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SYSTEMATIC REVIEW AND META-ANALYSIS

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The Effect of Subclinical Maternal Thyroid Dysfunction and Autoimmunity on Intrauterine Growth Restriction

A Systematic Review and Meta-Analysis

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Abstract: The objective of this study was to evaluate the association between maternal subclinical thyroid dysfunction and autoimmunity with the risk for intrauterine growth restriction (IUGR).

Design is a systematic review and meta-analysis.

A literature search was conducted using PubMed, Embase, and Cochrane database. A combination of 2 key words was used to search for the eligible studies: one indexed thyroid dysfunction or antithyroid antibodies; and the other one indexed the adverse neonatal outcomes of pregnancy, such as IUGR, small for gestational age, fetal growth restriction, or low birth weight.

Two reviewers selected the studies, and eligible studies met the following criteria: prospective cohort studies or case control studies, studies of maternal thyroid dysfunction and positive antithyroid antibodies as the exposure of interest, and studies of IUGR or small for gestational age as the outcome of interest.

Data were recorded, including data from maternal thyroid disorders and IUGR, and compared with a reference group.

There were 22 individual data from the 13 cohort articles. Among these, 7 were focused on subclinical hypothyroidism (SCH), 4 on subclinical hyperthyroidism, 7 on positivity for thyroid peroxidase antibody (TPOAb), and 4 on isolated hypothyroxinemia. Meta-analysis showed that there was no effect of subclinical hyperthyroidism (odds ratio (OR) = 0.98; 95% confidence interval (CI), 0.40–2.41), TPOAb positivity (OR = 1.57; 95% CI, 0.77–3.18), or isolated hypothyroxinemia (OR = 1.05, 95% CI: 0.37–2.92) on IUGR. However, SCH is associated with IUGR (OR = 1.54; 95% CI, 1.06–2.25).

SCH is associated with IUGR; however, subclinical hyperthyroidism, TPOAb positivity, or isolated hypothyroxinemia do not affect the risk of IUGR.

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Abbreviations: AITD = autoimmune thyroid disease, ATA = antithyroid antibodies, CI = confidence interval, FGR = fetal growth restriction, fT4 = free thyroxine, IUGR = intrauterine growth restriction, LBW = low birth weight, OH = overt hypothyroidism, OR = odds ratio, SCH = subclinical hypothyroidism, SD = standard deviation, SGA = small for gestational age, TH = thyroid hormone, TPOAb = thyroid peroxidase antibody, TSH = thyroid-stimulating hormone.

INTRODUCTION

The term intrauterine growth restriction (IUGR), or fetal growth restriction, is used to describe a fetus that cannot reach its growth potential. It is usually diagnosed by fetal biometry and Doppler flow.[1] Small for gestational age (SGA) is used to describe those infants who are smaller in size than normal for their gestational age, defined as a weight below the 10th percentile or 2 standard deviations (SD) for the gestational age.[2] Although the 2 terms are different, SGA is widely considered to be a proxy for IUGR, and weights below 2 SD would capture the majority of fetuses with IUGR.[3]

Retarded development of the infants results in short-term adverse outcomes, such as increased mortality and morbidity, prematurity, and hypoglycemia, as well as some long-term outcomes such as delayed growth during childhood, short stature, obesity, higher thyroid-stimulating hormone (TSH) levels, hypertension, and type 2 diabetes.[4–6]

Thyroid diseases are relatively common in women during their reproductive period. Normal maternal thyroid function is currently considered crucial for fetal growth and neurocognitive development. Many epidemiological studies also indicate a possible effect of thyroid dysfunction or antithyroid antibodies (ATA) on increased risks for pregnancy complications such as IUGR or SGA. However, the results vary between studies, and drawing conclusions remains controversial, especially with respect to subclinical thyroid dysfunction or positive ATA with euthyroid status. It is widely accepted that overt hypothyroidism (OH) and overt hyperthyroidism increase the risk for deleterious outcomes. Therefore, the aim of this meta-analysis was to review all of the eligible studies to evaluate the association between thyroid disorders, including subclinical hypothyroidism (SCH), subclinical hyperthyroidism, thyroid peroxidase antibody (TPOAb) positivity, and isolated hypothyroxinemia, and the risk for IUGR.

METHODS

Search Strategy and Study Selection

A literature search was conducted using PubMed, Embase, and Cochrane database in October, 2015 with a combination of

2 key words: one key word was related to thyroid dysfunction, including thyroid disease, thyroid function, thyroid dysfunction, hyperthyroidism, hypothyroidism, hypothyroxinemia, subclinical hyperthyroidism, subclinical hypothyroidism, thyroid peroxidase antibody, anti-TPO; autoantibodies to thyroid peroxidase, thyroperoxidase, and TPO; the other term was related to restricted development of fetus or infants, including SGA, small for gestational age, IUGR, intrauterine growth retardation, intrauterine growth restriction, fetal growth restriction, fetal growth retardation, fetal growth restriction, and low birth weight. All terms were searched without setting limits. We then performed citation tracking of selected studies and recent reviews. Studies were considered qualified if they met the following criteria: the research was a prospective cohort study or a case control study; the interested exposures were maternal mild thyroid disorders, including SCH, subclinical hyperthyroidism, isolated hypothyroxinemia, and TPO positivity; the outcome of the selected studies was IUGR or SGA; and the data concerning numbers for IUGR in each study were reported.

Data Extraction

The exposure was thyroid disorders and the outcome of interest was IUGR, defined as fetal weight below the 10th percentile of gestational age; SGA, defined as birth weight <2500 g at full-term delivery, or fetal weight below the 10th percentile or 2 SD of the gestational age. Diagnosis of thyroid disease in all selected articles was definitive. Data were recorded, including any incidence data for maternal thyroid disorders, and IUGR or SGA compared with a reference group. We extracted information from each selected article as to author, publication year, quality, and results.

Quality Assessment of the Included Studies

The Newcastle–Ottawa scale was used to assess the quality of the selected studies. Information on selection, comparability, and outcomes was evaluated for selected studies. A study scored a maximum of 4 for selection, 2 for comparability, and 3 for assessment of outcome or ascertainment of exposure.

Statistical Analysis

Stata (version 11) was used to analyze the data. The combined odds ratio (OR) was calculated with its 95% confidence interval (CI) to evaluate the strength of the relationships between thyroid disorders and IUGR risk. The significance of the combined OR calculated using the Mantel–Haenszel statistical method was determined by the Z test. Two models of meta-analysis were considered: the random-effects model and the fixed effects model. P value less than 0.05 was considered significant.

To assess the between-study heterogeneity, both the X^2-based Q statistic test and the I^2 statistic were calculated. I^2 values of 25%, 50%, and 75% were used as evidence of low, moderate, or high heterogeneity, respectively. Random-effects model was used to pool the results if high heterogeneity existed; fixed-effects model was used to pool the results if heterogeneity is not high. The influence of each study on the overall risk estimate was evaluated by sequential omission of each study to validate the credibility of outcomes in this meta-analysis. Begg funnel plots and Egger linear regression test were used to assess potential publication bias.

Ethics Committee Approval

This meta-analysis was based on published data; thus no ethical approval and patient consent were required.

RESULTS

Study Selection and Study Characteristics

Our search strategy initially retrieved 769 articles from PubMed, Embase, and Cochrane databases for critical appraisal. Six hundred seventy-three articles were excluded by reading their titles and abstracts. After full-text review of the remaining 96 articles, 13 prospective cohort studies were identified to be eligible articles. There were 22 individual data from the 13 articles. They were assessed as at a low risk of bias based on the Newcastle–Ottawa System. Among these studies, 7 were focused on SCH,[7–13] 4 on subclinical hyperthyroidism,[8–11] 7 on TPO positivity,[7,10,13–17] and 4 on isolated hypothyroxinemia.[11,13,18,19] Figure 1 shows the study selection.

Table 1 shows the characteristics of the 13 studies. These studies were published between 2009 and 2015. Most of the selected studies focused on the 1st and 2nd trimesters. A fixed-effects model was used to calculate the overall combined OR with its corresponding CI to evaluate the relationship between subclinical hyperthyroidism/SCH and IUGR. A random-effects model was used to evaluate the relationship between TPOAb+/ isolated hypothyroxinemia and IUGR.

IUGR and SCH

Meta-analysis of these 7 studies that reported relevant data on the association between SCH and IUGR showed that the combined OR of IUGR for SCH pregnant women was 1.54 (95% CI, 1.06–2.25), indicating that SCH was associated with IUGR (Figure 2). Among the 7 selected studies, 2 showed an association between IUGR and SCH.[9,12] Antibodies were not mentioned or measured in 5 studies;[9–13] therefore, we used the number of SCH cases without considering the effect of antibodies, even though 1 study divided the subjects based upon both thyroid function and antibodies.[7] In 1 study, TPOAb and free thyroxine (fT4) were measured only when TSH levels were aberrant.[8] Therefore, it was possible to miss patients with isolated hypothyroxinemia and those who were antibody positive but euthyroid. Both the Q statistic test ($P=0.16$) and I^2 statistic ($I^2=35.1\%$) showed low heterogeneity. Sensitivity analyses by sequential omission of each study did not change the overall OR. Begg test ($P=0.55$) and Egger test ($P=0.28$) did not identify any publication bias.

IUGR and Subclinical Hyperthyroidism

Meta-analysis of these 4 studies that reported relevant data on the association between subclinical hyperthyroidism and IUGR showed that the combined OR of IUGR for subclinical hyperthyroidism pregnant women was 0.98 (95% CI, 0.40–2.41), indicating that subclinical hyperthyroidism was not associated with IUGR (Figure 3). None of the 4 studies showed an association between IUGR and subclinical hyperthyroidism, and none considered the ATA of the subjects; in 1 study, the author measured TPOAb only when TSH was abnormal.[8] Both the Q statistic test ($P=0.26$) and I^2 statistic ($I^2=20.8\%$) showed low heterogeneity. Sensitivity analyses by sequential omission of each study did not change the overall OR. Begg test ($P=0.73$) and Egger test ($P=0.63$) did not identify any publication bias.

IUGR and TPO-Antibody Positivity

Meta-analysis of these 7 studies that reported relevant data on the association between TPO positivity and IUGR showed

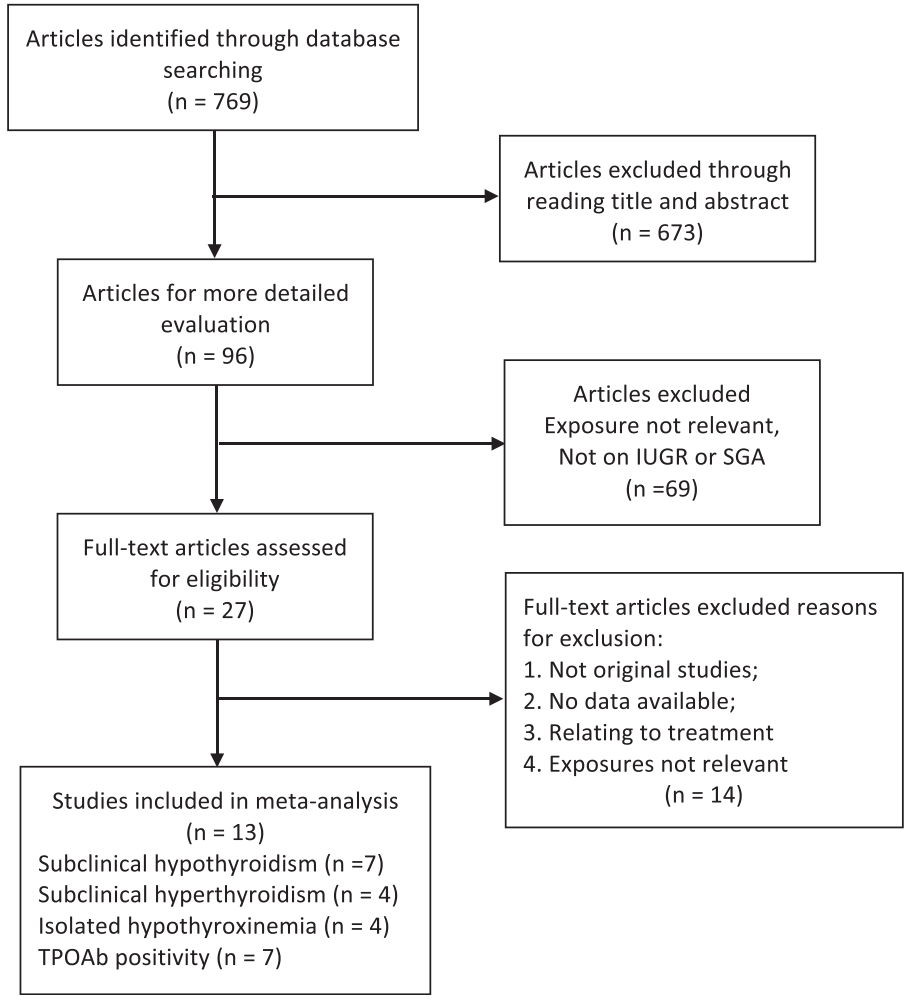

FIGURE 1. Flow chart of literature search and article selection.

that the combined OR of IUGR for TPOAb positive pregnant women was 1.57 (95% CI, 0.77–3.18), indicating that TPOAb positivity is not associated with IUGR (Figure 4). Among these 7 studies, only 1 showed an association between IUGR and TPOAb + status. The subjects of 4 studies were isolated TPO+ and euthyroid patients.[7,14,16,17] Both the Q statistic test ($P < 0.001$) and I^2 statistic ($I^2 = 82.9\%$) showed high heterogeneity. Therefore, random-effect model was used. One study[17] was the main cause of high heterogeneity; when this study was deleted, the heterogeneity decreased (Q statistic test, $P = 0.36$, $I^2 = 8.7\%$), and the OR was 0.96 (95% CI, 0.79–1.17). Begg test ($P = 0.76$) and Egger test ($P = 0.33$) did not identify any publication bias.

IUGR and Isolated Hypothyroxinemia

Meta-analysis of these 4 studies that reported relevant data on the association between isolated hypothyroxinemia and IUGR showed that the combined OR of IUGR for isolated hypothyroxinemia pregnant women was 1.05 (95% CI 0.37–2.92), indicating that isolated hypothyroxinemia was not associated with IUGR (Figure 5). Both the Q statistic test ($P = 0.06$) and I^2 statistic ($I^2 = 60.0\%$) showed high heterogeneity, and therefore, the random-effects model was used. Sensitivity analyses by sequential omission of each study did not change the overall OR. Begg test ($P = 1$) and Egger test ($P > 0.78$) did not identify any publication bias.

DISCUSSION

The current meta-analysis was aimed specifically at assessing an association between mild maternal thyroid disorders and IUGR. The OR of SCH, subclinical hyperthyroidism, TPOAb positivity, and isolated hypothyroxinemia indicated that SCH is a risk factor for IUGR; while subclinical hyperthyroidism, positive TPOAb status, and isolated hypothyroxinemia are not. Since in most studies, SGA is used as a proxy for IUGR, and the diagnosis criteria of SGA and IUGR are identical, we also searched for studies related to SGA. To our knowledge, this is the first meta-analysis to evaluate the association between mild thyroid disorders and fetal development.

Maternal thyroid function can influence fetal development in 2 different ways: thyroid hormone impacts the regulation of both proliferation and differentiated function of human trophoblast cells;[20] and maternal thyroid hormone is important for the development of the infant. Therefore, theoretically, maternal

TABLE 1. The Characteristics of Selected Studies

Reference	Country	Items	Method	Period	Measurement of Thyroid Function	IUGR/SGA Diagnostic Criteria	QA	Results
Chen 2015	China	TpoAb+	IMA	1.2.3t	TPOAb + (TPOAb≥ 50 IU/mL) 1st t: TSH 0.09–3.47 mIU/L, fT4 6.00–12.25 ng/L; 2nd t: TSH 0.20–3.81 mIU/L, fT4 4.30–9.74 ng/L; 3rd t: TSH 0.67–4.99 mIU/L, fT4 4.56–8.50 ng/L.	IUGR: fetal weight <2500 g at full-term delivery, or <P10 or 2SD for the gestational age.	7	TPOAb/TgAb was not associated with IUGR.
Wilson 2014	USA	TpoAb+	ELISA	16–25 w	TPOAb+: TPOAb >20 IU/mL	N/A	7	TPOAb/TgAb was not associated with SGA.
Kumru 2014	Turkey	TpoAb+; SCH	IMA	10–12 w	TPOAb + : TPOAb > 60 IUs/mL; TSH (P5-P95), FT4 (P5-P95), i.e., TSH (0.37–2.6 μIU/mL), FT4 (0.94–1.53 ng/dL).	SGA: birth weight <P10 for gestational age	7	TPOAb/TgAb was not associated with SGA.
Abbassi-Ghanavati 2010	USA	TpoAb+	IMA	6–20 w	TPOAb + (TPOAb > 50 IU/mL) TSH (0.08–3.0mUI/L) FT4 (0.86–1.9 ng/dL)	IUGR: birth weight <P10	7	TPOAb was not associated with IUGR.
Sahu 2009	India	SCH; OH	IMA	13–26 w	TSH (0.5–5.5 mIU/L)	IUGR: birth weight <P10 for gestational age	7	IUGR is not associated with SCH
Saki 2014	Iran	SCH; subclinical hyperthyroidism	IMA	15–28 w	TSH (0.2–3 mL U/L), FT4 (11.84 ± 3.86 pmol/L)	IUGR: birth weight <P10 for gestational age	7	SCH is associated with IUGR; only 2 subjects presented subclinical hyperthyroidism and had no complication.
Mannisto 2008	UK	SCH; subclinical hyperthyroidism; Tpo	IMA	12–24 w	SCH: TSH > p95, FT4 p5-p95 Subclinical hyperthyroidism: TSH < p5, FT4 p5-p95 TPOAb+: TPO > p95	N/A	6	SCH, subclinical hyperthyroidism, TPOAb + are not associated with SGA.
Su 2011	China	SCH; Subclinical hyperthyroidism; isolated hypothyroxinemia	IMA	1.2t	TSH: 0.3–3.6 mIU/L FT4: 0.8–1.7 ng/dL	N/A	8	Isolated hypothyroxinemia is associated with SGA.
Hamm 2009	Canada	Isolated hypothyroxinemia	IMA	15–16 w	OH T4: TSH 0.15–4.0 mU/L, FT4≤ 8.5 pmol/L	SGA: birth weight <P10 for gestational age and gender	7	Isolated hypothyroxinemia is not associated with SGA.
Chen 2014	China	SCH	IMA	1.2.3t	1st t: TSH 0.09–3.47 mIU/L, fT4 6.00–12.25 ng/L; 2nd t: TSH 0.20–3.81 mIU/L, fT4 4.30–9.74 ng/L; 3rd t: TSH 0.67–4.99 mIU/L, fT4 4.56–8.50 ng/L.	IUGR: fetal weight <P10 for gestational age	7	Maternal SCH increased the risk of IUGR of fetuses.

Reference	Country	Items	Method	Period	Measurement of Thyroid Function	IUGR/SGA Diagnostic Criteria	QA	Results
Breathnach 2013	Ireland	SCH; TpoAb+; isolated hypothyroxinemia	IMA	In the early 2t	TSH (0.17–4.0 mU/L); fT4 (10.7–17.4 pmol/L); TPOAb+: TPO > 34 IU/MI	IUGR: prenatal fetal biometry below P10 (associated with oligohydramnios or abnormal Doppler indices).	7	IUGR is not associated with OH, SCH, isolated hypothyroxinemia
Saki 2014	Iran	TpoAb+	TPOAb, TgAb: RIA TSH, FT4: IMA	15–28 w	TPOAb+: TPOAb > 35 IU/mL TgAb+: TgAb > 40 IU/mL TSH: 0.2–3 mIU/L FT4: 0.92 ± 0.3 ng/dl	IUGR < P10 for gestational age	7	TPOAb/TgAb is associated with IUGR.
Ong 2014	Australia	Isolated hypothyroxinemia	IMA	9–13 w	TSH: 0.02–2.15 mU/L, FT4: 10.4–17.8 pmol/L, TPOAb+: TPOAb > 5.61 mU/L, TgAb+: TgAb > 4.11 kU/L	SGA: birth weight <P10 of a nonindigenous Australian cohort	7	SGA is not associated with high TSH, Isolated ypothyroxinemia, TPOAb/TgAb+.

fT4 = free thyroxine, IMA = immunometric assay, IUGR = intrauterine growth restriction, OH = overt hypothyroidism, QA = quality assessment, RIA = radioimmunoassay, SCH = subclinical hypothyroidism, SGA = small for gestational age, t = trimester, TPOAb = thyroid peroxidase antibody, TSH = thyroid stimulating hormone, w = week.

FIGURE 2. Forest plots of studies comparing intrauterine growth restriction (IUGR) rates between subclinical hypothyroidism (SCH) and euthyroid pregnant women. Event 1: IUGR infant from SCH women; total 1: SCH women; event control 1: IUGR infant from euthyroid women; total 1: euthyroid women.

thyroid dysfunction can cause IUGR via both maternal and placental mechanisms.

OH and overt hyperthyroidism are relatively easy to diagnose and the treatments are not controversial.[21] Most studies demonstrate that OH and overt hyperthyroidism can increase the risk of IUGR or low birth weight.[22–25] Although 2 studies also observed a higher prevalence of large for gestational age infants with hyperthyroid pregnant women,[10,26] these results were at borderline significance or lost its significance after adjusting for parity.

Subclinical disorders and euthyroid autoimmune thyroid disease are often missed since they are asymptomatic. However, SCH, subclinical hyperthyroidism, positivity for TPOAb, and isolated hypothyroxinemia during pregnancy are proven to be associated with many adverse outcomes. SCH was proven to be related to spontaneous abortion, abruptio placentae, premature delivery, and impaired fetal neurological development.[27–29] Subclinical hyperthyroidism during pregnancy is not thought to be associated with adverse outcomes and does not require treatment.[30,31] About 5% to 20% of women of childbearing age

FIGURE 3. Forest plots of studies comparing intrauterine growth restriction (IUGR) rates between subclinical hyperthyroidism and euthyroid pregnant women. Event 2: IUGR infant from subclinical hyperthyroidism women; total 2: subclinical hyperthyroidism women; event control 2: IUGR infant from euthyroid women; total 2: euthyroid women.

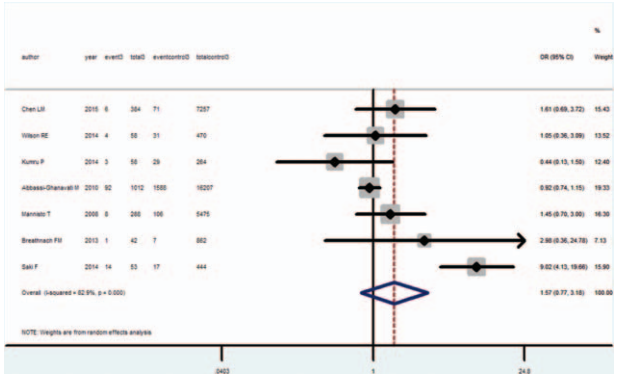

FIGURE 4. Forest plots of studies comparing intrauterine growth restriction (IUGR) rates between thyroid peroxidase antibody (TPOAb) positive and negative pregnant women. Event 3: IUGR infant from TPOAb positive pregnant women; total 3: TPOAb positive pregnant women; event control 1: IUGR infant from TPOAb negative pregnant women; total 1: TPOAb negative pregnant women.

are autoimmune thyroid disease, but most of them are euthyroid. Pregnant women who are positive for TPO antibodies are reported to be at increased risk for spontaneous abortion, preterm delivery, and postpartum thyroiditis.[21,32–35] Authors of a meta-analysis reviewed these studies and demonstrated a significant relationship between ATA and pregnancy loss.[36] Isolated hypothyroxinemia is defined as normal TSH concentration but fT4 concentrations in the lower 5th or 10th percentile;[37] even transient hypothyroxinemia was proven to exert an adverse effect.[38] Isolated hypothyroxinemia has been shown to affect the process of neuronal migration in the cortex and hippocampus during early pregnancy.[39]

IUGR, as one of these adverse outcomes, is not clearly understood as to its association with subclinical thyroid dysfunction or autoimmunity. IUGR is a heterogeneous condition, and the reasons for its manifestation usually arise from maternal, placental, or fetal mechanisms. Investigator using meta-analysis attempted to evaluate biomarkers for IUGR and divided them into angiogenesis-related, endothelial function/oxidative stress-related, placental protein/hormone-related, and other biomarkers.[40]

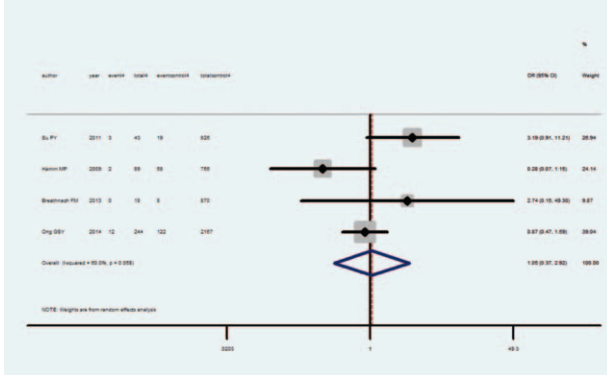

FIGURE 5. Forest plots of studies comparing intrauterine growth restriction (IUGR) rates between isolated hypothyroxinemia and euthyroid pregnant women. Event 4: IUGR infant from isolated hypothyroxinemia women; total 4: isolated hypothyroxinemia women; event control 4: IUGR infant from euthyroid women; total 4: euthyroid women.

In the present analysis, we found that SCH, rather than subclinical hyperthyroidism, was associated with IUGR. Although adult hypothyroid patients increase their weight, and hyperthyroid patients decrease their weight since thyroid hormones increase metabolic rates, thyroid hormone in early life is an important hormone for development. Therefore, it is plausible that thyroid hypofunction, even subclinical, would impair the development of infants.

It is a confusing finding that isolated hypothyroxinemia showed a negative result. Compared with SCH, isolated hypothyroxinemia is a clinical disorder. Theoretically, if SCH, which shows normal thyroid hormone levels, exerts impact on fetal development, isolated hypothyroxinemia should also have an impact on it. The reasons for the contrasting results may be that: there are only 4 studies that focus on the relationship between isolated hypothyroxinemia and IUGR, and none of them considered the impact of antibodies or other confounding factors; the type 2 and 3 deiodinases and transporters expressed on the placenta would change with maternal thyroid dysfunction, which would compensate for the impairment caused by maternal thyroid disorders; and adverse pregnant outcomes, such as child loss and neonatal death, have been observed to be related to higher TSH levels, rather than FT4 concentrations.[41] Therefore, TSH levels would play a role in these conflicting result. However, the mechanism is unclear and this hypothesis still needs further investigation.

One of the major limitations of this review is that IUGR cannot be measured directly, and SGA is used as a substitute. In most of the selected studies, IUGR was defined as birth weight below the 10th percentile for gestational age, which is the same as the definition for SGA; only 1 study defined IUGR by Doppler ultrasound. However, some children diagnosed as SGA are constitutionally small and healthy. Therefore SGA is not a perfect indicator for restricted fetal development within the uterus.

In conclusion, among these mild thyroid disorders, only SCH exhibited a statistically significant association with IUGR, while others showed none. However, evidence was limited because only a few studies were available for each analysis. Further studies are certainly required to update supporting the evidence in this area.

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