Journal of Endocrinological Investigation

TPO-antibody in euthyroid pregnant women and cognitive ability in the offspring: a focused review

--Manuscript Draft--

Manuscript Number:	JENI-D-21-00496R1
Full Title:	TPO-antibody in euthyroid pregnant women and cognitive ability in the offspring: a focused review
Article Type:	Original Article
Funding Information:	
Abstract:	A link between maternal thyroid dysfunction during pregnancy and the risk of cognitive and behavioral problems in the offspring has previously been established; however, the potential effects of maternal thyroid autoimmunity on neurodevelopment in the absence of maternal hypothyroidism are less clear. The present review aims to highlight the gaps in knowledge in this regard and provide a thorough assessment of relevant literature. There is some evidence that neuropsychological and intellectual developments of offspring are adversely affected by maternal thyroid autoimmunity, although the results of available studies are not concordant. The tools and measurements that have been applied in different studies to assess neurodevelopment or IQ vary widely and the children born to mothers with thyroid autoimmunity have been assessed at different chronological stages of life. Such variations may explain some of the differences across studies. In addition, the definition of thyroid autoimmunity has been based on TPOAb cut points provided by manufacturers in most cases, but it is preferable to define these values based on age, trimester, and method-specific reference ranges. Finally, well-designed studies are needed to assess verbal and non-verbal neurocognition of offspring born to mothers with autoimmune thyroid disease before or during pregnancy.
Corresponding Author:	Fereidoun Azizi, MD Research Institute for Endocrine Sciences IRAN, ISLAMIC REPUBLIC OF
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Research Institute for Endocrine Sciences
Corresponding Author's Secondary Institution:	
First Author:	Fereidon Azizi
First Author Secondary Information:	
Order of Authors:	Fereidon Azizi
	Atieh Amouzegar, MD
	Elizabeth N. Pearce, MD
	Ladan Mehran, MD
	John Lazarus, Prof
	Miralireza Takyar, MD
	Fereidoun Azizi, MD
Order of Authors Secondary Information:	
Author Comments:	To the Editor-in-Chief Journal of Endocrinological Investigation Greetings Attached please find the manuscript entitled “TPO-antibody in euthyroid pregnant women and cognitive ability in the offspring: a focused review” which we would like to

	be considered for publication in Journal of Endocrinological Investigation. The authors hereby affirm that the manuscript is original, that all statements asserted as facts are based on authors' careful investigation and accuracy, that the manuscript has not been published in total or in part and the author(s) hereby confirms that neither the manuscript nor any part of it, except for abstracts of less than 400 words, has been published or is being considered for publication elsewhere, and that authors have full power of authority to enter into this copyright assignment and to make the grants herein contained. The authors declare that they have no conflict of interest. Yours sincerely Fereidoun Azizi, MD Professor of Internal Medicine and Endocrinology Director, Research Institute for Endocrine Sciences P.O.Box: 19395-4763, 1985717413 TEHRAN – IRAN Tel: +98 (21) 22409309 Fax: +98 (21) 22402463 url: http://endocrine.ac.ir/ e-mail: azizi@endocrine.ac.ir
Response to Reviewers:	Dear Editor-in-chief Journal of Endocrinological investigation Greetings Thank you for valuables comments. We tried to answer all he comments one by one as bellow: Reviewer #1 Thank you for your valuable comments. We are trying to write another review paper to explain all available studies in details regarding the effect of maternal hypothyroxinemia on the cognitive function of the offspring. C: The Authors should indicate the searching strategy used for the present review. R: Agreed. We added the search searching in the main text. Page 3-4 Line 77-82 C: A recent paper by Kampouri et al (J epidemiol community heath) assessed the association between maternal hypothyroxinemia and thyroid autoimmunity and neuropsychological development from infancy to early childhood. I suggest to consider this paper in your discussion. R: Thank you for your valuable comment. We add the study in the main text and also the table. Page 7, Line 153-157& Table 1 Reviewer #2 1. Introduction, page 3, lines 72-73. The Authors state that "adverse effects result from the facilitating effects that pregnancy may have on autoimmune processes in general". This point is not clear and should be better explained R: Agreed. We have changed the sentence and clarified it. Page 3, Line 70-74 2 .Paragraph Offspring neurocognitive aspects of thyroid autoimmunity, page 4, lines 81-90. When reporting the study by Pop et al (ref#17), the Authors first state that "children of 230 TPOAb-positive women" were studied (line 81) but later in the text one reads that "just 19 out of 230 mothers were TPOAb positive" (line 88). Please clarify. R. Agreed. We change it as the total number of pregnant women was 230 and 19 were TPOAb positive. 3. Paragraph Offspring neurocognitive aspects of thyroid autoimmunity, page 6, lines 138-141. When commenting on the results by Derakhshan et al (ref#26) in relation to the iodine status of the two cohorts, it should be pointed out that either in Generation R or in ALSPAC cohort iodine data were available for a small subset of women only, and the study was not powered for investigating the potential role of iodine intake R: Thank you for your valuable comment. We add it in the main text. Page, 7 Line 149-151 4. Table 1. Rather than the total number of examined children, it would be helpful to the reader if the number of cases (i.e., children born to TPOAb+ve women) included in each study was indicated R: Agreed. We showed the numbers in a separate column in Table 1. 5. Table 1. The number of participants indicated for the study by Derakhshan et al (ref#26) is slightly different from that reported in the original paper (Generation R: n = 3564; ALSPAC: n = 2362). Please check and correct.

	R. Agreed. We have put the numbers as they have shown in the figure 1 of the original paper; now we change it as the numbers have reported in the main text.
Suggested Reviewers:	Maryam tohidi tohidi@endocrine.ac.ir I know her from office

TPO-antibody in euthyroid pregnant women and cognitive ability in the offspring: a focused review

Atieh Amouzegar MD [1], Elizabeth N. Pearce MD [2], , Ladan Mehran MD [1], John Lazarus Prof [3],Miralireza Takyar MD[1] Fereidoun Azizi MD[1]

1) Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2) Section of Endocrinology, Diabetes and Nutrition, Boston University School of Medicine, Boston MA, USA
3) Thyroid Research Group, Systems Immunity Research Institute, Cardiff University School of Medicine, Cardiff, UK.

Amouzegar.A and Pearces EN are contributed equally to this article and are co-first authors.

Atieh Amouzegar, Amouzegar@endocrine.ac.ir, Telephone: +98 21 22432500
Elizabeth N. Pearce, elizabeth.pearce@bmc.org, 88 East Newton Street, Evans 201, Boston, Massachusetts 02118
Miralireza Takyar, ftakyar@gmail.com, Tel: +98 21 22432500
Ladan Mehran,lmehran@endocrine.ac.ir, Tel: +98 21 22432500
John Lazarus, lazarus@cf.ac.uk, Tel: +44 2920 744 326
Fereidoun Azizi, azizi@endocrine.ac.ir, Tel: +98 21 22409309

Running Head: thyroid autoimmunity and offspring cognition

Corresponding author:
Fereidoun Azizi, M.D
Professor of Internal Medicine & Endocrinology
Address: Endocrine Research Centre, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences,
P.O. Box: 19395-4763
Tehran, I.R. Iran
Telephone: +98 21 22409309
Fax: +98 21 22402463
Email: azizi@endocrine.ac.ir

Key words: thyroid, autoimmunity, pregnancy, offspring, cognitive ability

Abstract

A link between maternal thyroid dysfunction during pregnancy and the risk of cognitive and behavioral problems in the offspring has previously been established; however, the potential effects of maternal thyroid autoimmunity on neurodevelopment in the absence of maternal hypothyroidism are less clear. The present review aims to highlight the gaps in knowledge in this regard and provide a thorough assessment of relevant literature. There is some evidence that neuropsychological and intellectual developments of offspring are adversely affected by maternal thyroid autoimmunity, although the results of available studies are not concordant. The tools and measurements that have been applied in different studies to assess neurodevelopment or IQ vary widely and the children born to mothers with thyroid autoimmunity have been assessed at different chronological stages of life. Such variations may explain some of the differences across studies. In addition, the definition of thyroid autoimmunity has been based on TPOAb cut points provided by manufacturers in most cases, but it is preferable to define these values based on age, trimester, and method-specific reference ranges. Finally, well-designed studies are needed to assess verbal and non-verbal neurocognition of offspring born to mothers with autoimmune thyroid disease before or during pregnancy.

Introduction:

Maternal thyroid dysfunction may exert lasting adverse effects on the wellbeing of offspring. Many well-designed studies have characterized associations between such maternal thyroid dysfunction and child brain morphology (1-3). Overt maternal hypothyroidism is associated with profound neuropsychiatric and developmental defects in offspring (4, 5). In addition, it has been shown that low and high maternal thyroid function is associated with smaller cortical volume and gray matter (6). Although not shown by all studies, some elegant reports have depicted a range of neurocognitive deficits in the offspring of mothers suffering mild thyroid dysfunction (1, 7-9). Maternal thyroid autoimmunity as demonstrated by high TPOAb levels is reported to occur in 4-15% of euthyroid pregnant women worldwide (10-15). However, the implications of maternal thyroid autoimmunity during pregnancy on offspring neurocognitive development are unclear. Although some retrospective studies have shown TPOAb positivity during pregnancy to be associated with adverse neurodevelopmental outcomes during childhood, the findings should be viewed cautiously due to methodological issues such as small sample sizes and likely residual confounding. Moreover, it is unclear whether any effects of thyroid autoimmunity on fetus neurodevelopment during pregnancy are because of a decreased thyroid reserve and TPOAb as a cause of thyroid dysfunction, or antibody to thyroperoxidase is a marker of a more generalized autoimmunity in the body that can affect neurodevelopmental outcomes of a pregnancy and thyroid autoimmunity is just a part of it. The present focus- review aims to highlight the gaps in knowledge in this regard and provide a thorough assessment of relevant literature with specific focus just on TPOAb.

Search strategy

We searched MEDLINE, Web of Science, and Scopus till January 2021 with restriction in the English language. The key search terms included ("adverse pregnancy outcomes" OR"offspring neurocognition"OR "offspring IQ") AND ("Thyroid peroxidase antibody" OR TPOAb OR "TPO antibodies" OR "Antithyroid antibodies") AND (pregnancy OR "euthyroid pregnant women" OR "pregnant with normal thyroid function". Also, bibliographies of all relevant papers identified by the search strategy were scanned for additional papers.

Offspring neurocognitive aspects of thyroid autoimmunity

There is some evidence that neuropsychological and intellectual development of offspring can be adversely affected by maternal thyroid autoimmunity. The number of studies investigating the impact of mothers' autoimmunity during pregnancy on an offspring's IQ is growing but findings are still equivocal. A summary of the studies included in this review is shown in Table 1.

In a study by Pop et al. children of 230 women (tested during 32 weeks) were found to be at risk for cognitive dysfunction based on the Dutch translation of McCarthy Scales of Children's Abilities (MSCA) (16), which consists of six scales: verbal, perceptual-performance, quantitative, general cognitive (GCS), memory, and motor. The greatest differences were seen in the scores for GCS. This finding suggests a potential role for thyroid autoimmunity, in euthyroid pregnant women, in child neurodevelopment; but the role of maternal thyroid autoimmunity in child cognition should be considered cautiously in this study, as the number of TPOAb positive mothers was low and just 19 out of 230 mothers were TPOAb positive during late gestation. In addition thyroid function was assessed at 32 weeks of gestation for the first time and the probability of hypothyroidism during early pregnancy was not taken into account (17).

Li et al. evaluated intellectual and motor development using the Bayley Scale of Infant Development (BSID I) in children of euthyroid (TSH 0.12-0.42 mIU/, TT4 101.79–218.49 nmol/l,

and FT4 11.9–24.6 pmol/l),TPOAb positive mothers (gestational age 16–20 weeks) at the age of 25– 30 months. BSID I, includes intelligence and a motor scales. The intelligence scale assesses adaptive behaviors, language, and exploratory activities while the motor scale is used to assess gross motor function and fine motor function. The study showed lower motor and intellectual development in these infants compared to infants of mothers without thyroid autoimmunity (2).

In another analysis from the Generation R cohort, Ghassabian et al. found no association between elevated maternal TPOAb titers during early pregnancy (13.5± 1.8 gestational age) and offspring verbal development at 2.5 years of age, using the Language Development Survey (LDS) (18) to identify children with language delay and assessing nonverbal cognitive function using the parent-administered and the parent-report parts of the Parent Report of Children's Ability (PARCA) (19) (8). However, the authors reported that high titers of TPOAb during early pregnancy predicted some scales such as attention problems and aggressive behavior in children at age 3. Although mean TSH was higher in the TPOAb-positive women compared with those who were TPOAb negative (3.83 ± 4.13 vs. 1.53±1.04 IU/L), the authors claimed that the effect of elevated TPOAb titers on child's behavior was not exclusively mediated by maternal TSH and passing of antibody through placenta and its effect on neonate thyroid function during few months after birth has an important role. This finding suggests that the effects on problem behavior may be mediated via TPOAb effects on thyroid function.

Another study, from Baltimore, demonstrated an association between maternal serum TPOAb levels late in pregnancy (during the third trimester) in 1,527 mothers and childhood IQ scores in 1,733 offspring (20). The Stanford–Binet Scale and Wechsler Intelligence Scales (21) were used for children aged 4 and 7 years, respectively. The investigators found early and transient developmental delays at the age of 4 years which were attenuated by the age of 7, resulting in a small effect of

maternal TPOAb positivity on offspring IQ (20). Previously the same group had demonstrated that TPOAb elevation during the third trimester of pregnancy was strongly (prevalence odds ratio 7.5, 95% CI: 2.4- 23.3) associated with sensorineural hearing loss in offspring with increasing strength of the association as the level of TPOAb increased. It is unknown whether the observed TPOAb-mediated hearing loss is part of the causal pathway for cognitive delays or whether the two effects are independent (22).

In another study, Williams et al. found no association between elevated levels of maternal TPOAb, measured at 10 and 34 weeks of gestation, and cognitive function as evaluated by the MSCA (16) and a British Picture Vocabulary Scale (BPVS II) (23) when the children were assessed at the age of 5.5 years. In this study just, 14 of 93 mothers were TPOAb-positive in at least one sampling period in pregnancy; all mothers were euthyroid with median maternal TSH levels between 1.03 and 1.66mU/L during pregnancy and at delivery. Attention deficit/hyperactivity in offspring was assessed at 5.5 years of age (24).

Another study utilizing data from two prospective birth cohorts, Generation R (Rotterdam, the Netherlands) and the Avon Longitudinal Study of Parents and Children (ALSPAC; United Kingdom), aimed to assess the association of maternal TPOAb positivity during pregnancy with child IQ (25). In the Generation R study offspring were evaluated at the age of 5 to 8 years using a well-validated age-adjusted shortened form of the Wechsler Intelligence Scale (21). This is a standardized assessment of performance and verbal intelligence which does not rely on child language skills during assessment, but instead evaluates spatial visualization and abstract reasoning abilities. In the ALSPAC cohort children were studied at age 7 to 10 years using a well-validated age-adjusted shortened form of the Wechsler Intelligence Scale for Children, with a standardized assessment of performance and verbal intelligence for evaluation of child IQ (21). Data from these

cohorts demonstrated an association of TPOAb positivity in mothers during early gestation (<18 weeks) with lower child IQ in the iodine sufficient Dutch cohort but TPOAb positivity was not associated with child IQ in the mildly iodine-deficient UK cohort. Either on Generation R or in ALSPAC cohort, iodine data were available only for a small subset of women, and the study was not powered enough for investigating the potential role of iodine intake. Results were not altered by adjustment for maternal FT4 or TSH, suggesting that the observed associations were not mediated by thyroid dysfunction. Recently Kampouri et al. in a 757 mother-child pairs from a prospective cohort in Greece, using MCSA, found maternal thyroid autoimmunity to be associated with decreased child perceptual and motor ability at the age of 4 years and also have an adverse effect on non-verbal cognitive development from infancy to early childhood, in an iodine-sufficient area (26).

In interpreting the available literature on this important issue, the ascertainment of possible confounders such as maternal age, educational level, ethnicity, family socioeconomic status and family income, number of children, available educational resources, family attitude toward having a new child, nutritional deficits or exposure to environmental hazards, should be carefully considered. Outcomes should be assessed using tools appropriate for child age.

Limitation of the tools for measuring offspring IQ

Different studies have used various tools to assess child developmental outcomes. These include the McCarthy Scales of Children's Abilities (MSCA) (16), Wechsler Intelligence Scale (21), Stanford–Binet Scale, Bayley Scale of Infant Development (BSID I), and British Picture Vocabulary Scale (BPVS II) for assessing various aspects of neurocognition in the studies described previously. The choice of instruments may have significant effects on study findings. For instance, results from tests that are in the form of self-administered questionnaires should be approached differently from those

that are based on objective neurocognitive testing. The use of different assessment tools has made direct comparison of results from different studies largely infeasible. It may be better if future studies will be done with unique most applicable tools.

Some of the above mentioned IQ assessment tools were applied to evaluate verbal and nonverbal IQ tests (27) or more extensive approach had been taken to assess both verbal and nonverbal cognitive functioning as well as problem behavior in children e.g.by using Language Development Survey (LDS). This test has excellent test-retest reliability as well as extremely high validity, sensitivity and specificity, and can be used to identify children with language delay (18).

Apart from neurocognitive and IQ testing, there are other factors that affect findings reported by studies assessing neurocognition. One critical complicating factor is the lack of a gold standard neuropsychological test for the assessment of neurocognitive development specifically related to thyroid status (28). Moreover, available assessment tools are subject to cultural and environmental influences and such factors can have significant effects on results (29). Training of the administrators of IQ tests can potentially affect test results. The performance and cooperation of children while they are performing the tests may also play an important role, particularly at younger ages, when attention span may be limited. It is worth mentioning that subtle changes in social, verbal, mathematical and other aspects of IQ may not be detectable by current tools and more comprehensive assessments are needed in this regard.

TPOAb positivity level during pregnancy

Another complicating issue for studies assessing associations between maternal thyroid autoimmunity and offspring neurodevelopment is the variability in TPOAb titers across the course of gestation. In some women the levels of TPOAb may remain elevated throughout pregnancy, but in many there is a decrease in TPOAb titers concomitant with the general decrease in autoimmunity

by late gestation. Therefore, associations between maternal TPOAb and child outcomes may depend in part on timing of assessment of the TPOAb titer during pregnancy. Assessment of maternal TPOAb late in pregnancy may have resulted in some misclassification, since TPOAb titers may tend to wane after the first trimester. One study that has addressed this issue is the report by Glinoer et.al which has shown that women who are TPOAb positive early in gestation experience a significant decrease in TPOAb titers later on (30). However, an important factor in this regard is the detailed definition of "TPOAb positivity" during each trimester of pregnancy, which can be affected by laboratory methodology and cutoff values used. Almost all relevant studies have used manufacturer-recommended cutoffs to define TPOAb positivity (31-33). An analysis of three prospective Dutch birth cohorts showed that using manufacturer-based cutoffs for TPOAb positivity may fail to identify up to one third of women with high TPOAb levels (34). Analyzing the population-based percentile cutoffs for TPOAb positivity in these cohorts showed that titers of TPOAb to higher than the 92nd percentile were associated with higher serum TSH levels (>2.5 mU/L) and there were significant differences in TPOAb cutoffs between values defined through population-based methods and manufacturer-recommended values in two out of three cohorts. In addition, the Generation R study considered "TPOAb positivity" as serum concentrations of 60 IU/mL and higher while a level of ≥ 6 IU/mL, using different assay, was considered positive in the ALSPAC study (25). These differences highlight the potential importance of defining population-based, trimester and/or method-specific reference ranges for optimizing the definition of TPOAb positivity. Due to non-normal distribution of TPOAb, determination of reference ranges for this antibody warrants sophisticated statistical analyses (35). Careful definition of thresholds for TPOAb positivity is essential if these values are to be used for delineating whether maternal thyroid

autoimmunity is an independent risk factor for adverse neurocognitive and developmental effects in offspring.

Large studies are needed to define TPOAb thresholds that are associated with adverse pregnancy and child neurodevelopmental outcomes and whether such associations are mediated by decreases in maternal thyroid function. Such studies, in turn, can inform future interventional trials." The question that needs to be answered is "what titers of TPOAb in each trimester should be considered as positive level that can predict child neurocognition, verbal and non-verbal brain development and IQ?" Well-designed randomized trials that consider offspring brain development as a primary outcome are needed in order to determine whether levothyroxine or other treatments may improve TPOAb-mediated child cognitive outcomes.

Iodine status:

The relationship between iodine deficiency during pregnancy and impaired offspring neurodevelopment is well documented (36-38). In addition, both low and high iodine intakes are associated with increased risk for thyroid autoimmunity (39). In a study by Xiaoguang et al. an increased prevalence of TPOAb positivity was observed in pregnant women with low urinary iodine concentration (UIC< 100 µg/L) compared to those with normal UIC.(39). Higher TPOAb concentrations were seen in in pregnant mothers with higher UIC in the ALSPAC study and sensitivity analyses suggested that the association of maternal thyroid autoimmunity, defined as higher TPOAb positivity, with child IQ may differ based on maternal iodine status (25). However, these findings need to be confirmed in future studies with robust designs and appropriate statistical power. Effects of mild-moderate maternal iodine deficiency on child neurodevelopmental outcomes are likely mediated by subtle changes in thyroid function or thyroid reserve during pregnancy; it is

unknown whether induction of autoimmunity by iodine deficiency may also influence offspring development independent of thyroid function abnormalities.

Conclusions:

Based on the current state of the literature, it is evident that we are in the early stages of defining the potential relationship of maternal thyroid autoimmunity to impaired child neurocognition, and verbal and non-verbal IQ development. More robustly-designed studies using valid and accurate neurocognitive assessment tools are required for this purpose. Additionally, age-, ethnicity-, trimester-, and method-specific ranges for TPOAb and other markers of thyroid autoimmunity in populations with various iodine-sufficiency status are urgently required as an initial step.

Acknowledgement: Not applicable

Conflict of Interest Statement

All authors declare that there is no conflict of interest.

Funding: there is no funding

Author Contributions

Conception and design of the work has done by EN,P, AA and FA,JL

Literature reviewing, has done by AA and EN,P

Drafting the work or revising it critically for important content has done by EN,P and AA and MA,T and LM

Final approval of the manuscript to be submitted has done by all authors.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References:

1. Modesto T, Tiemeier H, Peeters RP, Jaddoe VW, Hofman A, Verhulst FC, et al. Maternal Mild Thyroid Hormone Insufficiency in Early Pregnancy and Attention-Deficit/Hyperactivity Disorder Symptoms in Children. JAMA pediatrics. 2015;169(9):838-45.
2. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. Clinical endocrinology. 2010;72(6):825-9.
3. Drover SSM, Villanger GD, Aase H, Skogheim TS, Longnecker MP, Zoeller RT, et al. Maternal Thyroid Function During Pregnancy or Neonatal Thyroid Function and Attention Deficit Hyperactivity Disorder: A Systematic Review. Epidemiology. 2019;30(1):130-44.
4. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. The New England journal of medicine. 1999;341(8):549-55.
5. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clinical endocrinology. 2003;59(3):282-8.
6. Jansen TA, Korevaar TIM, Mulder TA, White T, Muetzel RL, Peeters RP, et al. Maternal thyroid function during pregnancy and child brain morphology: a time window-specific analysis of a prospective cohort. The lancet Diabetes & endocrinology. 2019;7(8):629-37.
7. Ghassabian A, Bongers-Schokking JJ, Henrichs J, Jaddoe VW, Visser TJ, Visser W, et al. Maternal thyroid function during pregnancy and behavioral problems in the offspring: the generation R study. Pediatric research. 2011;69(5 Pt 1):454-9.
8. Ghassabian A, Bongers-Schokking JJ, de Rijke YB, van Mil N, Jaddoe VW, de Muinck Keizer-Schrama SM, et al. Maternal thyroid autoimmunity during pregnancy and the risk of attention deficit/hyperactivity problems in children: the Generation R Study. Thyroid : official journal of the American Thyroid Association. 2012;22(2):178-86.
9. Levie D, Korevaar TIM, Bath SC, Dalmau-Bueno A, Murcia M, Espada M, et al. Thyroid Function in Early Pregnancy, Child IQ, and Autistic Traits: A Meta-Analysis of Individual Participant Data. The Journal of clinical endocrinology and metabolism. 2018;103(8):2967-79.
10. Huang K, Xu Y, Yan S, Li T, Xu Y, Zhu P, et al. Isolated effect of maternal thyroid-stimulating hormone, free thyroxine and antithyroid peroxidase antibodies in early pregnancy on gestational diabetes mellitus: a birth cohort study in China. Endocrine journal. 2019;66(3):223-31.
11. Medici M, de Rijke YB, Peeters RP, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VV, et al. Maternal early pregnancy and newborn thyroid hormone parameters: the Generation R study. The Journal of clinical endocrinology and metabolism. 2012;97(2):646-52.
12. Han C, Li C, Mao J, Wang W, Xie X, Zhou W, et al. High Body Mass Index Is an Indicator of Maternal Hypothyroidism, Hypothyroxinemia, and Thyroid-Peroxidase Antibody Positivity during Early Pregnancy. BioMed research international. 2015;2015:351831.
13. De Leo S, Pearce EN. Autoimmune thyroid disease during pregnancy. The lancet Diabetes & endocrinology. 2018;6(7):575-86.
14. Moreno-Reyes R, Glinoer D, Van Oyen H, Vandevijvere S. High prevalence of thyroid disorders in pregnant women in a mildly iodine-deficient country: a population-based study. The Journal of clinical endocrinology and metabolism. 2013;98(9):3694-701.
15. van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, Goddijn M, et al. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Human reproduction update. 2011;17(5):605-19.

16. McCarthy D. McCarthy scales of children's abilities (MSCA): Psychological Corporation; 1972.
17. Pop VJ, de Vries E, van Baar AL, Waelkens JJ, de Rooy HA, Horsten M, et al. Maternal thyroid peroxidase antibodies during pregnancy: a marker of impaired child development? The Journal of clinical endocrinology and metabolism. 1995;80(12):3561-6.
18. Achenbach TM, Rescorla LA. Manual for the ASEBA preschool forms and profiles: Burlington, VT: University of Vermont, Research center for children, youth …; 2000.
19. Saudino KJ, Dale PS, Oliver B, Petrill SA, Richardson V, Rutter M, et al. The validity of parent-based assessment of the cognitive abilities of 2-year-olds. British Journal of Developmental Psychology. 1998;16(3):349-63.
20. Wasserman EE, Pillion JP, Duggan A, Nelson K, Rohde C, Seaberg EC, et al. Childhood IQ, hearing loss, and maternal thyroid autoimmunity in the Baltimore Collaborative Perinatal Project. Pediatric research. 2012;72(5):525-30.
21. Wechsler D, Golombok S, Rust J. WISC-III UK Wechsler intelligence scale for children: UK manual. Sidcup, UK: The Psychological Corporation. 1992.
22. Wasserman EE, Nelson K, Rose NR, Eaton W, Pillion JP, Seaberg E, et al. Maternal thyroid autoantibodies during the third trimester and hearing deficits in children: an epidemiologic assessment. American journal of epidemiology. 2008;167(6):701-10.
23. Dunn LMD, Leota M.; Whetton, Chris; Burley, Juliet; . The British Picture Vocabulary Scale. . 2nd ed ed. Windsor, England: Windsor, England. National Foundation for Educational Research-Nelson Publishing Company Ltd.; 1997.
24. Williams FL, Watson J, Ogston SA, Visser TJ, Hume R, Willatts P. Maternal and umbilical cord levels of T4, FT4, TSH, TPOAb, and TgAb in term infants and neurodevelopmental outcome at 5.5 years. The Journal of clinical endocrinology and metabolism. 2013;98(2):829-38.
25. Derakhshan A, Korevaar TIM, Taylor PN, Levie D, Guxens M, Jaddoe VWV, et al. The Association of Maternal Thyroid Autoimmunity During Pregnancy With Child IQ. The Journal of clinical endocrinology and metabolism. 2018;103(10):3729-36.
26. Kampouri M, Margetaki K, Koutra K, Kyriklaki A, Karakosta P, Anousaki D, et al. Maternal mild thyroid dysfunction and offspring cognitive and motor development from infancy to childhood: the Rhea mother-child cohort study in Crete, Greece. Journal of epidemiology and community health. 2021;75(1):29-35.
27. Jenkinson J, Roberts S, Dennehy S, Tellegen P. Validation of the Snijders-Oomen Nonverbal Intelligence Test-Revised 2½-7 for Australian Children with Disabilities. Journal of Psychoeducational Assessment. 1996;14(3):276-86.
28. Bell MA, Ross AP, Goodman G. Assessing infant cognitive development after prenatal iodine supplementation. The American journal of clinical nutrition. 2016;104 Suppl 3:928S-34S.
29. Persaud K, Hemmer P, Kidd C, Piantadosi S. Seeing Colors: Cultural and Environmental Influences on Episodic Memory. i-Perception. 2017;8(6):2041669517750161.
30. Glinoer D, Riahi M, Grun JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. The Journal of clinical endocrinology and metabolism. 1994;79(1):197-204.
31. Jaddoe VW, van Duijn CM, Franco OH, van der Heijden AJ, van Iizendoorn MH, de Jongste JC, et al. The Generation R Study: design and cohort update 2012. European journal of epidemiology. 2012;27(9):739-56.
32. van Eijsden M, Vrijkotte TG, Gemke RJ, van der Wal MF. Cohort profile: the Amsterdam Born Children and their Development (ABCD) study. International journal of epidemiology. 2011;40(5):1176-86.
33. Truijens SE, Meems M, Kuppens SM, Broeren MA, Nabbe KC, Wijnen HA, et al. The HAPPY study (Holistic Approach to Pregnancy and the first Postpartum Year): design of a large prospective cohort study. BMC pregnancy and childbirth. 2014;14:312.

34. Korevaar TIM, Pop VJ, Chaker L, Goddijn M, de Rijke YB, Bisschop PH, et al. Dose Dependency and a Functional Cutoff for TPO-Antibody Positivity During Pregnancy. The Journal of clinical endocrinology and metabolism. 2018;103(2):778-89.
35. Amouzegar A, Bakhtiyari M, Mansournia MA, Etemadi A, Mehran L, Tohidi M, et al. Sex- and Age-Specific Reference Values and Cutoff Points for TPOAb: Tehran Thyroid Study. Thyroid : official journal of the American Thyroid Association. 2016;26(3):458-65.
36. Levie D, Korevaar TIM, Bath SC, Murcia M, Dineva M, Llop S, et al. Association of Maternal Iodine Status With Child IQ: A Meta-Analysis of Individual Participant Data. The Journal of clinical endocrinology and metabolism. 2019;104(12):5957-67.
37. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. The lancet Diabetes & endocrinology. 2015;3(4):286-95.
38. Velasco I, Bath SC, Rayman MP. Iodine as Essential Nutrient during the First 1000 Days of Life. Nutrients. 2018;10(3).
39. Shi X, Han C, Li C, Mao J, Wang W, Xie X, et al. Optimal and safe upper limits of iodine intake for early pregnancy in iodine-sufficient regions: a cross-sectional study of 7190 pregnant women in China. The Journal of clinical endocrinology and metabolism. 2015;100(4):1630-8.

Table1. Summary of offspring cognition evaluation results of euthyroid mothers with thyroid autoimmunity.

Author	Year	Country	Pregnant women (n)	TPOAb+ level	TPOAb+ Mother (n)	Number of evaluated children	The age of child assessment	Major findings
POP (17)	1995	Netherland	230	≥ 100 U/L	19	178	5 years	Children were at risk for impaired development
Li (2)	2009	China	1268	> 50 IU/ml	34	213	25–30 months	Euthyroidism with elevated TPOAb titers was predictors of lower motor & intellectual development.
Ghassabian (8)	2012	Netherlands	9778 4770*	≥ 100 IU/mL	147	3139	2.5 years	Children had risk of problem on behavior, attention deficit/hyperactivity
Wasserman (20)	2012	USA	1527	NA	NA	1733	4&7 years	Effect of maternal TPOAb on IQ may involve early developmental delays or transient effects rather than permanent deficits.
Williams (24)	2012	UK	93	≥ 35 IU/ml	14	93	5.5 years	Maternal levels of TPOAb and TSH levels showed no association with developmental scores
Derakhshan** (25)	2018	Netherlands UnitedKingdom	3637 2396	>60 >6 IU/mL	214*** 286	3753 2552	5 – 8 7 -10 years	Lower child IQ in Generation R Not associated with lower child IQ in ALSPAC
Kampouri et al (26)	2020	Greece	757(658*)	35 IU/mL	83#	695 #	4 years	Maternal thyroid autoimmunity was related to decreased perceptual performance and motor scores of their children at the age of 4 year

*Pregnant women were eligible for analyses

**The study included two different cohorts: Generation R Study& Avon Longitudinal Study of Parents and Children (ALSPAC); Mother-child pairs with available data on early pregnancy were 3637 and 2396 in two cohorts respectively.

*** Number of TPOAb positivity from data of mother-child pairs with available data on early pregnancy in two cohorts respectively.

Number of mothers participants at 4 years of age. NA; not given