Maternal Mild Thyroid Insufficiency and Risk of Attention Deficit Hyperactivity Disorder

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Summary

This study was embedded within the Generation R, a population-based birth cohort in the Netherlands where children were followed up from birth until young adulthood. Of the 4997 eligible mother-child pairs with data on maternal thyroid levels (excluding twins), 3873 pairs of children and caregivers (77.5%) were included in the main analyses. Maternal hypothyroxinemia, characterized by low levels of free thyroxine coexisting with reference thyrotropin levels, and children's symptoms of attention-deficit hyperactivity disorder (ADHD) were the main outcome measures. Maternal thyroid hormone levels (thyrotropin, free thyroxine, thyroid peroxidase antibodies) were measured at a mean (SD) of 13.6 (1.9) weeks of gestation. Children's ADHD symptoms were assessed at 8 years of age using the Conners' Parent Rating Scale–Revised Short Form; higher scores indicate more ADHD symptoms (possible range, 0-36). Maternal hypothyroxinemia (n=127) in early pregnancy was associated with higher scores for ADHD symptoms in children at 8 years of age after adjustments for child and maternal factors (increase in ADHD scores, 7% [95% CI, 0.3%, 15%]). The results remained essentially unchanged when women with elevated levels of thyroid peroxidase antibodies were excluded. The authors concluded that children exposed to maternal hypothyroxinemia in early pregnancy had more ADHD symptoms, independent of confounders. This finding suggests that intrauterine exposure to insufficient thyroid hormone levels influences neurodevelopment in offspring.

Commentaries

Evidence-based Medicine Viewpoint

Relevance: Fetal origin of disease(s) in later childhood and even adulthood has captured the attention and imagination of researchers all over the world. Many of these conditions are related to 'nature and nurture' encountered by the developing fetus in the internal and external maternal environment. An important example of this complex interaction is that fetal brain growth and development in early gestation are significantly influenced by maternal thyroxine levels, as fetal production of thyroid hormones does not begin until halfway through gestation. Thus maternal hypothyroidism in early pregnancy adversely impacts fetal neurodevelopment. More recently, it has been demonstrated that even in the absence of clinical or biochemical hypothyroidism, just the presence of low free thyroid hormone (FT4) without a concomitant increase in thyroid stimulating hormone (TSH/thyrotropin) – a condition referred to as hypothyroxinemia – can also result in adverse neurodevelopmental outcomes in infancy and childhood. This can manifest as developmental delay in all sectors, decreased psychomotor skill, lower intelligence quotient (IQ), and behavioral problems. This study [1] explores the association between maternal hypothyroxinemia in the first trimester of pregnancy and behavioral disorders in mid-childhood, especially ADHD.

Critical appraisal: This study provides an opportunity to critically appraise a well-designed and conducted cohort study using one of several tools available for the purpose. ***Table* I** presents the findings using the Critical Appraisal Skills Programme checklist [2]. In addition, there are several other items recommended to be presented in cohort study reports as per the STROBE (Strengthening the Reporting of Observational studies in Epidemiology**)** statement [3,4], but several of these are not related to the design or conduct of such studies; hence are not elaborated here.

Extendibility: Although the epidemiological setting of this study (in terms of population characteristics, health-care system, childhood outcomes *etc*) are very different from our setting, the biological plausibility of maternal hypothyroxinemia resulting in adverse impact on fetal neurodevelopment with neuro-cognitive and behavioral impacts in later life, makes it difficult to ignore the findings. However, replication of a similar study in India

TABLE I CRITICAL APPRAISAL OF THE STUDY

Criteria	*Report*
Did the study address a clearly focused issue?	Yes. This study sought to address the prevalence of ADHD (O=Outcome) among Dutch 8-year-old children (P=Population) born to mothers with hypothyroxinemia during the first trimester of pregnancy (E=Exposure), in comparison to those born to mothers who did not have hypothyroxinemia (C=Comparison).
Did the authors use an appropriate method to answer their question?	Yes. The PICO question framed above is best addressed through a prospective cohort study or a case-control study, the former being superior.
Was the cohort recruited in an acceptable way?	Yes The cohort was a subgroup of a Dutch cohort/population enrolled in an ongoing study recruiting participants from fetal life onwards (Generation R Study). Pregnant women (n=7069) were enrolled in early pregnancy and underwent measurement of thyroxine level (n=5099, 72%). Among these, 4997 women with single live births formed the maternal cohort. Of these, 3873 mothers' offspring presented for the outcome assessment of children per protocol. Table 1 in the publication (1) shows that 3873 mothers had FT4 levels and 3644 had thyrotropin levels; however 3687 were used to determine the presence of hypothyroxinemia (although both FT4 and thyrotropin levels were required for the diagnosis). This discrepancy is unexplained. The investigators compared characteristics of mothers whose children were not available for the outcome assessment. Most important, they confirmed that the risk factor (hypothyroxinemia) was distributed similarly between the groups of mothers with and without the outcome assessment, by demonstrating comparable levels of FT4 and thyrotropin. For these reasons, there does not appear to be selection bias.
Was the exposure accurately measured to minimize\bias?	Yes. Maternal FT4 and thyrotropin levels were measured using standard techniques. The investigators used additional quality control measures such as calculating intra- and inter-assay coefficients of variation for both hormones.A standard definition of hypothyroxinemia was used as per international recommendations to assign exposure. As an additional quality assurance step, the investigators calculated the ranges of FT4 and thyrotropin values obtained in this study, to define hypothyroxinemia. A sensitivity analysis using this definition *versus* the standard definition was undertaken to check the robustness of results.
Was the outcome accurately measured to minimize bias?	The primary outcome (ADHD) was determined using a standard instrument (Conners' Parent Rating Scale- Revised Short Form) that is previously validated. All children available for follow-up underwent the outcome measurement and the same instrument was used for all children. As an additional quality assurance step, the investigators undertook a sensitivity analysis determining the presence of ADHD using a different tool in a subgroup of children, and explored differences in results. However, one potential source of bias could be that mothers whose children were already diagnosed as ADHD or other behavioural disorders could have given higher scores in various domains on account of this prior knowledge. Similarly, the potential bias arising out of knowing the exposure status (maternal hypothyroxinemia or otherwise) could have affected the scoring of children.
Have the authors identified all important confounding factors?	Yes. The authors identified multiple potential confounders, including age of mother during pregnancy, socio-economic status, ethnicity, parity, educational status and smoking during pregnancy. Additionally, maternal psychological status was also determined. Prior to the outcome measurement in children, a behavioural assessment to detect autism like traits was also undertaken. However, it is unclear if infant and/or childhood thyroid hormone status

Contd...

Criteria	*Report*
	were assessed at any time. Appropriate statistical methods were used to adjust for potential confounders.
Was the follow up of subjects complete and long enough?	Although 4997 participants were eligible for long-term follow up, only 3873 (77.5%) were available or outcome measurement. The reasons for failure of outcome measurement in about one-fourth of the cohort are not specified.The age chosen for outcome measurement (8 y) is appropriate as the behavioural condition would have had sufficient time to manifest itself. Thus it is unlikely that any children with ADHD would be missed. On the other hand, it is also possible that some children may have been already diagnosed as ADHD and this could alter the parental scoring at 8 y (with or without treatment). It is also possible that some children with suspected behavioral problems may have been ruled out to have ADHD, and this could also alter the parental scores. Similarly it is possible to consider that a sibling with a confirmed or ruled-out diagnosis of ADHD (or other behavioral problem) could affect parental sensitivity in scoring the index child.
What are the results of this study? How precise are the results?	In summary, the study showed that there was a 7% (95% CI 3, 15) increase in the ADHD diagnosing component of the Behavioral scale used in this study (Conners' Parent Rating Scale- Revised Short Form) among children of mothers with first trimester hypothyroxinemia. The unadjusted (for confounders) analysis yielded similar results. In contrast, the component of the scale reflecting Oppositional defiant disorder did not show a statistically significant increase in the component of the score (adjusted and unadjusted analysis). Unfortunately, the authors did not provide the absolute number (or percentage) of children diagnosed as ADHD or Oppositional defiant disorder, in either arm of the cohort. This would have helped to better understand the clinical (and public health) significance of the 7% higher score mentioned above.
Do you believe the results?	The study describes results that are difficult to ignore as some of the nine Bradford Hill criteria for causation [5] are reasonably fulfilled, particularly Theoretical Plausibility and Coherence. However, the strength of association is modest (at best), and a 'dose-response relationship' (i.e more severe hypothyroxinemia being associated with more frequent and/or more severe ADHD) has not been demonstrated. In summary, the results of this study point towards (but do not confirm) a potential clinically significant association between maternal hypothyroxinemia in early pregnancy and the occurrence of ADHD in their children during mid-childhood.
Can the results be applied to the local population?	There are no biological reasons to expect that infants and children in developing countries may have different impact of maternal hypothyroxinemia (as defined in this study) on fetal neurodevelopment and its possible later consequences (including the development of ADHD and/or other behavioral problems). However, it should be emphasized that the population sensitivity to many of the items in the scoring system used to diagnose ADHD (in this study) could be quite different, meaning that some items appearing abnormal in a developed country setting, may be passed off as "normal" (or not unusual) in a developing country setting.
Do the results of this study fit with other available evidence?	In a sense, this study could be described to be in line with other pieces of evidence suggesting that the fetal thyroid environment in the first trimester is largely related to maternal sufficiency and that even mild perturbations can disrupt fetal neurodevelopment, resulting in neuro-cognitive and behavioral consequences in infancy and early childhood. This study is somewhat unique in the sense that it explored the effect of maternal hypothyroxinemia (as opposed to hypothyroidism) which does not have clinical manifestations, on the behavioral consequences as late as 8 years after birth.

could yield different results for the reasons explained.

Conclusions: This well-designed cohort study suggests that maternal hypothyroxinemia (even without clinical manifestations) in the first trimester of pregnancy could increase the risk of development and/or manifestation of ADHD-like behavioral disorders in mid-childhood.

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Developmental Pediatrician's Viewpoint

Relevance: Symptoms of hyperactivity, inattention and impulsivity can be a normal variation, a behavior problem (causing parental distress but no significant functional impairment) or a mental health disorder or Attention Deficit Hyperactivity Disorder (ADHD), causing significant functional impairment.

Critical appraisal: The Generation R study is a commendable study that has generated a lot of data that may apply to several health conditions. In the present study, the authors suggest that maternal hypothyroxinemeia may result in ADHD. From a developmental pediatrician's viewpoint, the most important concern is the case definition of ADHD used besides the limitations given. The Conners' Parent Rating Scales–Revised short version is a screening tool that is not used in isolation. Individual items are rated and raw scores converted to standardized T scores [1]. Children with T scores above certain levels are considered 'at risk' of ADHD and require detailed evaluation. In this study, only raw scores of all children were used. Thus even children who were 'not at risk' got included. Having higher scores is not paramount to having ADHD if cut-off levels are not applied. Since persistence of symptoms in multiple settings and functional impairment were not assessed, normal variants and behavior problems got inadvertently included. Given the limitations of epidemiological studies, 'probable' criteria could have been defined and relative/ attributable risks for children with and without 'probable' ADHD determined in exposed and not-exposed children.

Discussion: Maternal hypothyroxinemeia has also been associated with cognitive impairment and autistic features [2,3]. All three entities can exist in isolation or together (if symptoms are not accountable by cognitive level). Even though differentiation is not feasible by parental reports, it is not really required if we consider aberrant development and behaviour collectively. This gets explained by the neurobiological role of maternal thyroxine during embryogenesis and substantiated by the neuro-radiological abnormalities seen in some deficient models.

Clinical application: Proving causality becomes meaningless without available intervention. Although the role of prophylactic iodine in pregnancy is established, there are still conflicting results regarding efficacy of L-thyroxine supplementation in preventing adverse neuro-cognitive outcomes [4]. Extensive research is required before prophylaxis becomes a reality.

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Endocrinologist's Viewpoint

During pregnancy maternal thyroid hormone levels are increased upto 50% due to marked increase in thyroxine binding globulin (TBG), the direct stimulation of the thyroid gland by elevated levels of human chorionic gonadotropin, and increased enzymatic activity of Type III monodeiodinase. These physiological adaptations which are aimed for maintaining thyroid hormone levels are hindered by maternal factors like iodine deficiency and thyroid autoimmunity [1,2]. The consequent maternal thyroid deficiency is manifested as hypothyroxinemia

during pregnancy. The term hypothyroxinemia refers to low production of serum free thyroxine (FT_4) without concordant increase in thyroid stimulating hormone (TSH).

Relevance: There have been several studies in literature on the effects of maternal T_4 on fetal brain development and the negative impact of hypothyroxinemia on neurobehavioral performance in offspring. This may be due to the consequence of decreased availability of maternal T4 to the developing brain, its only source of thyroid hormone during the first trimester; T4 is the required substrate for the regulated generation of T3 in the amounts needed for optimal development in different brain structures [3]. Research till date evaluating the effect of isolated hypothyroxinemia on maternal and fetal outcomes has yielded conflicting results.

Critical appraisal: The strength of this population-based prospective study is the large sample size and that they followed-up the cohort over long-term. Several neurocognitive symptoms in children born to hypothyroxinemic mothers have been studied in the past, but there have been only very few studying ADHD and maternal hypothyroxinemia. This study also has several additional noteworthy methodological refinements. The most common age group of presentation of ADHD is between 6-8 yrs which the authors have precisely studied. The investigators also made effort to separately analyze the data by excluding TPO positive mothers and mothers who took thyroid medication which could have confounded the results; however the association still remained positive.

However there are certain caveats. One is regarding the accuracy of the FT4 measurement assay. Although the authors followed standard laboratory practices, conventional immunoassay methods are unreliable with often non-reproducible results among different kits. The most accurate would have been an equilibrium dialysis assay. Another problem routinely encountered in these types of studies is that the cut-off level of FT4 below the 5th centile is unclear because of regional differences due to difference in iodine status. The authors have not mentioned regarding the iodine status of the study population or the general population, and no mention regarding the presence or absence of goiter in the study subjects. Trimester-specific reference ranges in iodine-sufficient and thyroid peroxidase antibody-negative populations are yet to be determined. Though it has been proposed to adapt serum FT_4 reference ranges that are laboratory-specific and trimester-specific for use during pregnancy, no worldwide consensus has been reached on such "pregnancy-adapted" ranges [4,5]. Regression analysis in an earlier study showed that first-trimester maternal fT4 but not maternal TSH or fT4 later in gestation was a significant predictor of neurobehavior profile in children [6]. In the current study, the mean gestational age at which the FT4 analysis was done was 13.4 weeks in second trimester, but authors have done a subgroup analysis in a sample of pregnant women with FT4 levels measured in the first trimester of pregnancy and still found positive association between ADHD and maternal hypothyroxinemia. It would have been more informative if data regarding FT3 levels also were provided. Parental reporting of ADHD is a soft tool; no information regarding confirmation of the clinical diagnosis or medications for ADHD have been mentioned in the study. Multiple environmental factors influence the neurocognitive behavior of children which have not been taken into account, and most importantly the thyroid function test in the offspring has not been studied. Thyrotoxicosis in children is known to cause ADHD.

The association between maternal thyroid function and children's ADHD and oppositional scores were examined using linear regression. The statistical analysis could have been more refined by using a multiple logistic regression model.

Conclusions: Viewed in conjunction with the previously reported data, this study provides further support to the possible role of prenatal exposure to thyroid hormone insufficiency in causing adverse cognitive outcomes in offspring.

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