Maternal thyroid disease and pubertal timing in offspring: novel evidence for a potential association

Since the original publication of the *Barker hypothesis* in 1990, substantial evidence has accumulated to demonstrate the impact of the intrauterine environment on long-term health of offspring (1). Historically, much of the early work in this area focused on the association between neonatal birth weight and the subsequent development of cardiovascular disease. More recently, studies have focused on the effects of various fetal exposures on the timing of pubertal onset (2). These associations are of particular interest given that early pubarche is associated with obesity, diabetes mellitus, cardiovascular disease, cancer, and other adult diseases (3, 4).

It is well known that maternal thyroid hormones influence fetal brain development. Moreover, thyroid disease is extremely common among pregnant women. Given the high prevalence of thyroid disease and its known impact on the fetal brain, it is biologically plausible that maternal hypothyroidism or hyperthyroidism could influence pubertal timing by affecting the development of the fetal hypothalamic-pituitary-gonadal axis. It is not currently known whether such an association exists in humans, as the sparse existing literature comes from animal studies.

In this month's edition of *Fertility and Sterility,* Lunddorf et al. (5) used data from the Danish National Birth Cohort and its puberty cohort to examine the association between maternal thyroid disease and pubertal timing. Over 15,000 mother-child pairs were included in the analyses. The investigators demonstrated earlier pubertal development among sons of mothers with hyperthyroidism (average difference: −2.9 [95% CI, −5.0 to −0.7] months) compared with sons of mothers without a thyroid diagnosis. Although not statistically significant, early pubertal development was also noted for sons of mothers with benign goiter (average difference: −1.9 [95% CI, −4.6 to 0.9] months). Interestingly, these associations were not observed in daughters.

This large cohort study presents novel findings supporting an association between maternal thyroid disease and pubertal timing in sons. These findings are clinically relevant and important, given the high prevalence of maternal thyroid disease and the potential impact of early puberty on adult health. The study is strengthened by the frequent collection of data on pubertal development, every 6 months throughout puberty. The investigators also relied on self-assessment rather than clinical examinations, yielding a higher than typical participation rate of 70%.

Despite the potential benefit of self-assessment, the investigators correctly note that it is also a limitation because of the risk of misclassification. Interestingly, subjects were provided illustrations and descriptions of Tanner stages to improve the accuracy of their reporting. The investigators also comment on the possibility of recall bias given that 6 months elapsed between each survey. As with all cohort studies, residual confounding remains a possible limitation despite adjustment for confounders. Finally, the study is limited by a lack of data on the use of thyroid medications before and during pregnancy. It remains unknown whether adequate treatment of thyroid disease influences the association demonstrated in this study.

In summary, the large, national cohort study published in this month's issue of *Fertility and Sterility* suggests an association between maternal hyperthyroidism and early onset of puberty in sons. Although the underlying mechanisms are yet to be determined, these data are highly useful given the novelty and clinical relevance of the findings. Patients may be counseled that maternal hyperthyroidism may influence pubertal timing in boys. Whether adequate treatment negates this association is still unknown and should be the focus of future research.

Jennifer L. Eaton, M.D., M.S.C.I.
Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Women and Infants Hospital and Warren Alpert Medical School of Brown University, Providence, Rhode Island

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