
IN THE NAME OF GOD

Subclinical Hypothyroidism with Negative for Thyroid Peroxidase Antibodies in Pregnancy: Intellectual Development of Offspring

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Introduction

Subclinical hypothyroidism (SCH) is characterized by an elevated thyrotropin (TSH), accompanied by normal free thyroxine (fT4) levels. Results regarding whether a mildly elevated TSH concentration could increase adverse pregnancy outcomes have been vigorously debated (1,2).

The definitions of SCH in pregnancy have been changed in recent years. The 2011 “Guidelines of the American Thyroid Association (ATA) for the Diagnosis and Treatment of Thyroid Disease During Pregnancy and the Postpartum” recommended that the ideal upper limit of serum TSH was 2.5 mIU/L in early pregnancy (3), but a higher cutoff value of 4.0 mIU/L was recently proposed in the **2017 the ATA’s guidelines** (4).

Introduction

Endocrinologists have not yet reached a consensus on whether to treat women with negative TPOAb of gestational subclinical hypothyroidism (SCH-TPOAb-). The Endocrine Society recommends therapy in all pregnant women with SCH, irrespective of their autoimmunity status (5).

On the contrary, ATA supports the treatment of a specific subgroup of women with SCH who are TPOAb+ (SCH-TPOAb+) or TPOAb- but with TSH levels >10 mIU/L (4). However, no intervention trial has assessed the levothyroxine (LT4) impact, specifically in SCH-TPOAb- pregnant women.

Introduction

Two large randomized controlled trials investigating the effect of treatment in women experiencing SCH have failed to show any improvement in the cognitive function of the offspring (8,9).

It is worth noting that neither of the above mentioned two randomized controlled trials described the TPOAb status. Therefore, the adverse impact of maternal SCH-TPOAb on the development of the offspring has not yet been clearly identified. Therefore, this study was designed to evaluate the effect of maternal SCH-TPOAb on possible intellectual deficits in the offspring.

Materials and Methods

This was a historical cohort study conducted at the Second Affiliated Hospital of Wenzhou Medical University (Wenzhou, Zhejiang, China) from June 2016 to June 2019.

Women with a singleton gestation presenting for care before eight gestational weeks underwent thyroid and TPOAb screening.

Women with a serum TSH concentration between 2.5 and 10 mIU/L and fT4 and TPOAb in the normal range were considered to be SCH-TPOAb-.

Pregnant women with pregnancy complications including cardiac disease, hepatic disease, renal insufficiency, and abnormal hematopoietic system were excluded.

Materials and Methods

All subjects signed written informed consent forms. A comprehensive questionnaire, including the demographics and reproductive, medical, and prenatal history, as well as the feeding patterns and parents' education level, was completed during a face-to-face interview.

Women in the SCH treatment group received LT4 (Merck KGaA, Darmstadt, Germany) on the second day after the diagnosis with SCH. The median gestational age at the start of the LT4 treatment was **six gestational weeks and four days**.

The thyroid function was reexamined every two weeks. Based on the examination results, the dosage was adjusted to maintain the TSH level between **0.5 and 2.0 mIU/L**.

Assessment of intellectual development of children

The Chinese version of the Gesell Development Diagnosis Scale (GDDS) was used to evaluate the intellectual development of two-year-old infants.

The GDDS was designed to diagnose the psychological development of children in the age range from four weeks to three years (10).

The test was divided into five subtests. Each subtest examined a different aspect of developmental: gross motor quotient (GMQ), fine motor quotient (FMQ), adaptability quotient (ABQ), language quotient (LQ), and individual social behavior quotient (ISBQ). The mean values were expressed by the developmental quotient(DQ).

Assessment of intellectual development of children

The mean DQ was 100 points with a standard deviation (SD) of 15 points. A developmental score of **above -1 SD (>85) was regarded as average development, between 1 and 2 SDs below the average (85–70) was regarded as borderline development, and <2SD (<69) as a significant developmental delay (11).**

Cognitive performance tests were performed by expert psychologists at the Institute of Cognitive Sciences of the Second Affiliated Hospital of Wenzhou Medical University (Wenzhou, Zhejiang, China). The examiner was unaware of the result of mothers' thyroid function during pregnancy.

The protocol was reviewed and approved by the Ethics and Research Committee of the Second Affiliated Hospital of Wenzhou Medical University.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 for windows. The measurement data are expressed as mean-SD($\bar{x} - s$).

Categorical variables were assessed using Pearson's chi-squared test. Spearman's correlation test was adopted to evaluate the correlation among non-normally distributed data. A two-sided p-value < 0.05 was considered to indicate statistically significant difference.

Results

From June 2016 to June 2019, a total of 5383 pregnant women underwent thyroid function test (including thyroid antibody tests) before eight weeks of pregnancy.

The median and reference ranges of serum TSH, free triiodothyronine (fT3), and fT4 for pregnant women in our hospital before eight weeks of pregnancy were [1.12mU/L \(0.11–4.07mU/L\)](#), [3.16 pg/mL \(2.49–4.63 pg/mL\)](#), and [1.26 ng/dL \(0.99–1.98 ng/dL\)](#), respectively. The positive rate of TPOAb was 13.4%.

A total of 4762 women (88.5%) had results that were considered to be normal, 41 (0.76%) had overt hyperthyroidism, 55 (1.02%) had overt hypothyroidism, 65 (1.21%) had SCH-TPOAb+, and 89 (1.65%) had other types of thyroid dysfunction. A total number of 371 women were diagnosed with SCH-TPOAb-.

Results

They voluntarily chose to receive LT4 on the second day after their diagnosis with SCH, or did not take LT4 during the whole gestation.

Among the 163 pregnant women in the SCH treatment group, 69 were excluded owing to treatment abandonment, failure to follow the doctor's advice to adjust the LT4 dose, or for other reasons.

Meanwhile, among the 208 pregnant women in the SCH observation group, 111 were excluded owing to midway treatment, nonregular thyroid function screening, or other reasons.

Eventually, the remaining [191 pregnant women](#) met the inclusion criteria of our study.

Results

According to TSH levels and whether or not they received LT4 treatment, the SCH-TPOAb pregnant women were divided into four groups:

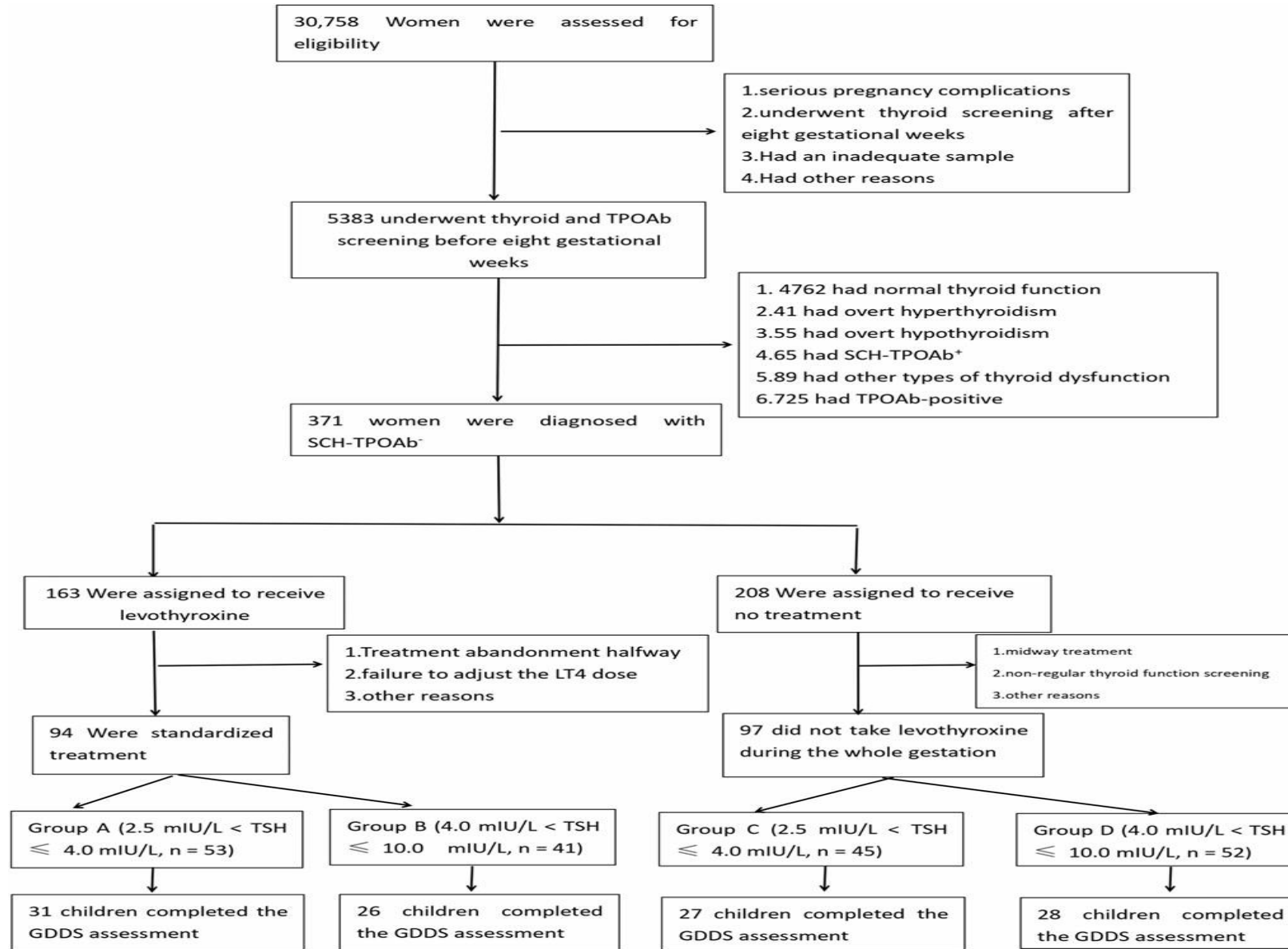
Group A (2.5 mIU/L < TSH <4.0 mIU/L, n = 53) and **Group B** (4.0 mIU/L < TSH <10.0 mIU/L, n = 41), who were treated with LT4 before eight gestational weeks,

And

Group C (2.5 mIU/L < TSH <4.0 mIU/L, n = 45) and **Group D** (4.0 mIU/L < TSH 10.0 mIU/L, n = 52), who received no treatment.

A number of 31 (58.5%), 26 (63.4%), 27 (60.0%), and 28 (53.8%) children completed the GDDS assessment at 24 months in groups A, B, C, and D, respectively (Fig. 1).

Twenty-seven children whose mother's serum TSH was <2.5 mIU/L and were TPOAb in their pregnancy served as the control group (**Group E**).



Results

Basic clinical characteristics of the parents

Highest attained educational level was divided into three categories according to the International Standard Classification of Education (ICSED) levels:

1. **short education** (primary or upper secondary education),
2. **medium education** (>4 years: vocational education), and
3. **long education** (>4 years: bachelor's or master's degree or a shorter cycle of higher education).

The average age of pregnant women was **20–28 years**.

Breastfeeding was the most common feeding pattern of offspring aged within six months.

The proportion of long-term education of parents in the offspring of the SCH treatment group (Group A and Group B) was higher than that of the observation group (Group C and Group D) and normal control group (Group E), but without a statistically significant difference.

The effects of parental educational level, feeding pattern, and other factors on the intelligence of offspring were similar in our study, supporting the comparability of data among the five groups (Table 1)

TABLE 1. BASIC CLINICAL CHARACTERISTICS OF PARENTS IN THE FIVE GROUPS

<i>Characteristic</i>	<i>Group A</i>	<i>Group B</i>	<i>Group C</i>	<i>Group D</i>	<i>Group E</i>	p
Mother's age (years)	28.68 ± 3.29	30.88 ± 4.56	29.56 ± 5.00	28.04 ± 4.26	29.63 ± 3.26	0.118
Mother's education						
Short education (%)	7 (22.6)	4 (15.4)	6 (22.2)	7 (25.0)	5 (18.5)	0.919
Medium educationl (%)	7 (22.6)	8 (30.8)	8 (29.6)	10 (35.7)	10 (37.0)	0.772
Long education (%)	17 (54.8)	14 (53.8)	13 (48.1)	11 (39.3)	12 (44.4)	0.750
Father's education						
Short education (%)	9 (29.0)	4 (15.4)	8 (29.6)	8 (28.6)	8 (29.6)	0.721
Medium educational (%)	4 (12.9)	9 (34.6)	8 (29.6)	10 (35.7)	10 (37.0)	0.223
Long education (%)	18 (58.1)	13 (50.0)	11 (40.7)	10 (35.7)	9 (33.3)	0.286
Feeding patterns						
Breastfeeding (%)	17 (54.8)	15 (57.7)	14 (51.9)	16 (57.1)	19 (70.4)	0.690
Milk powder feeding (%)	7 (22.6)	6 (23.1)	8 (29.6)	6 (21.4)	3 (11.1)	0.586
Both (%)	7 (22.6)	5 (19.2)	5 (18.5)	6 (21.4)	5 (18.5)	0.993

Results

Perinatal outcomes of SCH-TPOAb-

In our study, no difference was found in the average gestational age of the five groups (39.13 – 1.12, 38.17 – 2.93, 39.14 – 1.11, 39.07 – 1.43, and 39.07 – 1.43, $p > 0.05$).

We observed no significant difference in the incidence of adverse perinatal outcomes in the five groups ($p > 0.05$).

The effects of preterm birth, neonatal asphyxia, and other factors on the intelligence of offspring were similar in our study, suggesting the comparability of data among the five groups (Table 2).

TABLE 2. PERINATAL OUTCOMES OF SCH-TPOAB⁻

<i>Perinatal outcomes</i>	<i>Group A</i>	<i>Group B</i>	<i>Group C</i>	<i>Group D</i>	<i>Group E</i>	p
Delivery mode						
Caesarean section (%)	6 (19.4)	9 (34.6)	8 (29.6)	8 (28.6)	8 (29.6)	0.775
Eutocia (%)	25 (80.6)	17 (65.4)	19 (70.4)	20 (71.4)	19 (70.4)	
Gestational weeks (weeks)	39.13±1.12	38.17±2.93	39.14±1.11	39.07±1.43	38.54±1.23	0.130
Birth asphyxia (%)	1 (3.2)	0 (0)	0 (0)	0 (0)	0 (0)	0.476
Preterm labor (%)	1 (3.2)	4 (15.4)	1 (3.7)	2 (7.1)	2 (7.4)	0.428
Postpartum hemorrhage (%)	2 (6.5)	1 (3.8)	1 (3.7)	2 (7.1)	0 (0)	0.710
Low birth weight (%)	2 (6.5)	1 (3.8)	0 (0)	0 (0)	1 (3.7)	0.525

Results

Physical development of the offspring

Well-trained staff of the second Affiliated Hospital of Wenzho Medical University measured children's height and weight. The difference in the height and weight of each child was calculated according to the World Health Organization standards for infant and young child growth (12) and expressed as a t-value.

Although the weight-for-age values and height-for-age values of children in five groups were slightly higher than those in the WHO standards, the differences among the five groups were not statistically significant ($p > 0.05$).

In our study, no adverse effect was observed in SCH during pregnancy on short stature and weight loss of offspring (Table 3).

TABLE 3. PHYSICAL DEVELOPMENT OF OFFSPRING IN THE FIVE GROUPS

<i>Physical development</i>	<i>Group A</i>	<i>Group B</i>	<i>Group C</i>	<i>Group D</i>	<i>Group E</i>	p
Weight (kg)	11.93 ± 1.15	12.13 ± 1.32	12.82 ± 1.86	11.91 ± 1.59	12.09 ± 1.93	—
Weight <i>t</i> -value	0.14 ± 0.84	0.31 ± 1.17	0.63 ± 1.62	0.05 ± 1.27	0.31 ± 1.71	0.551
Height (cm)	85.49 ± 4.99	85.08 ± 4.26	87.85 ± 4.59	85.01 ± 5.06	85.63 ± 4.74	—
Height <i>t</i> -value	0.35 ± 2.54	0.35 ± 3.11	1.31 ± 3.80	0.02 ± 2.43	1.00 ± 3.31	0.510

Results

Neurobehavioral development of the offspring

The value of DQ in Group D was 8.67 lower than that in Group E ($p < 0.001$). The difference of DQ between the Group D and the Group E was mainly reflected in the following aspects: GMQ was lower by 7.00 ($p < 0.05$), FMQ was lower by 8.33 ($p < 0.05$), ABQ was lower by 9.08 ($p < 0.05$), LQ was lower by 13.86 ($p < 0.01$), and ISBQ was lower by 8.34 ($p < 0.05$).

There were no statistically difference in DQ including GMQ, FMQ, ABQ, LQ, and ISBQ among Group A, Group B, Group C, and Group E ($p > 0.05$) (Table 4)

TABLE 4. GESELL DEVELOPMENT DIAGNOSIS SCALE SCORES OF OFFSPRING IN THE FIVE GROUPS

<i>GDSS</i>	<i>Group A</i>	<i>Group B</i>	<i>Group C</i>	<i>Group D</i>	<i>Group E</i>
DQ					
$x \pm s$	100.23 ± 7.48	101.33 ± 8.79	99.34 ± 7.62	92.49 ± 7.89	101.16 ± 9.14
The <i>p</i> -value compare with Group E	0.666	0.939	0.416	0.000	
GMQ					
$x \pm s$	103.80 ± 9.76	102.93 ± 12.59	103.10 ± 8.15	98.40 ± 10.20	105.40 ± 11.72
The <i>p</i> -value compare with Group E	0.567	0.396	0.425	0.015	
FMQ					
$x \pm s$	104.84 ± 11.28	99.09 ± 10.98	100.21 ± 9.37	94.43 ± 12.51	102.76 ± 14.67
The <i>p</i> -value compare with Group E	0.507	0.263	0.432	0.010	
ABQ					
$x \pm s$	100.45 ± 13.08	102.60 ± 13.78	100.19 ± 10.40	92.10 ± 11.25	101.18 ± 11.65
The <i>p</i> -value compare with Group E	0.821	0.669	0.765	0.006	
LQ					
$x \pm s$	93.19 ± 14.07	99.24 ± 17.47	94.17 ± 12.33	84.33 ± 12.03	98.19 ± 15.84
The <i>p</i> -value compare with Group E	0.191	0.791	0.309	0.001	
ISBQ					
$x \pm s$	98.89 ± 12.97	102.67 ± 13.61	99.21 ± 11.00	93.20 ± 10.31	101.54 ± 13.43
The <i>p</i> -value compare with Group E	0.416	0.738	0.489	0.013	

Results

Neurobehavioral development of the offspring

We chose Group A and Group C to assess the effects of LT4 treatment on the neurobehavioral development of the offspring of pregnant women with SCH-TPOAb, whose TSH values were between 2.5 and 4.0 mIU/L.

The values of GMQ, FMQ, ABQ, LQ, and ISBQ of DQ were not statistically significant different between the two groups ($p > 0.05$) (Table 5).

TABLE 5. GESELL DEVELOPMENT DIAGNOSIS SCALE
SCORES OF OFFSPRING IN GROUP A AND GROUP C

<i>GD DS</i>	<i>Group A</i>	<i>Group C</i>	<i>p</i>
<i>n</i>	31	27	
DQ	100.23 ± 7.48	99.34 ± 7.62	0.681
GMQ	103.80 ± 9.76	103.10 ± 8.15	0.800
FMQ	104.84 ± 11.28	100.21 ± 9.37	0.141
ABQ	100.45 ± 13.08	100.19 ± 10.40	0.935
LQ	93.19 ± 14.07	94.17 ± 12.33	0.796
ISBQ	98.89 ± 12.97	99.21 ± 11.00	0.922

Results

Neurobehavioral development of the offspring

We chose Group B and Group D to assess the effects of LT4 treatment on the neurobehavioral development of the offspring of pregnant women with SCH-TPOAb, whose TSH values were between 4.0 and 10.0 mIU/L.

The DQ score in Group D was 8.84 lower than those in Group B ($p < 0.001$). Specifically, the following differences in DQ between Group B and Group D was mainly reflected in the following aspects: ABQ was lower by 10.50 ($p < 0.01$), LQ was lower by 14.91 ($p < 0.001$), and ISBQ was lower by 9.47 ($p < 0.01$) (Table 6).

TABLE 6. GESELL DEVELOPMENT DIAGNOSIS SCALE SCORES OF OFFSPRING IN GROUP B AND GROUP D

<i>GD DS</i>	<i>Group B</i>	<i>Group D</i>	<i>p</i>
<i>n</i>	26	28	
DQ	101.33 ± 8.79	92.49 ± 7.89	0.000
GMQ	102.93 ± 12.59	98.40 ± 10.20	0.118
FMQ	99.09 ± 10.98	94.43 ± 12.51	0.152
ABQ	102.60 ± 13.78	92.10 ± 11.25	0.002
LQ	99.24 ± 17.47	84.33 ± 12.03	0.000
ISBQ	102.67 ± 13.61	93.20 ± 10.31	0.006

Results

Correlation analysis of TSH level and DQ, GMQ, FMQ, ABQ, LQ, and ISBQ

The results of Spearman's rank correlation analysis showed that DQ, FMQ, ABQ, LQ, and ISBQ **were significantly negatively correlated with TSH ($p < 0.05$)** .

Factors influencing the intelligence level of the offspring of SCH-TPOAb-mothers

- The DQ values were categorized into three levels: 1 (>100points), 2 (85–100 points), and 3 (<85 points).
- Parental education levels were also classified into three levels: 1 (short education), 2 (medium education), and 3 (long education).
- The feeding patterns in the first six months were divided into two categories: 1 (exclusive breastfeeding in the first six months) and 2 (milk powder feeding in the first six months or breastfeeding + milk powder).
- The feeding elders were divided into two levels, 1: parental feeding and 2: grandparent feeding or parental + group parental feeding.
- The TSH level was divided into three levels: 1 (4.0 mIU/L < TSH <10.0 mIU/L), 2 (2.5 mIU/L < TSH <4.0 mIU/L), and 3 (TSH <2.5 mIU/L).

- The gender is categorized into two layers:1 (male) and 2 (female).

The Apgar score, birth weight, parental education level, feeding patterns, feeding elders, and gender were considered independent variables, and DQ was regarded as a dependent variable.

Multivariate logistic regression analysis showed that **mother's education (short education), mother's education (medium education), and TSH levels (4.0 mIU/L < TSH £10.0 mIU/L) were all riskfactors affecting the intelligence level of the offspring (all $p < 0.05$), and ORs were 8.50, 3.82, and 12.48, respectively (Table 7).**

However, the birth status (based on Apgar score), birth weight, mothers' educational level (long education), fathers' educational levels, TSH level (TSH <4.0 mIU/L), breastfeeding or not in the first six months, parental feeding or not, and the gender were not risk factors affecting the intelligence level of the offspring ($p > 0.05$) (Table 7).

TABLE 7. INFLUENCE FACTORS OF INTELLIGENCE LEVEL IN THE OFFSPRING

	OR	B	p	OR CI	
				2.5% [‡]	97.5% [‡]
Threshold value					
[DQ level = 1]	0.00	-8.412	0.093	0.00	4.10
[DQ level = 2]	0.01	-4.288	0.384	0.00	214.43
Kind					
Apgar score	0.48	-0.729	0.112	0.20	1.19
Birth weight	1.00	-0.001	0.103	1.00	1.00
[mothers' education = 1]	8.50	2.140	0.011	1.63	44.43
[mothers' education = 2]	3.82	1.341	0.035	1.10	13.33
[mothers' education = 3]	0 ^a				
[fathers' education = 1]	1.67	0.513	0.501	0.37	7.46
[fathers' education = 2]	0.92	-0.078	0.905	0.26	3.35
[fathers' education = 3]	0 ^a				
[TSH level = 1]	12.48	2.524	0.000	3.29	47.23
[TSH level = 2]	2.55	0.938	0.145	0.72	9.01
[TSH level = 3]	0 ^a				
[feeding pattern = 1]	1.61	0.477	0.391	0.54	4.78
[feeding pattern = 2]	0 ^a				
[the feed elders = 1]	1.02	0.018	0.972	0.38	2.75
[the feed elders = 2]	0 ^a				
[gender = 1]	1.09	0.089	0.862	0.40	2.99
[gender = 2]	0 ^a				

Discussion

Thyroid hormone (TH) is essential for brain cell proliferation. Before gestational week 20, TH-dependent brain development fully or partly depends on maternal TH (13).

A lingering controversy exists over the treatment of SCH diagnosed during pregnancy, questioning whether LT4 intervention may improve intelligence levels of the offspring.

Conflicting results have been reported regarding the association between subclinical thyroid dysfunctions during pregnancy and the neurodevelopmental disorders in the offspring (7,14–17).

Discussion

The following potential explanation for the uniform results can be considered:

- (i) Intervention time of LT4. No current evidence exists that LT4 treatment of pregnant women with SCH, especially when initiated after seven weeks of gestation, improves the neurocognitive functions in the offspring (8,9,18,19);
- (ii) Different trimester-specific reference upper limits for TSH;
- (iii) Different thyroid peroxidase antibody status: more TPOAb⁺ impairment on the neurocognitive outcome in the offspring (20).

Discussion

Investigations on the effect of maternal SCH-TPOAb on the developmental status of the child have been rarely conducted.

Moreover, the SCH diagnostic criteria have changed in recent years.

The 2017 ATA guidelines (4) recommended revision of the upper reference limit of TSH for a prescription from **2.5 to 4.0 mIU/L**.

ATA supports LT4 treatment for a specific subgroup of women with SCH who are TPOAb but with TSH levels >10mIU/L, and no treatment is recommended for a TSH level between 2.5 and 4 mIU/L (4).

Therefore, certain ambiguity is present concerning the feasibility of LT4 treatment for TSH levels between 4.0 and 10.0 mIU/L.

Discussion

The key strength of this study is the assessment of the neurodevelopmental status of the offspring of SCH-TPOAb women.

We stratified using the TSH value and set up a control group without LT4 treatment and a normal control group.

Our study results revealed that pregnant women with SCH-TPOAb had a TSH of 4.0–10.0 mIU/L and the DQ value of their offspring was 8.67 points lower than that of the normal control group, without standard treatment before eight weeks of pregnancy.

Conversely, early standardized treatment for these pregnant SCH-TPOAb women ($4.0 \text{ mIU/L} < \text{TSH} \leq 10.0 \text{ mIU/L}$) significantly improved the neurobehavioral development of their offspring, with no statistically significant difference in DQ between the values in GMQ, FMQ, ABQ, LQ, and ISBQ and those in the normal control group.

Discussion

No significant differences were observed in DQ between the offspring of the SCH-TPOAb mothers whose TSH values ranged from 2.5 to 4.0 mIU/L and that of the normal control group.

In addition, our study also assessed the physical development of the offspring of SCH-TPOAb women, revealing no statistically significant differences in the body weight or body length among the offspring of all studied subjects.

Spearman's rank correlation analysis showed that DQ, FMQ, ABQ, LQ, and ISBQ were significantly negatively correlated with the TSH level.

Our multivariate logistic regression analysis showed that mothers' education (short education), mothers' education (medium education), and TSH level ($4.0 \text{ mIU/L} < \text{TSH} < 10.0 \text{ mIU/L}$) were both risk factors affecting the intellectual development of the offspring.

Limitations of this study

1- **First**, this was a retrospective analysis, not a randomized trial. Therefore, the women who were diagnosed with SCH-TPOAb voluntarily choose to receive or not receive treatment, and, although we did our best to adjust for the most obvious potential confounders, unknown confounders might have influenced our findings.

2- **Second**, we measured the IQ of the children at a young age. Therefore, the children follow-up needs to be further improved.

3- **Finally**, our study was single-center, and our sample size was not sufficiently large, which has affected its representativeness. Future multicenter studies with larger sample sizes and prospective approaches are thus warranted.

In summary

the intellectual development of the offspring with SCH-TPOAb is related to the level of TSH of the mothers.

The standardized treatment of pregnant SCHTPOAb-women before eight gestational weeks whose TSH level is from 4.0 to 10.0 mIU/L may significantly improve the intellectual development levels of the approximately twoyear- old offspring.

Although this was a historical cohort study, our data provide supportive evidence for further investigation.

Further multicenter studies with larger sample sizes and prospective approaches are needed to confirm and extend our findings.

THAHANKS FORE YOUR ATTENTION

