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Isolated Maternal Hypothyroxinemia and adverse pregnancy outcomes: A systematic review

Short running title: IMH and adverse pregnancy outcomes

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Abstract

Maternal thyroid hormones are vital for a normal pregnancy and the development of fetus and childhood; inadequate availability of thyroid hormones during pregnancy is associated with adverse pregnancy outcomes. Isolated maternal hypothyroxinemia (IMH) is defined as a low maternal T4 in the absence of TSH elevation. This systematic review aimed to investigate the association between IMH and adverse pregnancy outcomes. PubMed, Scopus and Web of science were searched for retrieving observational studies published up to September 2020, investigating the association of IMH with adverse pregnancy outcomes. From a total of 308 articles, 17 met our eligibility criteria and were used for the purpose of the present study. Definition of IMH varied in different studies. While some studies reported no adverse pregnancy outcomes for IMH, other studies found a positive association between first trimester IMH and feto-maternal outcomes including gestational hypertension, gestational diabetes, preterm delivery, fetal distress, small for gestational age, musculoskeletal malformations, spontaneous abortion, placental abruption and macrosomia. IMH, identified in the second trimester was associated with an increase in the risk of gestational diabetes**,** and hypertensive disorders of pregnancy in one study. There is no consensus on the adverse effects of IMH on pregnancy outcomes. Further comprehensive cohort studies using one standard definition for IMH, with large sample size and control of important confounders such as iodine status and maternal Thyroid peroxidase antibody (TPOAb) are needed for precise assessment of this association.

Keywords: Isolated Maternal hypothyroxinemia, outcome, pregnancy, systematic review, thyroid.

Introduction

Normal fetal development is dependent on sufficient concentrations of triiodothyronine (T3) and thyroxine (T4) [1]. The fetal thyroid initiates iodine concentration and thyroid hormones synthesis after the first trimester of gestation [1, 2], necessitating a dependence on sufficient hormonal supplies from the mother [3]. Lack of maternal thyroid hormone availability during pregnancy is strongly correlated with adverse feto-maternal and neonatal outcomes, with a growing body of literature demonstrating that subclinical hypothyroidism during pregnancy, defined as elevated thyroid stimulating hormones (TSH) with normal levels of free triiodothyronine (fT3) and free thyroxine (fT4), particularly during early gestation, may elevate the risk of both short and long term adverse pregnancy outcomes [4, 5].

Isolated maternal hypothyroxinemia (IMH) in pregnancy is defined as a low maternal fT4 concentration with a maternal TSH level within the normal reference range [6]; prevalence of the condition has been reported to range between 1% and 2.3% depending on the ethnicity, iodine insufficiency status of the population and diagnostic criteria [7, 8]. Although the exact underlying cause of IMH has not been clearly understood, one of the mentioned etiologies is iodine deficiency [7, 9], which could potentially affect both mother and child health. However, IMH seems to be pregnancy-specific disease with a multifactorial underlying pathophysiology and results of studies focusing on IMH and risk of adverse pregnancy outcomes are controversial. Some literature shows that IMH is associated with adverse feto-maternal and neonatal outcomes [6, 10, 11], even cognitive function in childhood [12, 13], in despite, some data not confirming this association [14-16].

The present systematic review aims to summarize existing evidence available on the effect of IMH on adverse pregnancy outcomes, while also discussing the need to treatment.

Methods

The present systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [17]. This study was approved by the ethics committee of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences and the study was registered in the International Prospective Register of Systematic Reviews (PROSPERO).

PICO of this systemic review are as follows: population (P): pregnant women and/or newborns; intervention (I): not applicable; comparison (C): two groups of IMH with euthyroid pregnant women; outcome (O): adverse feto-maternal and neonatal outcomes.

Search Strategy

A comprehensive electronic literature searching was conducted independently by two authors, who were familiar with search methods and information sources, without any restrictions, in the PubMed [including Medline] and Scopus databases for retrieving original articles published in English language assessing the association between IMH and adverse pregnancy outcomes up to September 2019. Furthermore, in order to maximize the identification of eligible studies, review articles and the reference lists of studies included were manually evaluated as well.

The following keywords, either alone or in combination, were used for the search: (“isolated hypothyroxinemia” OR “hypothyroxinemia” OR “Isolated maternal hypothyroxinemia” OR “MIH”) AND ("pregnancy" OR “pregnant women” OR “maternal” OR “gestational”) AND ("adverse pregnancy outcomes" OR "pregnancy outcomes” OR “pregnancy complications” OR “abortion” OR “miscarriage “OR “pregnancy loss” OR “fetal death” OR “stillbirth” OR “preeclampsia” OR “gestational hypertension” OR “pregnancy induced hypertension” OR “PIH” OR “gestational diabetes” OR “GDM” OR “hemorrhage” OR “postpartum hemorrhage”

OR “PPH” OR “Placenta abruption” OR “placenta previa” OR “preterm” OR “premature rupture of membrane” OR “PROM” OR “Intra uterine growth restriction” OR “IUGR” OR “small for gestational age” OR “SGA” OR “Low birth weight” OR “LBW” OR “oligohydramnios” OR “Apgar” OR “fetal distress” OR “neonatal distress” OR “RDS” OR “neonatal death” OR “neonatal mortality” OR “neonatal admission” OR “NICU admission” OR “malformation” OR “anomalies”) (Supplementary table 1).

Selection criteria, study selection and data extraction

In this systematic review, all case-control studies, randomized controlled trials (RCTs), non-randomized trials (NRS), and prospective or retrospective cohort studies were included. The study was considered to be eligible if 1) the pregnant women had not received any LT4 treatment, 2) The exposure of interest was maternal isolated hypothyroxinemia, and 3) the outcome of interest was at least one adverse pregnancy outcome, including abortion, gestational diabetes (GDM), gestational hypertension or preeclampsia, placenta abruption, placenta previa, antenatal or postpartum hemorrhage, preterm birth, premature rupture of membrane (PROM), intra uterine growth restriction (IUGR), macrosomia, large for gestational age (LGA), small for gestational age (SGA), low birth weight (LBW), fetal or neonatal distress and low Apgar score, fetal malformation, stillbirth, neonatal death and NICU admission. We also excluded non-original studies including guidelines, review articles, case reports, animal studies, commentaries, editorials, letters to the editor, meeting abstracts, as well as studies that did not provide accurate and clear data.

The screening of titles, abstracts and full-text articles was conducted independently by the authors for determining final eligibility criteria. Disagreements were resolved through scientific discussions; the general characteristics of the studies, including the first author's name, article title, journal name, country of study, publication year, study design, sample size,

116 population characteristics, and pregnancy outcomes were extracted from the studies and
117 assessed. To prevent extraction and data entry errors, a control check between the final data
118 used in the systematic review and the original publications was conducted by all authors.

119 **Quality assessment and risk of bias**

120 Quality of the studies was critically appraised for their methodology and results' presentation.
121 Two authors, blinded to study author, journal name and institution, evaluated the quality of the
122 studies independently. The quality of observational studies was also assessed using the
123 modification of the Newcastle– Ottawa Quality Assessment Scale for nonrandomized studies
124 [18] which evaluates the quality of published nonrandomized studies in terms of selection,
125 comparability and outcomes. Studies with scores above 6 were considered as high quality, 4-6
126 as moderate and those with scores below 4, as low quality.

127 We also evaluated risk of bias for studies included, using the Cochrane Collaboration's tool for
128 assessing risk of bias for other methodological studies [19]. Seven domains related to risk of
129 bias were assessed for bias in selection of exposed and non-exposed cohorts, bias in assessment
130 of exposure, bias in presence of outcome of interest at study initiation, bias in control of
131 prognostic variables, bias in assessment of the presence or absence of prognostic factors, bias
132 in assessment of outcome, and bias in adequacy regarding follow up of cohorts. Authors'
133 judgments were categorized as "low risk", "high risk", and "unclear risk" of bias (probably low
134 or high risk of bias).

135

136 # Results

137 The search strategy yielded 308 potentially relevant articles. Based on selection inclusion
138 criteria, 18 articles were identified for further full-text assessment; finally, we included 17
139 articles, which included data of 112994 pregnant women (figure 1).

Characteristics of the studies

Table 1 presents a summary of studies, assessing adverse pregnancy outcomes among women with IMH.

Participants

The articles were published in various geographical region: North America [15] and USA [14, 20], South America (Brazil [16]), Europe (Netherland [21-23] , Spain [24], Finland [25] and Ireland [26]) and Asia / Australia (China [6, 11, 27-30] and Australia [31]). All studies were prospective or retrospective cohorts and 47% (7/17) had a population-based design [21, 23-25, 27, 28, 32]. In seven studies, IMH was diagnosed in the first trimester[16, 21, 22, 25, 29-31], 5 in the first and second trimesters, before 20-24 weeks of gestations [11, 14, 24, 26, 27], 4 in the both first and second trimesters, separately [6, 20, 23, 28], one study in only in second trimester [15].

The prevalence of IMH among included studies in the first and second trimesters of pregnancy varied widely and ranged from 1.3% [14] to 18.8% [6], although, its prevalence in epidemiological data of population based studies included were less sparse, ranging between 2% -3% [21, 24, 25, 27, 28].

Diagnostic criteria used in studies included were quite variable and heterogeneous. In this respect, in terms of TSH, 10 studies used population-derived 2.5th - 97.5th [6, 14, 20-22, 26, 28-31] percentiles as the TSH reference interval for diagnosis and 3 studies used the population-derived of 5th - 95th percentiles [24, 25, 27]. Two studies used the ATA 2017 fixed ranges of 0.05-4 mIU/L [11, 15] and two study used the ATA 2011 fixed ranges of 0.1- 2.5 mIU/l during pregnancy [16, 23]. Regarding fT4, the cut point of fT4 also varied between studies. Three studies applied the population-derived >10th percentile [15, 23, 31], three studies used the population-derived >5th percentile [24, 25, 27] and also Eight studies used the

164 population-derived >2.5th percentile [6, 11, 14, 20-22, 26, 28], and one study used the three
165 criteria of the population-derived >10th and >5th percentiles as the fT4 cut point and also total
166 T4 < 7.8 ng/dL for diagnosis of IMH [16].

167 **Quality assessment and risk of bias**

168 Details of the quality assessment of studies included are presented in table 2. This assessment
169 showed that 13 studies were classified as being of high quality [6, 14, 15, 20-22, 24, 25, 27-
170 31] and four had moderate quality [11, 16, 23, 26]. In addition, cohort studies had a low risk of
171 bias for selection of exposed and non-exposed cohorts, assessment of exposure, presence of
172 outcome of interest at start of study, outcome assessment, and adequacy of follow up of cohorts;
173 however, approximately 29% had a problem risk of bias in the domain of control of prognostic
174 variables, 12% in existence of outcome at start of study and 6% in outcome evaluation (figure
175 2).

176 **Feto-maternal outcomes**

177 The association between IMH and feto-maternal outcomes, investigated by 16 studies [6, 11,
178 14-16, 20-27, 29-31], had wide variations in amplitude of findings between studies included in
179 this review.

180 ***Preterm birth***

181 Regard this association, 12 studies examined the risk of preterm birth among women with IMH
182 [6, 11, 14-16, 20, 21, 24, 26, 27, 30, 31]. The prevalence of preterm birth among women with
183 IMH ranged between 2.3%-10.3%. However, results of studies focusing on maternal
184 hypothyroxinemia and preterm birth were controversial. Although 9 studies [6, 11, 14-16, 24,
185 26, 27, 31] reported there were no any association between those IMH and preterm birth,
186 however, 3 studies [20, 21, 30] showed significant those association. In a well-designed
187 prospective population-based cohort study with large sample size from Netherlands, it was
188 reported that IMH in the first trimester of pregnancy was associated with a 2.5-fold increased

risk of preterm birth (adjusted OR: 2.54, 95% CI: 1.42– 4.54), a 3.4-fold increased risk of spontaneous preterm birth (adjusted OR: 3.44, 95% CI: 1.76–6.70) and a 3.6-fold increased risk of early preterm birth before 34 week of gestations (adjusted OR: 3.56, 95% CI: 1.50–8.43) (all $P \leq .01$) [21]. In addition, one [21] of four studies [6, 20, 21, 26] evaluating the risk of preterm PROM, showed a positive association between IMH and preterm PROM (adjusted OR: 2.35, 95% CI: 1.18–4.69).

GDM

Of publications included, 7 evaluated the risk of GDM among women with hypothyroxinemia in first and second trimesters of pregnancy [6, 11, 16, 20, 25, 26, 29] and reported that prevalence of GDM varied between 0-18.2% and 1-14.7% in women with and without IMH; of these studies, 5 found no association [6, 11, 16, 25, 29], two reported that maternal hypothyroxinemia in the second trimester of pregnancy was significantly associated with a higher prevalence / risk of GDM compared to non-IMH counterparts [20, 26].

Gestational hypertension, preeclampsia and eclampsia

Nine studies investigated the association of maternal IMH and gestational hypertension (HTN), preeclampsia and eclampsia [6, 11, 14, 16, 20, 22, 25, 26, 31]. Neither preeclampsia nor eclampsia were associated with IMH diagnosed in first or second trimesters of pregnancy; in addition, all the above studies except for two [6, 11] found no significant association between maternal IMH and gestational HTN. Gong et al. (2019) however reported that IMH identified in the second trimester was associated with increased risk of only gestational HTN, particularly among women with BMI< 25 kg/m^2, (adjusted OR: 4.2, 95% CI: 1.61–10.96)[6]. Moreover, Su et al. (2019), showed that IMH was associated with a 2.2-fold increased risk of gestational HTN (adjusted OR: 2.2, 95% CI: 1.28–3.82) [11].

Placental mediated complications

Of 8 studies [6, 11, 14, 16, 20, 25, 26, 31] that assessed the association between maternal IMH and placenta abruption, all except one [26], showed no association between IMH and placenta abruption.

Breech presentation

Two studies assessed the risk of breech presentation in mothers with IMH [6, 23] and one [23] reported increased risk of breech presentation in women diagnosed with IMH in the first trimester of pregnancy (adjusted OR: 4.7, 95% CI: 1.1–19).

Others

Moreover, there were no associations between maternal IMH and other adverse feto-maternal outcomes, including cesarean section [14], miscarriage [6, 20, 27], placenta previa [11, 20, 31], maternal weight gain >20 kg [25], fetal deaths [27], fetal loss [16, 27, 31] or IUGR [26] among studies included.

Neonatal outcomes

Macrosomia and LGA

Among studies included, 6 examined the association between IMH and macrosomia [6, 11, 14, 20, 26, 27]; 50% of these studies showed positive associations, indicating that the IMH diagnosed in the first [20], second [6] and < 20 weeks of gestation [11] was associated with around 1.5-fold increased risk of macrosomia. Furthermore, 2 other studies showed an increased risk of LGA and among IMH women in the second trimester (OR: 2.088, 95% CI: 1.193–3.654) [28] and significant higher birthweight [24] in the first half of pregnancy.

SGA

Six studies assessed the risk of SGA among women diagnosed with IMH [11, 15, 24, 27, 28, 31], and Of just one [27] demonstrated that IMH was related to SGA (adjusted OR: 3.55, 95% CI:1.01–12.83). This study also showed that isolated hypothyroxinemia was associated with

fetal distress (adjusted OR:2.95, 95% CI:1.08–8.05) and musculoskeletal malformations (adjusted OR:9.12, 95% CI:1.67– 49.70) [27].

Others

However, IMH was not associated with other neonatal outcomes including NICU admission [14, 16], low Apgar score [14, 15], umbilical artery blood pH <7 [14], RDS [14], necrotizing enterocolitis [14, 16], intraventricular haemorrhage [14, 16], major malformations [14, 16, 27, 31], perinatal mortality and neonatal death [14, 16, 20, 27, 31] or neurodevelopmental disturbances [27].

Discussion

The results of this systematic review shows that the relationship between maternal isolated hypothyroxinemia and feto-maternal and neonatal outcomes is still surrounded by many controversies, as shown by the conflicting results of studied assessed; while some studies have shown associations between IMH and adverse outcomes, others documented conflicting findings.

Lack of maternal thyroxine, in the absence of TSH elevation is one of the important thyroid dysfunctions during pregnancy. Although the exact underlying pathophysiology of IMH has not been completely understood, emerging evidence shows that iodine deficiency during pregnancy plays a crucial role in the etiology of IMH. In this respect, in iodine deficient mothers, the thyroid gland shifts its secretion from T4 to T3 to maintain iodine; consequently, IMH is more prevalent in iodine deficiency [9]. However, other novel factors, including exposure with environmental pollutants which may activate the hepatic glucuronidation, competitive inhibition of sodium iodine symporter and binding to the nuclear thyroid hormone receptor [33-36], obesity leading to increased peripheral deiodination [37-41], iron deficiency

due to reduced activity of the heme-dependent thyroid [42-45], peroxidase antibodies [21] and pro/antiangiogenic factors [46] are associated with increased risk of IMH.

Some data suggest that IMH may be involved in the increased risk of adverse pregnancy outcomes.

Thyroid hormones act directly, through anabolic effects on fetal metabolism and induce fetal oxygen consumption. These hormones also act indirectly by controlling the bioavailability and effectiveness of insulin-like growth factors and catecholamines, which both have important effect of fetal growth and development [47]. In addition, higher insulin resistance index was reported in euthyroid pregnant women with low fT4 levels, which may potentially associate with to GDM [48, 49]. This situation can further lead to an increase in circulating glucose leading to a higher placental transfer of glucose to the fetus and subsequently to fetal weight gain [50, 51]. Moreover, higher BMI has been reported in pregnant women with IMH in many studies [28, 37, 52-54], which may lead to decreased thyroid function capacity [54]. Therefore, maternal obesity may have a mediating effect between IMH and macrosomia [6]. In addition, oxytocin and vasopressin, two hormones stimulating uterine contractions are increased among women with lack of thyroid hormones [55, 56] and may play a role in the onset of labor. However, there are hypotheses suggesting that lack of thyroid hormones may decrease adequate fetal movement, essential for cephalic position and adequate umbilical cord length and has been associated with breech position [23].

As shown in the present systematic review, the prevalence of IMH among studies reviewed had a wide range from 1 to 18 percent. Despite the American Thyroid Association's recommendation about IMH detection being based on normal maternal TSH in conjunction with FT4 in the lower 5th or 10th percentile of the reference range [57], there is strong controversy over the identification of IMH among studies included herein. In this respect, different fT4 and TSH threshold pregnancy-specific reference ranges values as well as different

laboratory assays were used. In addition, iodine status, autoimmunity status, as well as variation in ethnicity of population significantly affect the prevalence of IMH. Furthermore, no consistency was observed about the time of IMH definition which increased variability in data. Results of studies focusing on the association between IMH and risk of adverse pregnancy outcomes are clearly insufficient; unfortunately, there is no consensus regarding the effect of IMH on risk of adverse feto-maternal and neonatal outcomes and most of the current evidence has been derived from studies with small sample sizes.

In this respect, since the most adverse pregnancy outcomes are generally scarce, this possibly leads to underpowered analyses [9]. Furthermore, as stated before, diagnostic criteria among studies were very heterogonous, particularly in terms of fT4 lower threshold and prespecified TSH normal range.

Moreover, time of IMH diagnoses among pregnant women varied in the first and/or second trimester separately, first half of pregnancy, and even up to 32 weeks of gestations, which leads to this hypothesis that IMH trimester-specific diagnosis may have had different effect on pregnancy outcomes.

However, another potential reason of this controversies may be related to iodine sufficient and Thyroid peroxidase antibody (TPOAb) positive status of the population. There are some data showing that iodine insufficiency [58, 59], as well as TPOAb-positivity [60-62] in pregnant women, independent of thyroid hormones, may related to adverse pregnancy outcomes which may consequently confound the estimation of the adverse pregnancy risk in IMH diagnosed mothers. In addition, due to unadjusted potential confounders in the most of the analyses, the findings should be interpreted with caution.

However, of all the outcomes, researchers paid particular attention to the preterm birth. Also, the results of original studies were conflicting. In addition, there are three published meta-analysis that evaluated the risk of preterm birth in women diagnosed with IMH [63-65];

interestingly, these meta-analyses also had conflicting findings too. However, However, in a recent published meta-analysis on unpublished data sets and published cohorts, the consortium on thyroid and pregnancy study group on preterm birth reported that among pregnant women without overt thyroid disease, isolated hypothyroxinemia were significantly associated with higher risk of preterm birth (pooled OR: 1.46, 95% CI: 1.12-1.90) [65].

However, it is assumed that iatrogenic or spontaneous preterm birth should be analyzed and interpreted separately due to differences in the underlying etiology [21].

There are some limitations to this systematic review. First, this systematic review was able to evaluate only what was reported in studies included, not what may in fact have been done. Second, in this systematic study, only the short term adverse pregnancy outcomes were evaluated and the long-term outcome related to the future neurodevelopment of children were not examined. In addition, publications only written in English were included; high-quality articles written in other languages might have been missed. However, It has been shown that restricting the search for systematic reviews to English language only does not affect the quality of most reviews [66].

Conclusion

In conclusion, many major uncertainties remain about the effect of IMH on pregnancy complications. Publication about the association between maternal hypothyroxinemia and risk of adverse feto-maternal and neonatal complications are insufficient and controversial. However, according to the available literature, there is not conclusive evidence supporting about the treatment of IMH in pregnancy with LT4 or iodine. In addition, since there is some evidence reported that IMH identified in the second trimester was associated with increased risk of adverse pregnancy outcome [6, 20, 28], thyroid function follow-up during the second trimester is suggested, even if thyroid function is normal during the first trimester. however, the further well-designed interventional studies are needed to show whether treatment can

decrease adverse outcomes. Well-designed community-based studies with large sample sizes, control of important confounders such as of iodine status of population and maternal TPOAb status, using consistent criteria for IMH definition with pre-specified thresholds of thyroid hormones and adverse pregnancy outcomes and precise timing of serum collection is warranted to eventually clarify the precise impact of this disorder on pregnancy complications.

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Disclosure

The authors declare that they have no competing interests.

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Fingers legends

Figure 1: Flow chart of the literature search for the systematic review.

Figure 2: Risk of bias in Cohort studies.

Table legend

Table 1. Characteristics of studies included in the Systematic review

Table 2. Quality assessment of included studies using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Supplementary Table

Table S1. Search strategy

588 Table 1. Characteristics of studies included in the Systematic review

First author (year); Country	Study design	Gestational age of IMH assessment	IMH definition	Sample size	Prevalence of IMH (%)	Significant associations between IMH and feto-maternal outcomes	Significant associations between IMH and neonatal outcomes	No association
Pop et al. (2004); Netherlands	prospective community-based cohort	First trimester and 24-32 weeks of gestation	TSH: 0.15–2.0 mIU/L) fT4 <10th percentiles (12.4 pmol/L)	1361	9.9%	*First trimester:* **Breech presentation**	-	-
Casey et al. (2007); USA	prospective cohort	< 20 weeks of gestation	-TSH: 2.5th - 97.5th (0.08 –2.99 mU/L) -fT4 <2.5th (0.86 ng/dL)	17298	1.3%	-	-	**feto-maternal outcomes:** **Gestational** HTN, Severe preeclampsia, Diabetes, Placental abruption, Preterm Delivery ≤ 36 w, Preterm Delivery ≤ 34 w, Preterm Delivery ≤ 32 w, C/S. **neonatal outcomes:** VLBW, LBW, macrosomia, NICU, 5-Min Apgar score ≤3, umbilical artery blood pH <7.0, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, major malformations, fetal death, neonatal death
Cleary-Goldman et al., (2008); USA	prospective cohort	First and second trimesters	-TSH: 2.5th-97.5th percentiles -fT4 < 2.5th (0.86 ng/dL)	10990	*First trimester:* 2.1% *Second trimester* 2.3%	*First trimester:* **Preterm labor**[#] *Second trimester* **GDM**[#]**.**	*First trimester:* **Macrosomia**[#]	**feto-maternal outcomes:** *First trimester:* Miscarriage, Gestational HTN, Preeclampsia, GDM, Placenta previa, Placental abruption, Preterm PROM, Preterm delivery *Second trimester* Miscarriage, Gestational HTN, Preeclampsia, Placenta previa, Placental abruption, Preterm labor, Preterm PROM, Preterm delivery **neonatal outcomes:** *First trimester:* LBW, Perinatal mortality *Second trimester* LBW, Macrosomia, perinatal mortality
Hamme et al., (2009); Canada	prospective cohort	Second trimester	-TSH: 0.15–4.0 mU/L -f T4 ≤ 10th (8.5 pmol/L)	879	10.1%	-	-	**feto-maternal outcomes:** preterm delivery **neonatal outcomes:** SGA, Apgar score < 7: 0 vs. 0
Mannisto et al,. (2010); Finland	prospective population-based cohort	First trimester	-TSH 5th – 95th percentiles -fT4< 5th (11.96pmol/L)	5805	3.9%	-	-	**feto-maternal outcomes:** Gestational HTM, Preeclampsia, GDM, Placental abruption, Maternal weight gain >20 kg

Su et al., (2011); China	prospective population-based cohort	< 20 weeks of gestation	-TSH 5th – 95th percentiles fT4< 5th (11.96 pmol/L)	1017	2.9%		**fetal distress**[¶] **SGA**[¶] **Musculoskeletal malformations**[¶]	**feto-maternal outcomes:** Spontaneous abortions, Fetal deaths, Fetal loss, Medically induced labor, Preterm births **neonatal outcomes:** Neural malformations, Eye, ear, face malformations, Circulation malformations, Reproductive malformations, Other malformations, Total malformations, LBW, Macrosomia, Neonatal death, Poor vision development, Hearing dysplasia, Neurodevelopmental delay
Korevaar et al. (2013); Netherlands	prospective population-based cohort	Early pregnancy	-TSH: 2.5th - 97.5th percentiles -fT4 <2.5th (10.4 pmol/L)	5971	2.6%	**Preterm delivery <37 w[λ], Preterm delivery <34 w[λ], Spontaneous preterm delivery <37 w[λ], Spontaneous preterm delivery <34 w[λ], PROM <37 w[λ], Spontaneous PROM <37 w[λ]**	-	-
Breathnach et al. (2013); Ireland	Cohort	< 20 weeks of gestation	-TSH 2.5th – 97.5th percentiles -fT4 < 2.5th	904	IMH: 1.9%	**Placenta abruption** **GDM**[†]	-	**feto-maternal outcomes:** Gestational HTN, Preterm PROM, Preterm Birth, IUGR **neonatal outcomes:** Macrosomia
Medici et al., (2014); Netherlands	prospective population-based cohort	Early pregnancy	-TSH 2.5th - 97.5th percentiles -fT4 < 2.5th (10.4 pmol/L)	5153	NM	-	-	**feto-maternal outcomes:** Hypertensive Disorders overall, gestational HTN, preeclampsia
Ong et al., (2014); Australia	Cohort	First trimester	-TSH: 2.5th – 97.5th percentiles (0.02–2.15 mU/L) -fT4 < 10th (11.5 pmol/L)	2411	10.1%	-	-	**feto-maternal outcomes:** placenta previa, placental abruption, preeclampsia, pregnancy loss after 20 w, preterm labor, preterm birth **neonatal outcomes:** SGA, Neonatal death, birth defects
Leon et al., (2015); Spain	prospective population-based cohort	< 24 weeks of gestation	-TSH 5th – 95th -fT4 < 5th	2170	2.3%	-	**higher birth weight** [ð]	**feto-maternal outcomes:** Preterm delivery **neonatal outcomes:** SGA, LGA
Zhu et al., (2018); China	prospective population-based cohort	First and second trimesters	-TSH 2.5th – 97.5th percentiles -fT4 < 2.5th	3178	*First trimester:* 2.4% *Second trimester* 2.4%	-	*Second trimester* **LGA**[§]	**neonatal outcomes:** *First trimester:* SGA, LGA *Second trimester* SGA
Rosario et al., (2018); Brazil	prospective cohort	First trimester	Three criteria: -TSH: 0.1- 2.5 mIU/l and 1. fT4 < 5th (0.86 ng/dL)	596	*Criteria 1:* 4.3% *Criteria 2:* 9% *Criteria 3:* 7%			**feto-maternal outcomes:** *Criteria 1:* Gestational HTN, GDM, placental abruption, Preterm delivery <37 w, Preterm delivery <34 w, Fetal loss

			2. fT4 < 10th (0.92 ng/dL) 3. Total T4 < 7.8 ng/dL					*Criteria 2:* Gestational HTN, GDM, placental abruption, Preterm delivery <37 w, Preterm delivery <34 w, Fetal loss *Criteria 3:*[€] Gestational HTN, GDM, placental abruption, Preterm delivery <37 w, Preterm delivery <34 w, Fetal loss **neonatal outcomes:** *Criteria 1:* Birth weight<2500 g, Birth weight<1500 g, NICU, Ventilation > 24 h, NEC, IVH grade 3 or 4, Malformations, Neonatal death *Criteria 2:* Birth weight<2500 g, Birth weight<1500 g, NICU Ventilation > 24 h, NEC, IVH grade 3 or 4, Malformations, Neonatal death *Criteria 3:* Birth weight<2500 g, Birth weight<1500 g, NICU, Ventilation > 24 h, NEC, IVH grade 3 or 4, Malformations, Neonatal death
Gong et al. (2019); China	prospective cohort	First and second trimester	-TSH 2.5th–97.5th percentile -fT4 <2.5th (13.35 pmol/L)	3398	*First trimester:* 7.3% *Second trimester:* 18.8%	*Second trimester* **gestational HTN** [µ]	**Macrosomia**	**feto-maternal outcomes:** *First trimester:* Miscarriage, gestational HTN, eclampsia, GDM, placental abruption, PROM, preterm delivery, breech delivery *Second trimester:* Miscarriage, eclampsia, GDM, placental abruption, PROM, preterm delivery, breech delivery, **neonatal outcomes:** *First trimester:* LBW, Macrosomia *Second trimester:* LBW
Su et al. (2019);China	hospital-based Retrospective cohort	< 20 weeks of gestation	-TSH: 0.06–3.83 mIU/L -fT4 < 2.5th (1.01ng/dL)	8173	4.18%	**Gestational HTN**[‡]	**Macrosomia** [‡]	**feto-maternal outcomes:** GDM, Preeclampsia, preterm delivery, placenta previa, placenta abruption **neonatal outcomes:** LBW, SGA, LGA
Huang et al. (2019); China	cohort study	First trimester	-TSH: 2.5th–97.5th -fT4 < 2.5th (0.716 ng/dL)	1,779	2%	-	-	GDM
Yang et al. (2020); China	prospective cohort	First trimester	-TSH: 2.5th–97.5th (0.03-3.64mU/L) -FT4 < 2.5th (11.7-pmol/L)	41,911	2.3%	**preterm birth** [ϑ]	-	very preterm birth

IMH: Isolated maternal hypothyroxinemia. SCH: subclinical hypothyroidism; SGA: small for gestational age; LGA: large for gestational age; GDM: gestational diabetes mellitus; PROM: Premature rupture of membranes; LBW: low birth weight; IUGR: Intrauterine growth retardation; PIH: pregnancy induced hypertension; C/S: cesarean section; NEC: Necrotizing enterocolitis; IVH: Intraventricular hemorrhage; HTN: hypertension; NM: Not mentioned.
Bold indicates statistical significance, P < 0.05.

[‡] Adjusted for BMI, health insurance, gravidity, parity, family history of chronic disease and newborn sex

€: Compared to TT4 ≥ 7.8

Adjusted for maternal age, prior pregnancy, BMI, and study site.

¶ Adjusted for maternal age, parity, and BMI

ð Adjusted for cohort, maternal age, country of origin, employed during pregnancy, maternal and paternal height, maternal BMI, parity, weight gain during pregnancy, smoking during pregnancy, and season of delivery.

§ Adjusted for maternal age, paternal age, pre-pregnant BMI, gestational age, metabolic dysfunctions, parity, birth type, GWG and fetal gender

λ Adjusted for gestational age at blood sampling, maternal age, smoking, SES, parity, ethnicity, maternal BMI, maternal height and child sex

† Adjusted for maternal smoking status and body mass index

♈Adjusted for maternal age, maternal education level, residence, pre-pregnancy BMI, previous adverse pregnancy outcomes, parity, pregnancy-specific stress; TSH and FT4 in early pregnancy

♉Adjusted for maternal age, BMI, parity, education level, fetal sex, TPOAb status, GDM.

µ adjusted for smoking, passive smoking, alcohol, GW, AC, SBP, DBP, HR, TSH, maternal education, social-economic status, multiparous

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605 Table 2. Quality assessment of included studies using the Newcastle-Ottawa Quality Assessment Form for
606 Cohort Studies

Author, years	SELECTION				COMPARABILITY	Outcome			Total scores	quality
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts		
Pop et al., (2004)	**1**	**1**	**1**	**1**	**0**	**0**	**1**	**1**	**6**	Moderate
Hamme et al., (2009)	**0**	**0**	**1**	**1**	**2**	**1**	**1**	**1**	**7**	High
Gong et al., (2019)	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**9**	High
Su et al., (2019)	**0**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**6**	Moderate
Casey et al., (2007)	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**9**	High
Korevaar et al., (2013)	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**9**	High
Medici et al., (2014)	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**9**	High
Rosario et al., (2018)	**0**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**6**	Moderate
Cleary-Goldman et al., (2008)	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**9**	High
Leon et al., (2015)	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**9**	High
Su et al., (2011)	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**9**	High
Mannisto et al., (2010)	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**9**	High
Zhu et al., (2018)	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**9**	High
Ong et al., (2014)	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**8**	High
Breathnach et al., (2013)	**0**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**6**	Moderate
Huang et al., (2019)	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**9**	High
Yang et al. ,(2020)	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**9**	High

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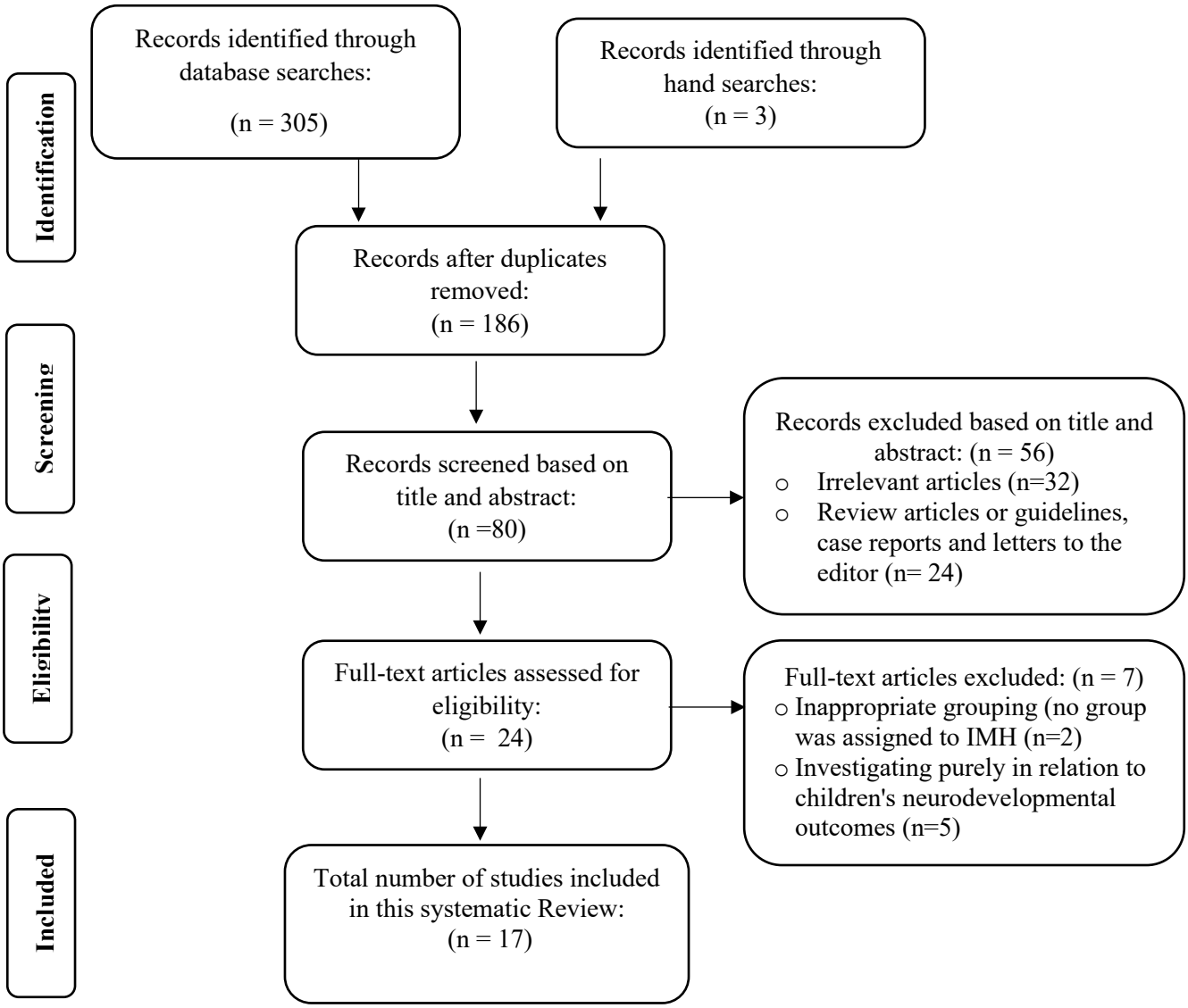

Figure 1: Flow chart of the literature search for the systematic review.

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type	Authors, years	Was selection of exposed and non-exposed cohorts drawn from the same population?	Can we be confident in the assessment of exposure?	Can we be confident that the outcome of interest was not present at start of study?	Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?	Can we be confident in the assessment of the presence or absence of prognostic factors?	Can we be confident in the assessment of outcome?	Was the follow up of cohorts adequate?
Cohort	Pop et al. (2004)							
	Hamme et al., (2009)							
	Gong et al. (2019)							
	Su et al. (2019)							
	Casey et al. (2007)							
	Korevaar et al. (2013)							
	Medici et al., (2014)							
	Rosario et al., (2018)							
	Cleary-Goldman et al., (2008)							
	Leon et al., (2015)							
	Su et al., (2011)							
	Mannisto et al., (2010)							
	Zhu et al., (2017)							
	Ong et al., (2014)							
	Breathnach et al. (2013)							
	Huang et al., (2019)							
	Yang et al. ,(2020)							

B

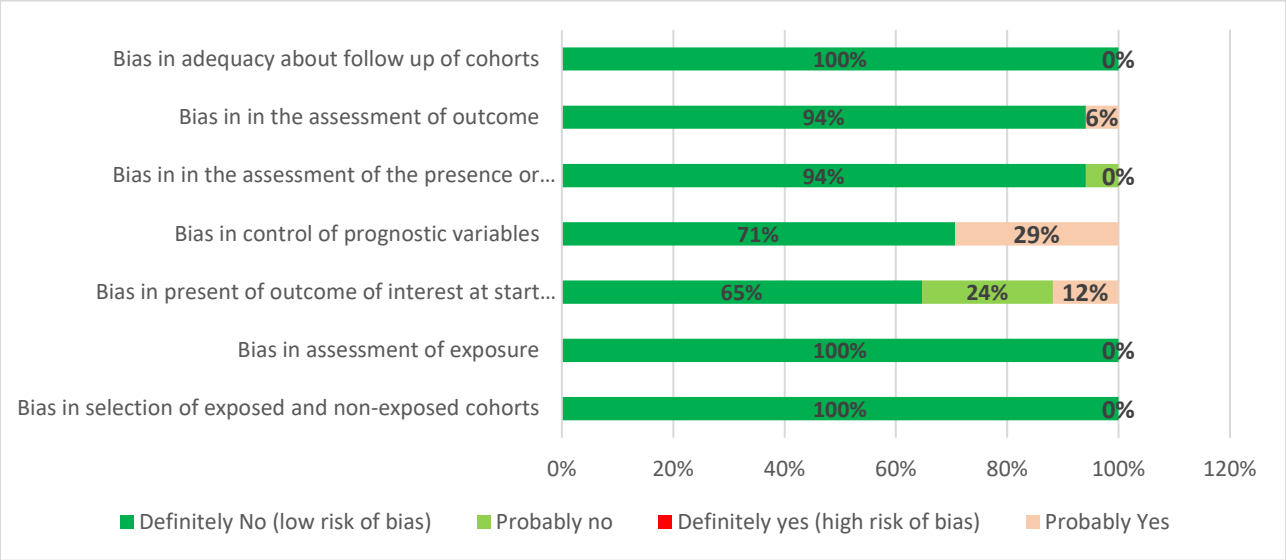

Figure 2: Risk of bias in Cohort studies

636 Table S1. Search strategy.

Database	Search strategy
PubMed	121 results: ((("isolated hypothyroxinemia"[Title/Abstract] OR "hypothyroxinemia")[Title/Abstract]) AND (("pregnancy"OR "pregnant women"[Title/Abstract] OR "maternal"[Title/Abstract] OR "gestational")[Title/Abstract])) AND (("adverse pregnancy outcomes"[Title/Abstract] OR "pregnancy outcomes"[Title/Abstract] OR "pregnancy complications"[Title/Abstract] OR "abortion"[Title/Abstract] OR "miscarriage "[Title/Abstract] OR "pregnancy loss"[Title/Abstract] OR "fetal death"[Title/Abstract] OR "stillbirth"[Title/Abstract] OR "preeclampsia"[Title/Abstract] OR "gestational hypertension"[Title/Abstract] OR "PIH"[Title/Abstract] OR "gestational diabetes"[Title/Abstract] OR "hemorrhage"[Title/Abstract] OR "postpartum hemorrhage"[Title/Abstract] OR "PPH"[Title/Abstract] OR "Placenta abruption"[Title/Abstract] OR "placenta previa"[Title/Abstract] OR "preterm"[Title/Abstract] OR "premature rupture of membrane"[Title/Abstract] OR "PROM"[Title/Abstract] OR "Intra uterine growth restriction"[Title/Abstract] OR "IUGR"[Title/Abstract] OR "small for gestational age"[Title/Abstract] OR "Low birth weight"[Title/Abstract] OR "LBW"[Title/Abstract] OR "oligohydramnios"[Title/Abstract] OR "Apgar"[Title/Abstract] OR "fetal distress"[Title/Abstract] OR "neonatal distress"[Title/Abstract] OR "RDS"[Title/Abstract] OR "neonatal death"[Title/Abstract] OR "neonatal mortality"[Title/Abstract] OR "neonatal admission"[Title/Abstract] OR "NICU admission"[Title/Abstract] OR "malformation"[Title/Abstract] OR "anomalies")[Title/Abstract])
Scopus	184 results (TITLE-ABS-KEY (("isolated hypothyroxinemia" OR "hypothyroxinemia ") AND ("pregnancy" OR "pregnant women" OR "maternal" OR "gestational")) AND TITLE-ABS-KEY (("pregnancy" OR "pregnant women" OR "maternal" OR "gestational")) AND TITLE-ABS-KEY (("adverse pregnancy outcomes" OR "pregnancy outcomes" OR "pregnancy complications" OR "abortion" OR "miscarriage " OR "pregnancy loss" OR "fetal death" OR "stillbirth" OR "preeclampsia" OR "gestational hypertension" OR "PIH")) OR TITLE-ABS-KEY (("gestational diabetes" OR "hemorrhage" OR "postpartum hemorrhage" OR "PPH" OR "Placenta abruption" OR "placenta previa" OR "preterm" OR "premature rupture of membrane" OR "PROM" OR "Intra uterine growth restriction" OR "IUGR")) OR TITLE-ABS-KEY (("small for gestational age" OR "Low birth weight" OR "LBW" OR "oligohydramnios" OR "Apgar" OR "fetal distress" OR "neonatal distress" OR "RDS" OR "neonatal death" OR "neonatal mortality" OR "neonatal admission" OR "NICU admission")) OR TITLE-ABS-KEY (("malformation" OR "anomalies"))) AND DOCTYPE (ar) AND PUBYEAR > 2018 AND (LIMIT-TO (LANGUAGE , "English"))

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