in males. The investigators, however, reported that an association was found between fetal testosterone and autistic traits, but not salivary testosterone, in 18- to 24-month-old toddlers. Collectively, these disparate findings reveal that imbalances in the postnatal hormone milieu may also be positively associated with autistic traits.<sup>2,3</sup>

The work of Gustafsson et al.<sup>4</sup> suggests an explanation that reconciles Auyeung et al.'s salivary testosterone results with Whitehouse et al.'s finding. Studies report that salivary testosterone is a reliable marker of serum-free or bioavailable testosterone.<sup>5</sup> As demonstrated in rats,<sup>4</sup> the brain's inactivation of testosterone to the neuroprotective, anti-androgenic hormone, epitestosterone, may be higher in human females than in males. Further, there may be sex differences in systemic epitestosterone production and concentrations. Therefore, a decreased head circumference in females as demonstrated by Whitehouse et al. may be more accurately associated with a higher salivary or serum-free testosterone-to-epitestosterone ratio, whereas an increased head circumference would be associated with the opposite profile. Thus, increased testosterone levels per se may not be a prerequisite for elevated head circumference in autism.<sup>3</sup>

Interestingly, Auyeung et al.'s association of fetal testosterone and autistic traits in children<sup>2</sup> may implicate the co-occurrence of sulfotransferase (SULT) and/or uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase, UGT) polymorphisms affecting sex steroid metabolism

as a key genetic risk factor for later diagnosis of autism spectrum disorder (ASD). According to the investigators, fetal testosterone was determined as a measure of total extractable testosterone in amniotic fluid.<sup>2</sup> Sex steroid glucuronide and sulfate conjugates, which are produced in a wide range of tissues (including the lung, liver, gut, and brain), are excreted in urine at levels known to be influenced by genetic factors. For example, UGT2B17 polymorphism and promoter polymorphism in the *CYP17* gene affect the excretion of testosterone glucuronide and epitestosterone glucuronide respectively. Moreover, steroid conjugates in urine stored at 37°C are sensitive to deconjugation, undoubtedly even in the amniotic sac. Consequently, free and total sex steroid levels in amniotic fluid may not reflect levels in the fetal circulation. On the other hand, steroid conjugates, because they are water soluble, do not readily cross the placenta back to the mother and can be recycled in the fetus via amniotic fluid and fetal swallowing. Nevertheless, homeostatic control of endogenous fetal testosterone is most likely to be maintained by both product inhibition and the continuous hepatic metabolism of testosterone. Thus, agents that disrupt the activity of SULT or UGT-isozymes in genetically vulnerable individuals may be a critical factor contributing to ASD, while increased testosterone in amniotic fluid may simply predict the risk for a later diagnosis of ASD triggered postnatally.

In conclusion, a finding of lower (or even higher) free testosterone-to-epitestosterone in 3- to 24-month-old children, in association with elevated head circumference, autistic traits, and sex differences in epitestosterone levels (without sex differences in free testosterone), would challenge the fetal androgen theory of autism and offer a sound rebuttal to Baron-Cohen's arguments against the finding of Whitehouse et al.<sup>3</sup> Finally, it would raise questions of whether the extreme male brain theory can find support where the fetal androgen theory of autism ignores genetic differences affecting the urinary excretion of sex steroids.

## REFERENCES

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