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Maternal Thyroid Disease and Neonatal Low Birth Weight: A Systematic Review and Meta-Analysis

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Abstract

Objective: Thyroid disorder is a common endocrine complication in pregnant women: the association between neonatal low birth weight (LBW) and thyroid dysfunction during pregnancy has not been definitely confirmed. We conduct a systematic literature review and meta-analysis of the adverse fetal complication of LBW in maternal thyroid disease, including overt and subclinical hyperthyroidism and hypothyroidism. **Methods:** Relevant studies in English published between 1990 and 2016 were identified by searching PubMed, Medicine, and Embase databases. Cohort studies that evaluated the association between LBW infants and overt and subclinical hyperthyroidism or hypothyroidism during pregnancy and included a healthy pregnancy reference group were selected. The combined odds ratio (OR) with 95% confidence intervals (CI) were calculated to evaluate this relationship. **Results:** A total of 11 cohort studies (1,171,052 participants) assessed the association between maternal thyroid disease and LBW infants. An increased risk for LBW in hyperthyroidism pregnancies was demonstrated (OR: 1.30, 95% CI 1.11 - 1.54; $p = 0.02$). No significant increased risk for LBW was detected in subclinical hyperthyroidism (OR 1.03; 95% CI 0.72 - 1.48; $p = 0.87$), or hypothyroidism pregnancies (overt: OR 0.98; 95% CI 0.88 - 1.10; $p = 0.75$; subclinical: OR 1.29; 95% CI 0.81 - 2.04; $p = 0.28$). **Conclusion:** Data show a higher trend towards an increased risk of LBW among infants from maternal hyperthyroidism pregnancies. No association was seen in subclinical cases of hyperthyroidism or hypothyroidism during pregnancy.

Keywords

Low Birth Weight, Pregnancy, Hyperthyroidism, Hypothyroidism, Meta-Analysis

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1. Introduction

Birth weight is often used as an indicator of fetal growth and development. Low birth weight is defined as birth weight less than 2500 g, according to the World Health Organization (WHO) [1]. Low birth weight (LBW) is associated with neonatal mortality and morbidity, as well as with the occurrence of diseases such as diabetes, cardiovascular and autoimmune disease in later life [2] [3]. In 2011, the WHO reported that the worldwide annual incidence of LBW infants is approximately 15.5% [1]. However, in the majority of cases, the cause of neonatal LBW cannot be identified; studies have shown that many different pathological processes may lead to LBW in newborns.

Thyroid disorder is a common endocrine problem in women of childbearing age [4] [5] [6]. According to previous studies, the prevalence of overt hypothyroidism is 0.3% - 1.5% and of subclinical hypothyroidism is 2% - 3% [6] [7] [8]. Hyperthyroidism and subclinical hyperthyroidism affects approximately 0.1% - 0.4%, and 0.4% - 1.7% of pregnant women, respectively [4] [5] [9], and the prevalence is higher in iodine deficiency areas [5] [7]. Over the last 20 years, several studies have investigated the effects of maternal thyroid dysfunction during pregnancy on neonatal birth weight. However, these results remain controversial, as some of the published data on maternal thyroid dysfunction have shown an associated increased risk of LBW [6] [7] [10], whereas other studies have found no association with neonatal birth weight [8] [11] [12] [13] [14].

To date, a series have evaluated the effect of maternal thyroid disease on neonatal birth weight. However, none of these studies examined all types of thyroid disorders (both overt and subclinical hyperthyroidism and hypothyroidism) and its impact on neonatal birth weight. Thus, we undertook a systematic review and analysis of all the types of maternal thyroid disorders and its possible association with neonatal LBW to demonstrate a clear view of the evidence and contribute information about related medical therapy and perinatal prevention for further research.

2. Materials and Methods

2.1. Literature Search Strategy and Study Selection

Systematic searches of the medical literature were conducted in the PubMed, Medline and Embase databases, from January 1990 to December 2016, using appropriate keywords for relevant manuscripts in English and human studies. The applied search criteria were related to thyroid function and infant birth weight. The search strategy was elaborated by using the structured method of the participants, interventions, comparison, outcome and study. Medical Subject Heading (MeSH) words: thyroid dysfunction, pregnancy outcome, hyperthyroidism, overt hypothyroidism, subclinical hyperthyroidism, subclinical hypothyroidism, low birth weight, and birth weight. These words were combined with "AND" to generate citations relevant to the research topic. In addition, citation tracking of included studies and recent reviews was performed.

2.2. Inclusion and Exclusion Criteria

Cohort studies including singleton pregnant women with either hyperthyroidism; overt hypothyroidism, subclinical hyperthyroidism, or subclinical hypothyroidism, and with LBW infants as the pregnancy outcome were selected. Case control studies, studies including women with multiple pregnancies, and studies without a reference group were excluded.

Neonatal LBW (defined as birth weight <2500 g) was classified following the WHO criteria [1]. The determination of maternal thyroid disease was based on thyroid function testing by measuring serum concentrations of thyroid- stimulating hormone (TSH) and free thyroxine (FT4). Hyperthyroidism is defined by a suppressed serum level of TSH and elevated concentration of the FT4. Subclinical hyperthyroidism is defined a low serum TSH concentration with normal FT4. Maternal hypothyroidism is defined as the presence of an elevated TSH concentration during gestation. To classify the patient's status as either subclinical or overt hypothyroidism, serum FT4 should be measured [5].

Maternal thyroid function changes during pregnancy as increased thyroid hormone-binding globulin (TBG) concentration; increased iodine clearance in the kidneys; and effects of high circulating human chorionic gonadotrophic (hCG). Thus, it is necessary to use gestation-specific reference intervals for the interpretation of various laboratory results for pregnant women [5] [15]. In the present study, no standard criteria were set for the range of thyroid function test results among the individual studies. Additionally, the reference values might differ among assays from different manufacturers.

2.3. Data Extraction

Data were extracted from each selected study on maternal thyroid disease (overt and subclinical hyperthyroidism and hypothyroidism) were defined as factors and the outcome of interest was LBW infants. Information was extracted from each selected article on the quality of the study characteristics and test results. Two independent authors reviewed the abstracts and full manuscripts for all selected citations that met our study objectives. Furthermore, to avoid missing any relevant studies, the reference lists of studies included in this review were screened in search of overlooked publications. When there were duplicate publications, the most recent and complete versions were selected. In the case of disagreement among the reviewers, a third review was undertaken and resolved through consensus and discussion.

2.3.1. Assessment of Quality of the Included Studies

We used the Newcastle-Ottawa Scale (NOS) to assess the methodological quality of the selected studies. Items of evaluation included adequacy of the definition of cohort studies, representativeness of the sample, selection and evaluation of controls, comparability, ascertainment of exposure, and outcome of studies. Since the assessment of quality related strongly in reporting of results, a well conducted study could score poorly if the methods and results were not reported

in sufficient detail. Therefore, we defined NOS scores as 1 - 3, 4 - 6, and 7 - 9 for low, intermediate, and high-quality studies, respectively. In other words, high quality of study was considered to be low risk of bias. The present study was scored intermediate quality.

2.3.2. Statistical Analyses

Review Manager (RevMan) software program (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) was used to perform the meta-analyses. The overall combined odds ratio (OR) and 95% confidence intervals (CI) were determined to estimate the effect size of thyroid disease on LBW risk. The significance of each pooled OR was determined using the Z test. A p-value of <0.05 was considered to indicate a statistically significant difference which was calculated using the Mantel-Haenszel method. The variation across studies attributable to heterogeneity was assessed by the x^2 based Q test and I^2 value was utilized to quantify the total variation resulting from heterogeneity. For I^2, a value of 25%, 50% and 75% were considered as low, moderate, and high heterogeneity, respectively. Fixed-effects models were used to evaluate the OR and 95% CI if no significant heterogeneity ($P > 0.05$, $I^2 < 50\%$). Otherwise, random-effects models were applied if heterogeneity was moderate or high ($P < 0.05$, $I^2 > 50\%$) [16] [17]. Additionally, sensitivity analyses were conducted to address outcome validity and credibility.

3. Results

3.1. Characteristics of the Studies Included in the Review

The search yielded 95 studies, and six additional studies were identified from the reference lists of the included articles. After excluding duplicated records, review articles, or irrelevant studies, 23 full-texts articles remained. These articles were examined to confirm that studies met the inclusion criteria. 12 articles were further excluded, either because the number of participants (n) was <10 or there was a lack of data. Finally, a total of 11 studies were included in the meta-analysis (Figure 1).

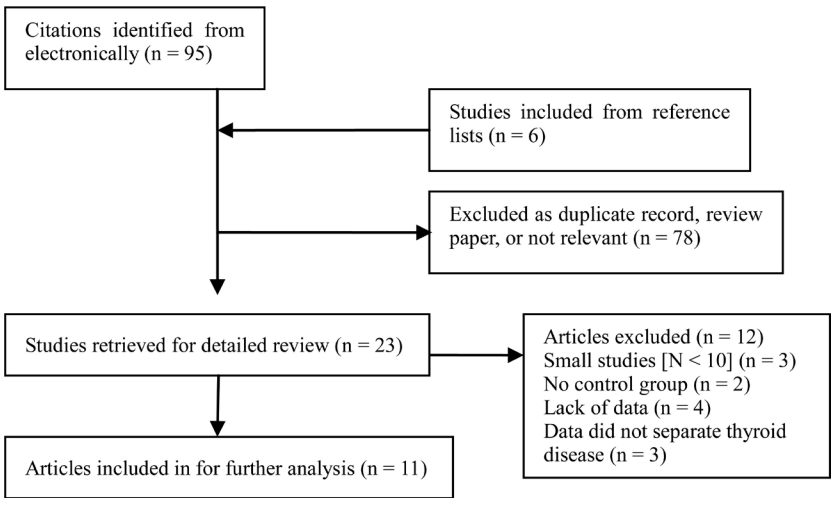

Figure 1. Flow chart of study selection criteria and process.

Table 1. Description of included studies for maternal thyroid dysfunctions.

Included Studies	Location	Observational Period	Participants	Number of Centers	Timing of Thyroid Function Testing	Laboratory Validation
Casey, 2005	USA	Apr. 2000-Apr. 2003	25,765	Single	<20 weeks	FT4, TSH
Casey, 2006	USA	Nov. 2000-Apr. 2003	25,765	Single	<20 weeks	FT4, TSH
Cleary-Goldman, 2008	USA	Oct. 1999-Dec. 2002	10,990	Multiple	1st & 2nd Trimesters	FT4, TSH TPO-Ab, TG-Ab
Wikner, 2008	Sweden	Jul. 1995-Dec. 2004	848,468	Multiple	<13 weeks	No
Mannisto, 2009	Finland	Jul. 1985-Jun.1986	9247	Multiple	<20 weeks	FT3, FT4, TSH TPO-Ab, TG-Ab
Luewan, 2011	Thailand	Jan. 1994-Dec. 2008	540	Single	All trimesters	FT4, TSH
Su, 2011	China	Oct. 2008-Dec. 2010	1017	Multiple	<20 weeks	FT4, TSH
Chen, 2011	Taiwan	Jan.-Dec. 2005	16,980	Multiple	Medical record	No
Wang, 2012	China	2007-2009	756	Multiple	<12 weeks	FT3, FT4, TSH
Mannisto, 2013	USA	2002-2008	223,512	Multiple	Medical record	No
Chen, 2014	China	Feb. 2009-Feb. 2012	8012	Single	All trimesters	FT4, TSH

FT3: Free Triiodothyronine FT4: Free Thyroxine TSH: Thyroid-stimulating hormone TPO-Ab: Thyroid peroxidase antibodises TG-Ab: Thyroglobulin antibodises.

Detailed descriptions of the included articles are presented in Table 1. Included studies were published from 2005 to 2014 and 1,171,052 participants in total were included in these studies. In addition, the observational period was between 1985 to 2012. Besides, three studies are different from the remainder in define thyroid disease from medical records coding, including two large population-based studies by Wikner *et al.* [14] and Mannisto *et al.* [18]. The inclusion of these studies might be considered to be a study limitation. Notably, the clinical diagnosis of maternal thyroid disease was using screening for laboratory criteria (serum FT4 and TSH) [5]; and selected studies produced their own laboratory reference ranges.

3.1.1. Low Birth Weight Infants and Hyperthyroidism

Five studies on LBW infants and hyperthyroidism pregnancies were retrieved [10] [13] [18] [19] [20]. A meta-analysis showed an increased risk of LBW infants by 1.3-fold with maternal hyperthyroidism compared with normal pregnancies (OR 1.30; 95% CI 1.11 - 1.54; $p = 0.002$; Figure 2). The study conducted by Chen *et al.* [19] contributed the highest weight for the result (77.6%) with small CI and a slight statistical significance for the result. The heterogeneity for included studies was low ($I^2 = 30\%$; $p = 0.22$), and it was pooled by the study of Mannisto *et al.* [18]. Sensitivity analyses were performed by sequential omission of individual studies, which yielded similar results and indicated that the combined OR was valid and credible.

3.1.2. Low Birth Weight Infants and Subclinical Hyperthyroidism

Three studies reported on neonatal LBW in the context of subclinical maternal hyperthyroidism [9] [10] [13]. A meta-analysis of these studies demonstrated that pregnant women with subclinical hyperthyroidism had no increased risk of

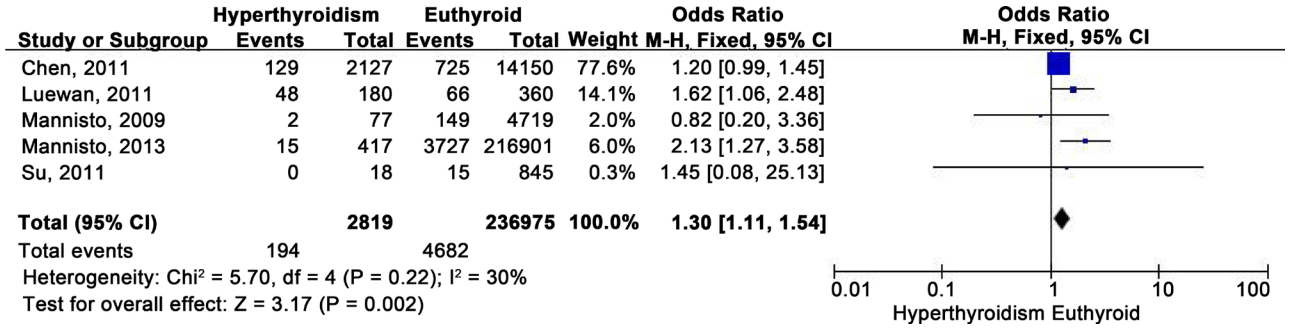

Figure 2. Forest plot of comparison LBW and hyperthyroidism. Detailed are given for events, numbers of subjects, odds ratios (OR) and 95% confidence intervals (CI). df: degrees of freedom; M-H: Mantel-Haenszel.

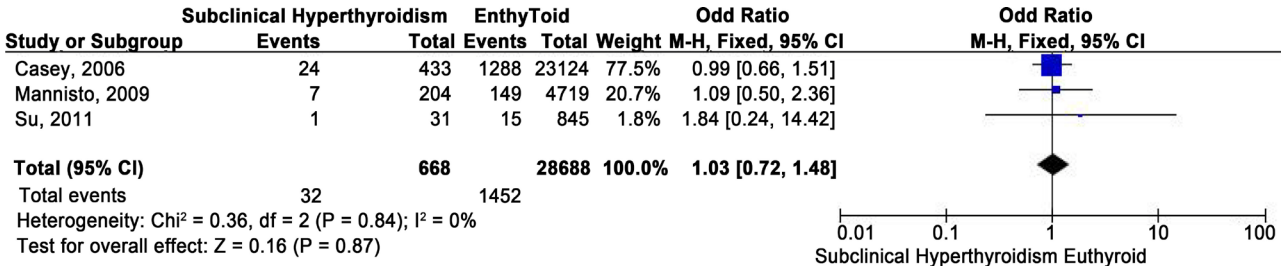

Figure 3. Forest plot of comparison LBW and subclinical hyperthyroidism. Detailed are given for events, numbers of subjects, odds ratios (OR) and 95% confidence intervals (CI). df: degrees of freedom; M-H: Mantel-Haenszel.

delivering LBW infants compared to reference population (OR 1.03; 95% CI 0.72 - 1.48; $p = 0.87$; Figure 3). Sensitivity analysis suggested that the combined OR was valid and credible. There was no heterogeneity among the studies ($I^2 = 0\%$), with x^2 of 0.36 ($p = 0.84$). In Addition to the largest sample study by Casey *et al.* [9], it contributed to a small CI and no increased risk of LBW among the infants.

3.1.3. Low Birth Weight Infants and Overt Hypothyroidism

As shown in Figure 4, three of the qualified studies reported on LBW infants in overt hypothyroidism pregnancies [13] [14] [18] including two of the largest studies [14] [18]. No significant association was observed for the LBW infants compared with the reference groups (OR 0.98; 95% CI 0.88 - 1.10; $p = 0.75$). Sensitivity analyses suggested that the combined OR was general remained unchanged. Notably, there was no heterogeneity between studies ($I^2 = 0\%$), with x^2 of 0.35 ($p = 0.84$).

3.1.4. Low Birth Weight Infants and Subclinical Hypothyroidism

As showed in Figure 5, six included studies [8] [10] [12] [13] [21] [22] had samples sizes range from small to moderate LBW infants in subclinical hypothyroidism. A meta-analysis showed that there was no increased OR of LBW among the pregnant women with subclinical hypothyroidism in comparison to normal pregnancy (OR 1.29; 95% CI 0.81 - 2.04; $p = 0.28$; Figure 5). Since there was moderate heterogeneity for studies in pregnant women with subclinical hypothyroidism ($I^2 = 58\%$; $p = 0.03$), random-effects models were applied for analysis. Sensitivity analyses with the omission of one study at a time and analysis of

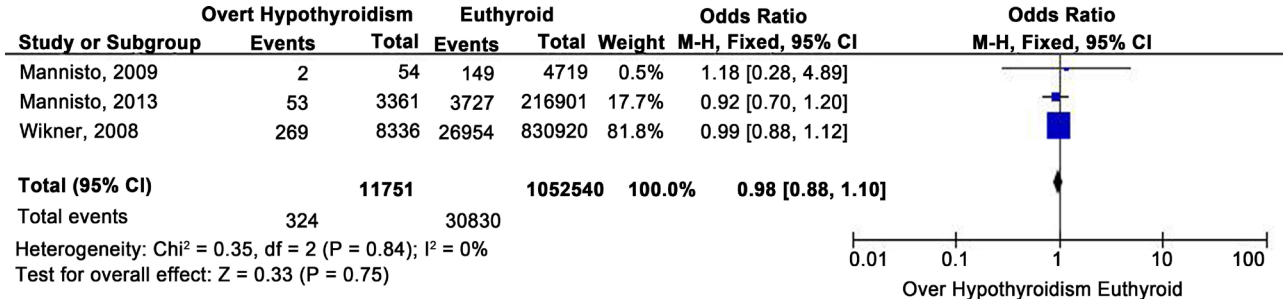

Figure 4. Forest plot of comparison LBW and hypothyroidism. Detailed are given for events, numbers of subjects, odds ratios (OR) and 95% confidence intervals (CI). df: degrees of freedom; M-H: Mantel-Haenszel.

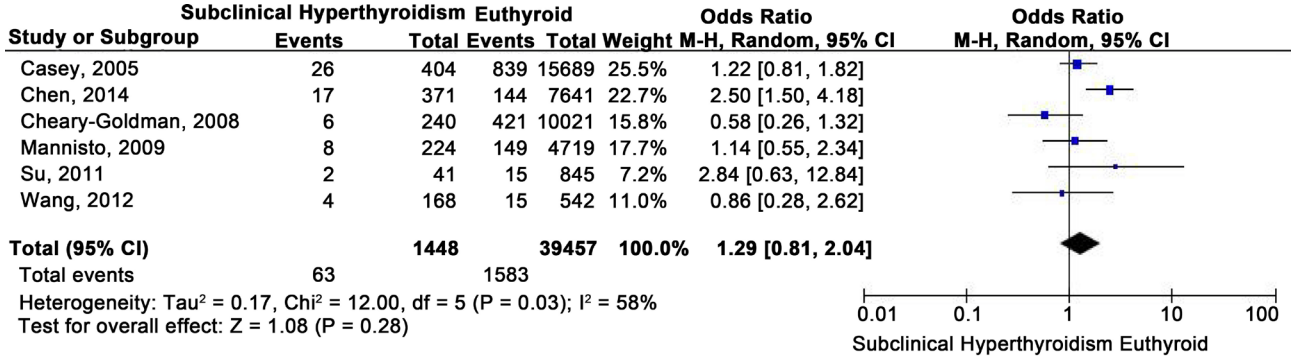

Figure 5. Forest plot of comparison LBW and subclinical hypothyroidism. Detailed are given for events, numbers of subjects, odds ratios (OR) and 95% confidence intervals (CI). df: degrees of freedom; M-H: Mantel-Haenszel.

the rest, the result was dependent on a study by Chen *et al.* [21], which was the only study that showed a significantly increased risk of LBW.

3.2. Publication Bias

Publication bias across studies was assessed by funnel plots with Begg's test. The symmetry of the funnel plot was seen ($p = 0.219$), which indicated a low probability of publication bias.

4. Discussion

The current study systematically evaluated the association of maternal thyroid disorders with neonatal LBW. Eleven eligible studies included in this meta-analysis, were determined to be at low risk of bias according to the Newcastle-Ottawa system. The results of the present study revealed that maternal hyperthyroidism is associated with a risk of LBW in infants. In contrast, LBW infants born to women with subclinical hyperthyroidism or hypothyroidism did not show a positive association.

Although hyperthyroidism in pregnancy is uncommon, its effect on the birth weight of infants is critical. Previous studies evaluating the impact of maternal hyperthyroidism have consistently showed an increased risk of neonatal LBW [5] [15] [23] [24], which were confirmed in this study. However, OR in our study was much lower than in previous studies. For instance, the infants born to women with uncontrolled hyperthyroidism had a nine-fold greater incidence of

LBW compared to the normal mother, according to a 16-year study by Millar and colleagues in 1994 [23]. However, we did not include it in our study because the study did not meet the defined criteria (*i.e.* categories such as including all of the births [singleton and multiples] and TSH data were only available for five years). Similarly, a study by Phoojaroenchanachal *et al.* [24] showed fourfold-greater increased risk of LBW in infants born to women with maternal hyperthyroidism, but it was only focused on women with present and past history of hyperthyroidism, so it was excluded as well. Nevertheless, we suggest that the risk of neonatal LBW with hyperthyroidism in pregnancy increased 1.3-fold compared with a healthy pregnancy. Generally, an explanation of the mechanisms supports this finding as follows. Maternal FT4 levels in the high-normal range increase lipid and protein degradation, which leads to a state of chronic caloric deficiency in pregnancy induces a direct catabolic state in the fetus, and thus negatively affects the birth weight [6] [15].

As confirmed by previous studies, subclinical hyperthyroidism was not associated with LBW infants in this study. In general, a low TSH in early pregnancy may reflect normal physiological changes due to transient placental hormone stimulation, which is inversely related to TSH [9] [15]. In addition, previous studies have reported that there are ethnic differences in the suppression of serum TSH concentrations during pregnancy; for example, TSH values in Black and Asian women are lower than in White women but are still within the normal range for a healthy pregnancy [5] [6] [15]. This information may help clinicians to distinguish subclinical hyperthyroidism from a normal pregnancy and to guide clinical follow-up, because a few studies have addressed the long-term adverse outcomes in adult life and progression to overt thyrotoxicosis due to subclinical hyperthyroidism [5] [25].

No relationship was seen in our meta-analysis for LBW infants in the presence of maternal hypothyroidism, despite the inclusion of large sample studies. Evidence from previous studies reported conflicting results among these patients. Several studies found an increased risk of LBW [6] [7] [10], while others showed no association [8] [12] [13] or even children with higher birth weight [11] [26]. Until now, the mechanism behind an association between maternal hypothyroidism and birth weight has not clarified yet. Several well-documented studies have advised that thyroxine deficiency in pregnant women leads to maternal and gestational diabetes. A high insulin resistance index will lead to increased circulating glucose, producing a higher placental transfer of glucose to the fetus, and consequently, fetal weight gain or macrosomia [11] [12] [27]. On the other hand, a series of studies also support the finding that maternal and fetal thyroid insufficiency impairs neurodevelopment [28] [29], and therefore, is a cause of intrauterine growth retardation (IUGR) and neonatal LBW. Admittedly, further research is necessary to elucidate the exact metabolic changes behind hypothyroidism in pregnancy. Though we failed to show a positive relationship between neonatal LBW and hypothyroidism in this study, perhaps potential confounding factors such as maternal age, race, smoking, and personal medical history af-

fected the statistical power of this study. Considering its higher prevalence in women of reproductive age, and these complex inter-relations between birth weight and thyroid function, physicians will need to be attentive to maternal thyroid disorders in their patients.

This study has several limitations. First, the prevalence of thyroid auto-antibodies is approximately about 6% - 20% in women of reproductive age [7] [30], which are more often associated with adverse perinatal outcomes [4] [7] [13]. In the absence of these data in this study, we speculate that the outcome results may be changed. Second, the included studies were unable to differentiate LBW newborns because of intrauterine growth retardation or a shorter duration of pregnancy. Therefore, the outcome results would be overestimated in this study. Finally, maternal thyroid functions change markedly during pregnancy and the interpretation of thyroid function tests depends on the stage of pregnancy. For instance, in early pregnancy, serum TSH concentrations decrease inversely to increasing serum hCG concentrations. Suppressed serum TSH can be seen in up to 10% of normal pregnant women [15], it is typically transient and resolve spontaneously. Therefore, inadequate diagnosis from medical records coding may mislead study results.

5. Conclusion

In summary, hyperthyroidism in pregnancy was associated with a higher increased risk of LBW infants compared with normal thyroid function in pregnancy, whereas, no association was found between LBW newborns and maternal subclinical hyperthyroidism or hypothyroidism. Due to the complex thyroid function alternation during the pregnancy process, which is essential for fetal development, further longitudinal studies are required to clarify the mechanism of thyroid physiology in pregnancy, taking the limitations of this study into account.

Competing Interests

The authors declare that there is no conflict of interest.

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Authors' Contributions

All authors make equally to this work.

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