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The Association of Maternal Thyroid Autoimmunity During Pregnancy with Child IQ

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Abstract

Context: During the first 18-20 weeks of pregnancy, the fetus depends on the placental transfer of maternal thyroid hormones, particularly for its brain development. During this time, high concentrations of human chorionic gonadotropin (hCG) stimulate the thyroid to ensure adequate thyroid hormone availability. Thyroperoxidase antibody (TPOAb) positivity, which is a major risk factor for gestational thyroid dysfunction, is associated with adverse pregnancy outcomes. We have recently shown that TPOAb positive women have an impaired thyroidal response to hCG stimulation.

Objective: To study the association of maternal TPOAb positivity during pregnancy with child IQ.

Design, Setting, Participants: This study was embedded in two prospective birth cohorts: Generation R (Rotterdam, the Netherlands) and the Avon Longitudinal Study of Parents and Children (ALSPAC; Avon, United Kingdom). Mother-child pairs with available data on TPOAbs in early pregnancy (≤18 weeks of gestation) and offspring IQ were included (N=3637, Generation R and N=2396, ALSPAC).

Intervention: None.

Main Outcome Measures: Child IQ at 5 to 10 years of age.

Results: In Generation R, TPOAb positivity was associated with a 2.0 ±0.9 point lower mean child IQ (*P*=0.03). Sensitivity analyses showed negative effect estimates already from TPOAb concentrations considerably lower than currently used manufacturer cut-offs. In ALSPAC, neither TPOAb positivity nor TPOAb concentrations below manufacturer cut-offs were associated with child IQ (TPOAb positivity: 0.7 ±1.0, *P*=0.45). Adjustment for maternal TSH or FT4 concentrations or urinary iodine/creatinine ratio did not change the results.

Conclusion: TPOAb positivity during pregnancy was associated with lower child IQ in Generation R but not in ALSPAC. Further studies are needed to elucidate if differences between the study populations, in particular maternal iodine status, could be the underlying cause for these differences.

Précis

We investigated the association of TPO antibody positivity during early pregnancy with child IQ and demonstrate that TPO antibody positive mothers have children with lower IQ in one of the two studied cohorts.

Introduction

Thyroperoxidase antibody (TPOAb) positivity occurs in about 5.6-22.1% of all pregnant women worldwide and its prevalence differs according to maternal iodine intake, ethnicity, parity and smoking (1-4). TPOAb positivity reflects thyroid autoimmunity, which typically results in higher serum thyroid stimulating hormone (TSH) concentrations, lower serum free thyroxine (FT4) concentrations and ultimately hypothyroidism (5,6). Human chorionic gonadotropin (hCG) is a pregnancy-specific hormone that exerts thyrotropic activity via its weak affinity for the TSH receptor (7,8). During pregnancy, high hCG concentrations lead to an increase in FT4 concentrations by up to 50% (9). This increase in thyroid hormone availability safeguards sufficient thyroxine transfer to the developing fetus (7). We recently showed that TPOAb positivity severely impairs the thyroidal response to hCG stimulation, and this could affect early fetal development (10).

The fetal thyroid gland is not functionally mature until the 18^{th} to 20^{th} week of pregnancy; therefore, fetal thyroid hormone availability during early development largely depends on the placental transfer of maternal thyroid hormones (7,11). In humans, neurogenesis starts from approximately the 5^{th} week of pregnancy and thyroid hormone receptors are detected in the fetal brain from the 8^{th} week of pregnancy (11). Various critical processes of fetal brain development that reach peak activity before the 18^{th} to 20^{th} week of pregnancy are regulated by thyroid hormone (12,13). Interestingly, the specific period during which early brain development is dependent on maternal thyroid hormone overlaps with the timeframe during which high hCG concentrations increase maternal thyroid hormone concentrations (roughly 6-15 weeks of pregnancy) (14,15).

The current guidelines of the American Thyroid Association (ATA) state that for TPOAb positive women, levothyroxine treatment can be considered when TSH concentrations are above 2.5 mU/l (4). This recommendation is predominantly based on studies showing that TPOAb positivity is associated with a higher risk of miscarriage and premature delivery (16-21). Although some studies show that low maternal thyroid function is associated with suboptimal child neurodevelopmental outcomes, such as lower IQ, autism and schizophrenia (22-26), studies on the association of maternal TPOAb positivity with child neurodevelopment remain sparse. Some studies indicate that maternal TPOAb positivity is associated with lower child IQ and a higher risk of autism or problem behavior (27-32); however, the majority of these studies were either retrospective, had a small sample size, were unable to adjust for potential confounders and/or did not investigate the combination of TPOAb positivity with a TSH concentration above 2.5 mU/l.

Considering that an attenuated thyroidal response to hCG stimulation in TPOAb positive women likely leads to a relative form of thyroid hormone shortage during early pregnancy, when fetal brain development depends on maternal thyroid hormone, we hypothesized that TPOAb positivity is associated with lower child IQ. Therefore, the main aim of the current study was to investigate the association of maternal TPOAb positivity during pregnancy with child IQ in two large, prospective, population-based cohorts.

Methods

This study was embedded in two prospective birth cohorts: Generation R (Rotterdam, the Netherlands) and the Avon Longitudinal Study of Parents and Children (ALSPAC), United Kingdom).

Study design and participants

In Generation R, 7069 women with a delivery date between April 2002 and January 2006 were enrolled during early pregnancy (≤18 weeks) in hospitals and midwife practices in the Rotterdam area (33). Blood samples were drawn in 6398 of these women and 5793 had enough material for measurement of TPOAbs. When the children reached 5 years of age, all enrolled mothers and children

were invited to visit the research center at the Erasmus MC Sophia Children's Hospital in Rotterdam, where 3753 (64%) children underwent IQ assessments. The general study design, all research aims, and the specific measurements in the Generation R Study have been approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam, Netherlands. Written informed consent was obtained from all participants and/or the children's parents or guardians.

In ALSPAC, eligible women were those living in the former Avon area in southwest England, United Kingdom, with an expected delivery date between April, 1991, and December, 1992. In total, blood samples were available in 7501 pregnant women, of which 4947 were enrolled during early pregnancy (≤18 weeks) (34) with 4916 women having TPOAb measurements. Subsequently, all participants were invited to attend a research clinic where trained psychologists measured the IQ of 2552 children.

The study website contains details of all the data that are available through a fully searchable database www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

Laboratory Measurements

In Generation R, maternal blood samples collected in early pregnancy were stored at -80° C. Maternal TPOAbs were measured using the Phadia 250 immunoassay (Phadia AB, Uppsala, Sweden) and considered positive when the serum concentrations were >60 IU/ml. FT4 and TSH were measured using chemiluminescence assays (Vitros ECI Immunodiagnostic System Ortho Clinical Diagnostics, Rochester, NY). The intra- and interassay coefficients of variation were <4.1% for TSH at a range of 3.97–22.7 mU/L and <5.4% for FT4 at a range of 14.3–25.0 pmol/L. Details of the urinary iodine and creatinine measurement are reported elsewhere (35).

In ALSPAC, TPOAb, FT4 and TSH were measured in stored serum samples using an Abbott Architect i2000. Inter- and intra-assay coefficients of variation were less than 5% for all analytes. TPOAbs were considered positive when the serum concentrations were ≥6 IU/ml. Details on urinary iodine and creatinine measurements are reported elsewhere (36).

Outcomes

In Generation R, non-verbal child IQ was evaluated using two subtests of a Dutch non-verbal intelligence test, the Snijders-Oomen Niet-Verbale Intelligentie Test when the children were 5 to 8 years of age. The test generally evaluates a range of intelligence functions without relying on language skills and is therefore suitable for assessing the cognitive abilities of ethnic minorities' children and children with verbal communication problems (37). The two subtests were mosaics (evaluating spatial visualization abilities) and categories (evaluating abstract reasoning abilities) and the correlation between subtests with complete test were: r=0.86. Raw test scores were converted into non-verbal IQ scores using normal values tailored to exact age. Research staff who did the IQ tests were unaware of any other mother-child measurements and outcomes.

In ALSPAC, child IQ was measured in a research clinic using a well-validated age-adjusted shortened form of the Wechsler Intelligence Scale for Children (WISC) which provides a well-standardized assessment of performance and verbal intelligence when children were 7 to 10 years of age (36,38). WISC assessments were administered by trained psychologists. To compare analyses to Generation R, the performance component of child IQ was used as the primary outcome, supplementary analyses were also performed for the verbal component.

Statistical analysis

We used multivariable linear regression analyses to investigate the association of maternal TPOAb positivity with child IQ. We have recently shown that thyroid function and the response to hCG stimulation is already lower from concentrations below currently used TPOAb positivity cut-offs as provided by assay manufacturers (39). Therefore, we also performed sensitivity analyses to evaluate the effects of cut-offs below the currently used manufacturer-based cut-offs. TPOAbs were categorized at 20, 30, 40, 50 and 60 IU/ml in Generation R (corresponding to population-based percentiles: 90.6, 92.2, 93, 93.6 and 94.1, respectively). To enable comparison between cohorts, population-based cut-offs equivalent to the cut-offs in Generation R were defined in ALSPAC (14.2, 29.6, 41.4, 54.8 and 63.1 IU/ml, respectively). The effect estimates for these cut-offs were compared

with TPOAb <10 IU/ml (population-based percentile of 83) in Generation R and the corresponding percentile (<4.16 IU/ml) in ALSPAC. The severely skewed distribution of (log-transformed) TPOAb concentrations did not allow for reliable analyses using TPOAb concentrations as a continuous exposure. Outliers of IQ were defined and excluded based on ±2.5*(median absolute deviation).

Based on the current ATA guidelines (4), we additionally investigated the group of TPOAb positive women with a TSH concentration >2.5 mU/L (N=118 (3.4 %) and N=52 (2.46 %), in Generation R and ALSPAC, respectively). Because maternal iodine status is a well-known determinant of both thyroid autoimmunity and child IQ (3,36), in a subset of mothers with available early pregnancy iodine data (N=753 in Generation R and N=1065 in ALSPAC) we investigated the possible effects of maternal iodine status on the association of TPOAbs with child IQ by: 1) studying the association of TPOAbs with maternal urinary iodine/creatinine ratio (UICr) using a linear regression model; 2) additionally adjusting all analyses for maternal UICr; and 3) stratify analyses in both cohorts according to a UICr below and above 150 µg/g. Furthermore, we also investigated if the association of maternal TPOAbs with child IQ would be (partially) mediated via changes in maternal thyroid function by additionally adjusting all models for maternal FT4.

All analyses were adjusted for maternal age, body mass index, parity, smoking status, education level, ethnicity, gestational age at the time of blood sampling, child sex and birth weight. We used multiple imputation by chained equations to deal with missing data of covariates (40). The maximum percentage of missing data was 10.3% in Generation R and 3.7% for ALSPAC. The number of imputations were based on the percentage of missing data using at least 1 imputation per percent of incomplete cases (41). All statistical analyses were performed using Statistical Package of Social Sciences version 21.0 for Windows (SPSS, Chicago, IL) or R statistical software version 3.3.2 (packages *mice* and *rms*; https://www.r-project.org/).

Results

After exclusions, the final study population comprised 6033 mother-child pairs (Generation R: N=3637; ALSPAC: N=2396, Figure 1). Mother-child characteristics of the study population are shown in Table 1. In Generation R, the prevalence of TPOAb positivity was 5.9%, the mean

gestational age at blood sampling was 13.4 (SD 1.9) weeks and the study population was mainly of Dutch ethnicity (57.3%). In ALSPAC, the prevalence of TPOAb positivity was 12.8%, the mean gestational age at blood sampling was 10.9 (SD 3.1) weeks and the study population was mainly of Caucasian ethnicity (98.5%). In both cohorts, there was no difference in maternal TPOAb positivity or thyroid function between mother-child pairs with or without IQ data available (Supplemental Tables 1 and 2).

In Generation R, maternal TPOAb positivity was associated with lower mean child IQ (-2.0 ±0.9 points, *P*=0.03; Table 2). Subsequent sensitivity analyses showed that mean child IQ was already lower at TPOAb cut-offs below the currently used manufacturer-based cut-off for TPOAb positivity (Table 2). In ALSPAC, neither TPOAb positivity nor TPOAb cut-offs below the manufacturer-based cut-off were associated with child IQ (TPOAb positivity: 0.7 ±1.0 points; *P*=0.45; Table 2). The combination of TPOAb positivity with a TSH above 2.5 mU/l was not associated with child IQ in Generation R (*P* for interaction=0.52) while this combination was associated with a higher mean child IQ in ALSPAC (*P* for interaction=0.09; Supplemental Table 3). All results remained essentially unchanged after adjusting for maternal FT4 concentrations (Table 2), UICr (Supplemental Table 4) or hCG concentrations (Generation R only; data not shown).

The median maternal UICr differed considerably between Generation R and ALSPAC (median (IQR): 277 (194-383) vs. 117 (80-190), *P*<0.001). In ALSPAC, but not in Generation R, higher TPOAb concentrations or TPOAb positivity were associated with higher maternal UICr, although these analyses did not reach statistical significance in the smaller subgroups (Supplemental Table 5). Sensitivity analyses indicated that the association of maternal TPOAb positivity with child IQ may differ according to maternal iodine status, although we lacked adequate statistical power for this analysis (Supplemental Table 6).

Discussion

In this study, we investigated the association of TPOAb positivity during early pregnancy with child IQ in two large prospective population-based cohorts. We show that TPOAb positivity as defined by currently used manufacturer-based cut-offs was associated with lower mean child IQ in the

Netherlands (Generation R) but not in the United Kingdom (ALSPAC). Furthermore, the association of TPOAbs with lower child IQ in the Netherlands was already present from TPOAb cut-offs below the currently used manufacturer-based cut-offs. Additional adjustment for maternal FT4 concentrations or UICr did not change the results but sensitivity analyses indicated a potential role for iodine status as an effect modifier.

The peak activity of fetal brain development overlaps with the period during which the fetus is dependent on the placental transfer of maternal thyroid hormones (8,11,13). However, TPOAb positive women have an impaired response to the thyroidal stimulation by hCG and low maternal thyroid hormone availability is associated with lower child IQ (42-45). In the current study, TPOAb positivity was associated with lower child IQ in Generation R. We speculate that the lower IQ in children of TPOAb positive mother could be a reflection of the lack of hCG mediated increase in FT4 concentrations during early pregnancy. Alternatively, TPOAb positivity could be associated with lower child IQ because it reflects a higher general susceptibility to autoimmunity. Thyroid autoimmunity is associated with higher T helper cytokines and an increased natural killer cell activity (46) and maternal autoimmunity or a familial history of autoimmune disorders has been associated with a higher risk of child autism (47,48). Another possible explanation could be a direct effect of TPOAbs on the brain. TPOAbs can cross the placenta and have been detected in the cerebrospinal fluid of patients with Hashimoto's encephalitis, possibly contributing to the pathogenesis of the disease by binding to cerebellar astrocytes or causing vasculitis (49,50).

Although TPOAb positivity was associated with a lower child IQ in Generation R, there was no association in ALSPAC, for which point estimates even suggested that TPOAb positivity is associated with a higher child IQ. The discrepancy between the two cohorts could be caused via different mechanisms. First of all, there is a large difference in iodine status of pregnant women between the Netherlands (more than sufficient) and United Kingdom (mild deficient), as was also reflected by the UICr analyses in the current study. Both low and high iodine intake are a risk factor for low maternal thyroid hormone availability and also increase the risk of thyroid autoimmunity (3,51). Previous studies show that low maternal UICr is not associated with child IQ in Generation R, while in

ALSPAC low UICr is associated with lower child IQ (36,52). In this study, higher TPOAb concentrations and TPOAb positivity were associated with higher maternal UICr in ALSPAC, although the size of the subset with available data did not allow these analyses to reach statistical significance. Taken together, this suggests that the difference between Generation R and ALSPAC, and also the positive point estimates in ALSPAC, could be due to the fact that TPOAbs coincide with a higher iodine concentrations in ALSPAC. Unfortunately, data on UICr was only available in a small subset for both studies, precluding adequate analyses to investigate the role of UICr as an underlying cause for the differences between the two cohorts. However, stratified analysis did show that in Generation R, the association of TPOAb positivity with lower child IQ was driven predominantly by women with a UICr $\geq$150 μg/g. This indicates that in Generation R, low iodine status is not the underlying mechanism. In addition, in studies from iodine sufficient populations, TPOAb positivity has been associated with impaired child cognition, autism and behavioral problems (27,30,31) whereas a Scottish study with 40% of women being iodine deficient did not find an association with neurodevelopmental outcomes (29).

Second, while in Generation R serum samples were collected between 2002 and 2005 and TPOAbs were measured in 2006, ALSPAC samples were collected between 1991 and 1992 and measured in 2016. A study from Finland shows that in stored serum samples, there is a strong positive association of storage time with TPOAb concentrations, with storage time explaining 19.7% of the total variation in TPOAb concentrations (53). This indicates that TPOAb concentrations in ALSPAC are much more likely to be subject to measurement error than those in Generation R. Although it is unknown whether the extent of the increase in TPOAb concentration by storage time is differential on factors that may affect IQ, the difference in storage time may hamper the comparisons between Generation R and ALSPAC in the current study.

The current ATA guidelines recommend that treatment can be considered in TPOAb positive women if the TSH concentration is >2.5 mU/l (18), however, no recommendations are currently provided for the definition of TPOAb positivity. In the current study, the association of TPOAb positivity with lower child IQ in Generation R did not differ according to a TSH below or above 2.5 mU/l.

Furthermore, two recent studies identified that any potential beneficial effects of levothyroxine treatment in TPOAb positive women or women with subclinical hypothyroidism, only occurs in women with a TSH above 2.5 mU/l (namely 4.0 mU/l) (20,21). Therefore, further studies are required to investigate from which TSH threshold the risk of adverse outcomes in TPOAb positive women starts to increase. In addition, a previous study from our group showed that TPOAb concentrations already below currently used manufacturer cut-offs are associated with a higher TSH and a higher risk of premature delivery (39). In the current study, we also showed that TPOAb cut-offs below the currently used manufacturer-based cut-offs for TPOAb positivity were associated with a lower child IQ. Taken together, this suggests that the clinically relevant cut-off for TPOAb positivity may differ from the currently used manufacturer-based cut-offs and that future studies should focus on identifying the optimal threshold for TPOAb positivity.

To the best of our knowledge, this is the first study to assess the association of early pregnancy TPOAb positivity with child IQ in two large prospective, population-based cohorts. We were able to study this association in two study populations with a different population iodine status with detailed data that allowed us to adjust the models for important confounders and run additional sensitivity analyses.

A potential limitation of this study is that data on maternal iodine status was not available for all mothers which left us with inadequate statistical power for sensitivity analysis investigating the potential role of iodine intake. Further studies are needed to investigate the role of maternal iodine status in the association of thyroid autoimmunity with child cognitive development. In addition, the number of TPOAb positive women with a TSH >2.5 mU/l was small, hampering an adequately powered analyses for this group.

In conclusion, we demonstrate that TPOAb positivity during early pregnancy is associated with lower child IQ in a Dutch, iodine sufficient population, but not in a mildly iodine deficient population from the United Kingdom. In addition, TPOAb cut-offs below the current manufacturer-based cut-offs were associated with lower mean child IQ in the Netherlands. Further studies are needed to investigate the association of TPOAbs with child neurodevelopment outcomes in different

populations, and evaluate whether factors that affect thyroid autoimmunity, such as iodine status, might possibly modify this association.

References:

1. Korevaar TI, Medici M, de Rijke YB, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VW, Hofman A, Ross HA, Visser WE, Hooijkaas H. Ethnic differences in maternal thyroid parameters during pregnancy: the Generation R study. The Journal of Clinical Endocrinology & Metabolism 2013; 98:3678-3686
2. Springer D, Zima T, Limanova Z. Reference intervals in evaluation of maternal thyroid function during the first trimester of pregnancy. Eur J Endocrinol 2009; 160:791-797
3. Shi X, Han C, Li C, Mao J, Wang W, Xie X, Li C, Xu B, Meng T, Du J. 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 & Metabolism 2015; 100:1630-1638
4. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 2017; 27:315-389
5. Glinoer D, Riahi M, Grün JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. The Journal of Clinical Endocrinology & Metabolism 1994; 79:197-204
6. Poppe K, Glinoer D. Thyroid autoimmunity and hypothyroidism before and during pregnancy. Human reproduction update 2003; 9:149-161
7. Thorpe-Beeston JG, Nicolaides KH, Felton CV, Butler J, McGregor AM. Maturation of the secretion of thyroid hormone and thyroid-stimulating hormone in the fetus. New England Journal of Medicine 1991; 324:532-536
8. Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nat Rev Endocrinol 2017;
9. Korevaar TI, de Rijke YB, Chaker L, Medici M, Jaddoe VW, Steegers EA, Visser TJ, Peeters RP. Stimulation of Thyroid Function by Human Chorionic Gonadotropin During Pregnancy: A Risk Factor for Thyroid Disease and a Mechanism for Known Risk Factors. Thyroid 2017; 27:440-450
10. Korevaar TIM, Steegers EAP, Pop VJ, Broeren MA, Chaker L, de Rijke YB, Jaddoe VWV, Medici M, Visser TJ, Tiemeier H, Peeters RP. Thyroid Autoimmunity Impairs the Thyroidal Response to Human Chorionic Gonadotropin: Two Population-Based Prospective Cohort Studies. The Journal of Clinical Endocrinology & Metabolism 2017; 102:69-77
11. Bernal J. Thyroid hormone regulated genes in cerebral cortex development. Journal of Endocrinology 2017; 232:R83-R97
12. Stiles J, Jernigan TL. The Basics of Brain Development. Neuropsychology Review 2010; 20:327-348
13. Rovet JF. The role of thyroid hormones for brain development and cognitive function. Endocrine development 2014; 26:26-43
14. Laurberg P, Andersen SL, Hindersson P, Nohr EA, Olsen J. Dynamics and Predictors of Serum TSH and fT4 Reference Limits in Early Pregnancy: A Study Within the Danish National Birth Cohort. The Journal of clinical endocrinology and metabolism 2016; 101:2484-2492
15. Korevaar T, de Rijke YB, Chaker L, Medici M, Jaddoe VW, Steegers EA, Visser TJ, Peeters R. Stimulation of thyroid function by hCG during pregnancy: a risk factor for thyroid disease and a mechanism for known risk factors. Thyroid 2017;

16. Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. Bmj 2011; 342:d2616

17. Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, Visser WE, Visser W, de Muinck Keizer-Schrama SM, Hofman A, Ross HA, Hooijkaas H, Tiemeier H, Bongers-Schokking JJ, Jaddoe VW, Visser TJ, Steegers EA, Medici M, Peeters RP. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. The Journal of clinical endocrinology and metabolism 2013; 98:4382-4390

18. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 2017; 27:315-389

19. Liu H, Shan Z, Li C, Mao J, Xie X, Wang W, Fan C, Wang H, Zhang H, Han C, Wang X, Liu X, Fan Y, Bao S, Teng W. Maternal subclinical hypothyroidism, thyroid autoimmunity, and the risk of miscarriage: a prospective cohort study. Thyroid 2014; 24:1642-1649

20. Maraka S, Mwangi R, McCoy RG, Yao X, Sangaralingham LR, Singh Ospina NM, O'Keeffe DT, De Ycaza AE, Rodriguez-Gutierrez R, Coddington CC, 3rd, Stan MN, Brito JP, Montori VM. Thyroid hormone treatment among pregnant women with subclinical hypothyroidism: US national assessment. BMJ 2017; 356:i6865

21. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majd H, Azizi F. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. Eur J Endocrinol 2017; 176:253-265

22. Modesto T, Tiemeier H, Peeters RP, Jaddoe VW, Hofman A, Verhulst FC, Ghassabian A. Maternal mild thyroid hormone insufficiency in early pregnancy and attention-deficit/hyperactivity disorder symptoms in children. JAMA pediatrics 2015; 169:838-845

23. Ghassabian A, Henrichs J, Tiemeier H. Impact of mild thyroid hormone deficiency in pregnancy on cognitive function in children: Lessons from the Generation R Study. Best Practice & Research Clinical Endocrinology & Metabolism 2014; 28:221-232

24. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, Teng X, Guo R, Wang H, Li J. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. Clinical endocrinology 2010; 72:825-829

25. Gyllenberg D, Sourander A, Surcel H-M, Hinkka-Yli-Salomäki S, McKeague IW, Brown AS. Hypothyroxinemia During Gestation and Offspring Schizophrenia in a National Birth Cohort. Biological Psychiatry 2016; 79:962-970

26. Roman GC, Ghassabian A, Bongers-Schokking JJ, Jaddoe VW, Hofman A, de Rijke YB, Verhulst FC, Tiemeier H. Association of gestational maternal hypothyroxinemia and increased autism risk. Annals of neurology 2013; 74:733-742

27. Pop VJ, de Vries E, van Baar AL, Waelkens J, De Rooy H, Horsten M, Donkers M, Komproe I, Van Son M, Vader H. Maternal thyroid peroxidase antibodies during pregnancy: a marker of impaired child development? The Journal of Clinical Endocrinology & Metabolism 1995; 80:3561-3566

28. Wasserman EE, Pillion JP, Duggan A, Nelson K, Rohde C, Seaberg EC, Talor MV, Yolken RH, Rose NR. Childhood IQ, hearing loss, and maternal thyroid autoimmunity in the Baltimore Collaborative Perinatal Project. Pediatric research 2012; 72:525-530

29. Williams FLR, 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 & Metabolism 2013; 98:829-838

30. Brown AS, Surcel H-M, Hinkka-Yli-Salomäki S, Cheslack-Postava K, Bao Y, Sourander A. Maternal thyroid autoantibody and elevated risk of autism in a national birth cohort. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2015; 57:86-92

31. Ghassabian A, Bongers-Schokking JJ, De Rijke YB, Van Mil N, Jaddoe VW, de Muinck Keizer-Schrama SM, Hooijkaas H, Hofman A, Visser W, Roman GC. Maternal thyroid autoimmunity during pregnancy and the risk of attention deficit/hyperactivity problems in children: the Generation R Study. Thyroid 2012; 22:178-186

32. Wilson RE, Salihu HM, Groer MW, Dagne G, O'Rourke K, Mbah AK. Impact of maternal thyroperoxidase status on fetal body and brain size. Journal of thyroid research 2014; 2014

33. Jaddoe VWV, van Duijn CM, Franco OH, van der Heijden AJ, van Iizendoorn MH, de Jongste JC, van der Lugt A, Mackenbach JP, Moll HA, Raat H. The Generation R Study: design and cohort update 2012. European journal of epidemiology 2012; 27:739-756

34. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Smith GD, Henderson J, Macleod J, Molloy L, Ness A. Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. International journal of epidemiology 2013; 42:97-110

35. Medici M, Ghassabian A, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VW, Visser WE, Hooijkaas H, Hofman A, Steegers EA, Bongers-Schokking JJ, Ross HA, Tiemeier H, Visser TJ, de Rijke YB, Peeters RP. Women with high early pregnancy urinary iodine levels have an increased risk of hyperthyroid newborns: the population-based Generation R Study. Clin Endocrinol (Oxf) 2014; 80:598-606

36. Bath SC, Steer CD, Golding J, Emmett P, Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). The Lancet 2013; 382:331-337

37. Tellegen PJ, Winkel M, Wijnberg-Williams BJ, Laros JA. Snijders-Oomen Niet-Verbale intelligentietest SON-R 2 ½-7. Handleiding en verantwoording.[Snijders-Oomen Non-verbal Intelligence test SON-R 2 ½-7. Manual]. Lisse, NL: Swets & Zeitlinger 1998;

38. Wechsler D, Golombok S, Rust J. WISC-III UK Wechsler intelligence scale for children: UK manual. Sidcup, UK: The Psychological Corporation 1992;

39. Korevaar TIM, Steegers EAP, Chaker L, Medici M, Jaddoe VWV, Visser TJ, de Rijke YB, Peeters RP. Thyroid Function and Premature Delivery in TPO Antibody-Negative Women: The Added Value of hCG. The Journal of clinical endocrinology and metabolism 2017; 102:3360-3367

40. Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. Journal of statistical software 2011; 45

41. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Statistics in medicine 2011; 30:377-399

42. Julvez J, Alvarez-Pedrerol M, Rebagliato M, Murcia M, Forns J, Garcia-Esteban R. Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. Epidemiol Camb Mass Jan 2013; 24:150-157

43. Korevaar TI, Muetzel R, Medici M, Chaker L, Jaddoe VW, de Rijke YB, Steegers EA, Visser TJ, White T, Tiemeier H, Peeters RP. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. Lancet Diabetes Endocrinol 2016; 4:35-43

44. Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol Oxf Feb 1999; 50:149-155

45. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, N., J. Maternal Thyroid Deficiency during Pregnancy and Subsequent Neuropsychological Development of the Child. Aug 19 1999; 341:549-555

46. Kim NY, Cho HJ, Kim HY, Yang KM, Ahn HK, Thornton S, Park JC, Beaman K, Gilman-Sachs A, Kwak-Kim J. Thyroid autoimmunity and its association with cellular and humoral immunity in women with reproductive failures. Am J Reprod Immunol 2011; 65:78-87

47. Chen S-w, Zhong X-s, Jiang L-n, Zheng X-y, Xiong Y-q, Ma S-j, Qiu M, Huo S-t, Ge J, Chen Q. Maternal autoimmune diseases and the risk of autism spectrum disorders in offspring: a systematic review and meta-analysis. Behavioural brain research 2016; 296:61-69

48. Wu S, Ding Y, Wu F, Li R, Xie G, Hou J, Mao P. Family history of autoimmune diseases is associated with an increased risk of autism in children: A systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews 2015; 55:322-332

49. Leyhe T, Müssig K. Cognitive and affective dysfunctions in autoimmune thyroiditis. Brain, behavior, and immunity 2014; 41:261-266

50. Seror J, Amand G, Guibourdenche J, Ceccaldi P-F, Luton D. Anti-TPO antibodies diffusion through the placental barrier during pregnancy. PloS one 2014; 9:e84647

51. Bliddal S, Boas M, Hilsted L, Friis-Hansen L, Juul A, Larsen T, Tabor A, Faber J, Precht DH, Feldt-Rasmussen U. Increase in thyroglobulin antibody and thyroid peroxidase antibody levels, but not preterm birth-rate, in pregnant Danish women upon iodine fortification. European Journal of Endocrinology 2017; 176:603-612

52. Ghassabian A, Steenweg-de Graaff J, Peeters RP, Ross HA, Jaddoe VW, Hofman A, Verhulst FC, White T, Tiemeier H. Maternal urinary iodine concentration in pregnancy and children's cognition: results from a population-based birth cohort in an iodine-sufficient area. BMJ open 2014; 4:e005520

53. Mannisto T, Surcel HM, Bloigu A, Ruokonen A, Hartikainen AL, Jarvelin MR, Pouta A, Vaarasmaki M, Suvanto-Luukkonen E. The effect of freezing, thawing, and short- and long-term storage on serum thyrotropin, thyroid hormones, and thyroid autoantibodies: implications for analyzing samples stored in serum banks. Clin Chem 2007; 53:1986-1987