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Journal of Endocrinological Investigation

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

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Full Title:	TPO-antibody in euthyroid pregnant women and cognitive ability in the offspring: a focused review
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Abstract:	<p>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.</p>
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Author Comments:	<p>To the Editor-in-Chief Journal of Endocrinological Investigation Greetings</p> <p>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</p>

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

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Response to Reviewers:

Dear Editor-in-chief
Journal of Endocrinological investigation
Greetings
Thank you for valuable comments. We tried to answer all the comments one by one as follows:

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 health) 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

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1 TPO-antibody in euthyroid pregnant women and cognitive ability in the 2 offspring: a focused review

3

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20 **Running Head:** thyroid autoimmunity and offspring cognition

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

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34 **Abstract**

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

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56 **Introduction:**

57 Maternal thyroid dysfunction may exert lasting adverse effects on the wellbeing of offspring. Many
58 well-designed studies have characterized associations between such maternal thyroid dysfunction
59 and child brain morphology (1-3). Overt maternal hypothyroidism is associated with profound
60 neuropsychiatric and developmental defects in offspring (4, 5). In addition, it has been shown that
61 low and high maternal thyroid function is associated with smaller cortical volume and gray matter
62 (6). Although not shown by all studies, some elegant reports have depicted a range of
63 neurocognitive deficits in the offspring of mothers suffering mild thyroid dysfunction (1, 7-9).
64 Maternal thyroid autoimmunity as demonstrated by high TPOAb levels is reported to occur in 4-
65 15% of euthyroid pregnant women worldwide (10-15). However, the implications of maternal
66 thyroid autoimmunity during pregnancy on offspring neurocognitive development are unclear.
67 Although some retrospective studies have shown TPOAb positivity during pregnancy to be
68 associated with adverse neurodevelopmental outcomes during childhood, the findings should be
69 viewed cautiously due to methodological issues such as small sample sizes and likely residual
70 confounding. Moreover, it is unclear whether any effects of thyroid autoimmunity on fetus
71 neurodevelopment during pregnancy are because of a decreased thyroid reserve and TPOAb as a
72 cause of thyroid dysfunction, or antibody to thyroperoxidase is a marker of a more generalized
73 autoimmunity in the body that can affect neurodevelopmental outcomes of a pregnancy and thyroid
74 autoimmunity is just a part of it. The present focus- review aims to highlight the gaps in knowledge
75 in this regard and provide a thorough assessment of relevant literature with specific focus just on
76 TPOAb.

57 **Search strategy**

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4 78 We searched MEDLINE, Web of Science, and Scopus till January 2021 with restriction in the
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6 79 English language. The key search terms included (“adverse pregnancy outcomes” OR”offspring
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8 80 neurocognition“OR “offspring IQ”) AND (“Thyroid peroxidase antibody” OR TPOAb OR “TPO
9
10 81 antibodies” OR “Antithyroid antibodies”) AND (pregnancy OR “euthyroid pregnant women” OR
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12 82 “pregnant with normal thyroid function”. Also, bibliographies of all relevant papers identified by
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14 83 the search strategy were scanned for additional papers.
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20 84 **Offspring neurocognitive aspects of thyroid autoimmunity**

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23 85 There is some evidence that neuropsychological and intellectual development of offspring can be
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25 86 adversely affected by maternal thyroid autoimmunity. The number of studies investigating the
26
27 87 impact of mothers’ autoimmunity during pregnancy on an offspring’s IQ is growing but findings are
28
29 88 still equivocal. A summary of the studies included in this review is shown in Table 1.
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32 89 **In a study** by Pop et al. children of **230 women** (tested during 32 weeks) were found to be at risk for
33
34 90 cognitive dysfunction based on the Dutch translation of McCarthy Scales of Children’s Abilities
35
36 91 (MSCA) (16), which consists of six scales: verbal, perceptual-performance, quantitative, general
37
38 92 cognitive (GCS), memory, and motor. The greatest differences were seen in the scores for GCS.
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40 93 This finding suggests a potential role for thyroid autoimmunity, in euthyroid pregnant women, in
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42 94 child neurodevelopment; but the role of maternal thyroid autoimmunity in child cognition should be
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44 95 considered cautiously in this study, as the number of TPOAb positive mothers was low and just 19
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46 96 out of 230 mothers were TPOAb positive during late gestation. In addition thyroid function was
47
48 97 assessed at 32 weeks of gestation for the first time and the probability of hypothyroidism during
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50 98 early pregnancy was not taken into account (17).
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57 99 Li et al. evaluated intellectual and motor development using the Bayley Scale of Infant
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59 100 Development (BSID I) in children of euthyroid (TSH 0.12-0.42 mIU/, TT4 101.79–218.49 nmol/l,
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101 and FT4 11.9–24.6 pmol/l),TPOAb positive mothers (gestational age 16–20 weeks) at the age of
102 25– 30 months. BSID I, includes intelligence and a motor scales. The intelligence scale assesses
103 adaptive behaviors, language, and exploratory activities while the motor scale is used to assess
104 gross motor function and fine motor function. The study showed lower motor and intellectual
105 development in these infants compared to infants of mothers without thyroid autoimmunity (2).

106 In another analysis from the Generation R cohort, Ghassabian et al. found no association between
107 elevated maternal TPOAb titers during early pregnancy (13.5 ± 1.8 gestational age) and offspring
108 verbal development at 2.5 years of age, using the Language Development Survey (LDS) (18) to
109 identify children with language delay and assessing nonverbal cognitive function using the parent-
110 administered and the parent-report parts of the Parent Report of Children’s Ability (PARCA) (19)
111 (8). However, the authors reported that high titers of TPOAb during early pregnancy predicted some
112 scales such as attention problems and aggressive behavior in children at age 3. Although mean TSH
113 was higher in the TPOAb-positive women compared with those who were TPOAb negative ($3.83 \pm$
114 4.13 vs. 1.53 ± 1.04 IU/L), the authors claimed that the effect of elevated TPOAb titers on child’s
115 behavior was not exclusively mediated by maternal TSH and passing of antibody through placenta
116 and its effect on neonate thyroid function during few months after birth has an important role. This
117 finding suggests that the effects on problem behavior may be mediated via TPOAb effects on
118 thyroid function.

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

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124 maternal TPOAb positivity on offspring IQ (20). Previously the same group had demonstrated that
125 TPOAb elevation during the third trimester of pregnancy was strongly (prevalence odds ratio 7.5,
126 95% CI: 2.4- 23.3) associated with sensorineural hearing loss in offspring with increasing strength
127 of the association as the level of TPOAb increased. It is unknown whether the observed TPOAb-
128 mediated hearing loss is part of the causal pathway for cognitive delays or whether the two effects
129 are independent (22).

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

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

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

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

163 Limitation of the tools for measuring offspring IQ

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

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

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

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

188 TPOAb positivity level during pregnancy

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

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

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

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

225 **Iodine status:**

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

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

239 Conclusions:

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

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248 All authors declare that there is no conflict of interest.

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250 Author Contributions

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

252 Literature reviewing, has done by AA and EN,P

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

254 MA,T and LM

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

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

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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

