Isolated Maternal Hypothyroxinemia and Adverse Pregnancy Outcomes: A Systematic Review

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Abstract

Background

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. This systematic review aimed to investigate the association between Isolated Maternal hypothyroxinemia (IMH) and adverse pregnancy outcomes.

Method:

PubMed, Scopus and Web of science were searched for retrieving observational studies published up to September 2019, investigating the association of IMH with adverse pregnancy outcomes. From a total of 267 articles, 15 met our eligibility criteria and were used for the purpose of the present study.

Results

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.

Conclusions

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.

Background

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, 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 free thyroxine (fT4) concentration with a maternal thyroid-stimulating hormone (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 most common etiologies is iodine deficiency (7, 9), which could potentially affect both mother and child health. However, 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 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). The systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (17).

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

Quality Assessment And Risk Of Bias

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

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

Results

Search results, study selection and characteristics

The search strategy yielded 267 potentially relevant articles. Based on selection inclusion criteria, 18 articles were identified for further full-text assessment; finally, we included 15 articles, which included data of 68956 pregnant women. Table 1 presents a summary of studies, assessing adverse pregnancy outcomes among women with IMH.

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 (%)	Feto-maternal outcome in women with vs. without IMH (%)	Neonatal outcome in women with vs. without IMH (%)	Significant associations between IMG and adverse outcomes
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%	**Breech presentation: 9 vs. 2**	-	First trimester: **Breech presentation**: **OR : 4.7 (95% CI:1.1–19)**
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%	gestational HTN: 8 vs.9; Severe preeclampsia: 4 vs 5; Diabetes: 4 vs 5; Placental abruption: 0.4 vs. 0.3; Preterm Delivery ≤ 36 w: 6 vs. 6; Preterm Delivery ≤ 34 w: 2 vs. 2.5; Preterm Delivery ≤ 32 w: 1 vs. 1; C/S: 25 vs. 25	VLBW: 0.4 vs. 0.6; LBW: 3 vs. 6; macrosomia: 13 vs. 11; NICU: 1.3 vs. 2.2 ; 5-Min Apgar score ≤ 3: 0 vs. 0.7; umbilical artery blood pH < 7.0: 3 vs. 1.7 respiratory distress syndrome: 1.3 vs. 1.5; necrotizing enterocolitis: 0 vs. 0.1 intraventricular hemorrhage: 0.4 vs. 0.1; major malformations: 0.4 vs. 1.1; fetal death: 0 vs. 0.5; neonatal death: 0 vs. 0.2	-
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: Miscarriage: 0 vs. 0.6; Gestational HTN: 0.4 vs. 5.5; Preeclampsia: 1.3 vs. 1; GDM: 6.2 vs. 3; Placenta previa: 0.4 vs. 0.4; Placental abruption: 1.8 vs. 0.9; **Preterm labor: 8.4 vs. 6.1**; Preterm PROM: 1.3 vs. 1.4; Preterm delivery: 9.3 vs. 7.2 Second trimester Miscarriage: 0 vs. 0.6; Gestational HTN: 9.5 vs. 5.4; Preeclampsia: 1.7 vs. 1; **GDM: 7.4 vs. 3**; Placenta previa: 0 vs. 0.4; Placental abruption: 0.4 vs. 0.9; Preterm labor: 7 vs. 6.2; Preterm PROM: 1.7 vs. 1.4; Preterm delivery: 9.1 vs. 7.3	First trimester: LBW: 2.7 vs. 4.2; **Macrosomia: 16.9 vs. 8.9**; Perinatal mortality: 0.4 vs. 0.3 Second trimester LBW: 4.6 vs. 4.2; Macrosomia: 13.6 vs. 8.9; perinatal mortality: 0 vs. 0.3	First trimester: **Preterm labor**: **OR: 1.6 (95% CI: 1.00–2.62);** **Macrosomia**: **OR 1.97 (95% CI: 1.37–2.83).** Second trimester **GDM: OR: 1.7 (95% CI: 1.02–2.84).**

First author (year); Country	Study design	Gestational age of IMH assessment	IMH definition	Sample size	Prevalence of IMH (%)	Feto-maternal outcome in women with vs. without IMH (%)	Neonatal outcome in women with vs. without IMH (%)	Significant associations between IMG and adverse outcomes
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%	preterm delivery: 5.2 vs. 7.2	SGA: 5.6 vs. 7.6 Apgar score < 7: 0 vs. 0	-
Mannisto et al,. (2010); Finland	prospective population-based cohort	First trimester	-TSH 5th – 95th percentiles -fT4 < 5th (11.96 pmol/L)	5805	3.9%	Gestational HTM: 3.3 vs. 3; Preeclampsia: 1.4 vs. 1.9 GDM: 0 vs. 1; Placental abruption: 0.5 vs. 0.5; Maternal weight gain ≥20 kg: 8.7 vs. 9.8	-	-
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%	Spontaneous abortions: 0 vs. 1.3; Fetal deaths: 0 vs. 0.5; Fetal loss: 0 vs. 2.2; Medically induced labor: 0 vs. 0.5; Preterm births: 2.3 vs. 4.1	Neural malformations: 0 vs. 0.4; Eye, ear, face malformations: 0 vs. 0.6; Circulation malformations: 4.7 vs. 1.3; Reproductive malformations: 0 vs. 0.1; **Musculoskeletal malformations: 4.7 vs. 0.7**; Other malformations: 0 vs. 1.2; Total malformations: 4.7 vs. 4.4; **Fetal distress: 11.6 vs. 1.7**; LBW: 2.3 vs. 1.8; Macrosomia: 7 vs. 9.9; **SGA: 7 vs. 2.3**; Neonatal death: 0 vs. 0.1; Poor vision development: 2.3 vs. 1; Hearing dysplasia: 0 vs. 0.5; Neurodevelopmental delay: 0 vs. 0.2	**fetal distress**: **OR:2.95 (95% CI:1.08–8.05)** **SGA: OR: 3.55 (95% CI:1.01–12.83)** **Musculoskeletal malformations**: **OR = 9.12 (95% CI:1.67– 49.70)**

First author (year); Country	Study design	Gestational age of IMH assessment	IMH definition	Sample size	Prevalence of IMH (%)	Feto-maternal outcome in women with vs. without IMH (%)	Neonatal outcome in women with vs. without IMH (%)	Significant associations between IMG and adverse outcomes
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: 10.3 vs. 4.7; Preterm delivery < 34 w: NM; Spontaneous preterm delivery < 37 w: NM; Spontaneous preterm delivery < 34 w: NM; PROM < 37 w: 7.2 vs. 3.7; Spontaneous PROM < 37 w: NM**	-	**Preterm delivery < 37 w:** **OR = 2.54 (95% CI: 1.42– 4.54)λ** **Preterm delivery < 34 w:** **OR = 3.56 (95% CI: 1.50–8.43) λ** **Spontaneous preterm delivery < 37 w: OR = 3.44 (95% CI: 1.76–6.70) λ** **Spontaneous preterm delivery < 34 w: OR = 4.21 (95% CI: 1.34 – 13.3) λ** **PROM < 37 w: OR = 2.35 (95% CI: 1.18–4.69) λ** **Spontaneous PROM < 37 w:** **OR = 2.74 (95% CI: 1.30 – 5.75) 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: NM;** Gestational HTN: NM; Preterm PROM: NM; **GDM: NM;** Preterm Birth: NM; IUGR: NM	Macrosomia: NM	**Placenta abruption: P-value: 0.04** **GDM: P-value: 0.001**
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	Hypertensive Disorders overall: 6.4 vs. 6.2; gestational HTN: 4.7 vs. 4; preeclampsia: 3.8 vs. 2.5	-	-
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%	placenta previa: NM; placental abruption: NM preeclampsia: NM; pregnancy loss after 20 w: NM; preterm labor: NM; preterm birth: NM	SGA: NM Neonatal death: NM; birth defects: NM	-
Leon et al., (2015); Spain	prospective population-based cohort	< 24 weeks of gestation	-TSH 5th – 95th -fT4 < 5th	2170	2.3%	Preterm delivery: NM	**Mean birth weight: NM;** SGA:NM; LGA: NM	**higher birthweight**: **β = 109 (95% CI: 31–187)**

First author (year); Country	Study design	Gestational age of IMH assessment	IMH definition	Sample size	Prevalence of IMH (%)	Feto-maternal outcome in women with vs. without IMH (%)	Neonatal outcome in women with vs. without IMH (%)	Significant associations between IMG and adverse outcomes
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%	-	First trimester: SGA:NM; LGA:NM Second trimester SGA:NM; **LGA:NM**	Second trimester **LGA**: **OR = 2.088 (95% CI:1.193–3.654)****
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) 2. fT4 < 10th (0.92 ng/dL) 3. Total T4 < 7.8 ng/dL	596	Criteria 1: 4.3% Criteria 2: 9% Criteria 3: 7%	Criteria 1: Gestational HTN: 7.7 vs. 8.6; GDM: 11.5 vs. 10.3; placental abruption: 0 vs. 0.3; Preterm delivery < 37 w: 3.8 vs. 2.7; Preterm delivery < 34 w: 0 vs. 0.9; Fetal loss: 0 vs. 2.9 Criteria 2: Gestational HTN: 9.2 vs. 8.6; GDM: 11.1 vs. 10.3; placental abruption: 0 vs. 0.3; Preterm delivery < 37 w: 3.7 vs. 2.7; Preterm delivery < 34 w: 1.8 vs. 0.9; Fetal loss: 3.7 vs. 2.9 Criteria 3:[€] Gestational HTN: 9.5 vs. 9; GDM: 12 vs. 10.8; placental abruption: 0 vs. 0.3; Preterm delivery < 37 w: 4.7 vs. 2.8; Preterm delivery < 34 w: 2.4 vs. 0.9; Fetal loss: 4.7 vs. 2.8	Criteria 1: Birth weight < 2500 g: 3.8 vs. 5.9; Birth weight < 1500 g: 0 vs. 1.4; NICU: 0 vs. 2 Ventilation > 24 h: 0 vs. 2; NEC: 0 vs. 0.2 ; IVH grade 3 or 4: 0 vs. 0; Malformations: 0 vs. 0.9 ; Neonatal death: 0 vs. 0.5 Criteria 2: Birth weight < 2500 g: 3.7 vs. 5.9; Birth weight < 1500 g: 1.8 vs. 1.4; NICU: 1.8 vs. 2 Ventilation > 24 h: 1.8 vs. 2; NEC: 0 vs. 0.2; IVH grade 3 or 4: 0 vs. 0; Malformations: 1.8 vs. 0.9 ; Neonatal death: 0 vs. 0.5 Criteria 3: Birth weight < 2500 g: 4.7 vs. 5.9; Birth weight < 1500 g: 2.3 vs. 1.6; NICU: 2.3 vs. 2; Ventilation > 24 h: 2.3 vs. 2; NEC: 0 vs. 0.2; IVH grade 3 or 4: 0 vs. 0; Malformations: 0 vs. 1; Neonatal death: 0 vs. 0.5	-

First author (year); Country	Study design	Gestational age of IMH assessment	IMH definition	Sample size	Prevalence of IMH (%)	Feto-maternal outcome in women with vs. without IMH (%)	Neonatal outcome in women with vs. without IMH (%)	Significant associations between IMG and adverse outcomes
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%	First trimester: Miscarriage: 5.7 vs. 7.4; gestational HTN: 4.7 vs. 3; eclampsia: 0.9 vs. 0.6; GDM: 11.3 vs. 15.9; placental abruption: 0 vs. 0.2; PROM: 0 vs. 0.5; preterm delivery: 1.9 vs. 3.2; breech delivery: 6.6 vs. 4.2; Second trimester Miscarriage: 0.8 vs. 0.8; **gestational HTN: 8.3 vs. 3.5;** eclampsia: 0 vs. 1.2; GDM: 19 vs. 14.8; placental abruption: 0 vs. 0.4; PROM: 1.7 vs. 0.6; preterm delivery: 3.3 vs. 3.3; breech delivery: 4.1 vs. 3.3	First trimester: LBW: 1.9 vs. 2; Macrosomia: 14.2 vs. 10.5 Second trimester LBW: 1.7 vs. 2.5; **Macrosomia: 21.5 vs. 13.4**	**Second trimester** **gestational HTN: P-value: 0.019** **OR: 4.2 (95% CI: 1.61–10.97) μ** **Macrosomia: P-value: 0.024**
Su et al. (2019);China	hospital-based Retrospective cohort	< 20 weeks of gestation	-TSH: 0.06–3.83 mIU/L -fT4 < 2.5th (1.01 ng/dL)	8173	4.18%	GDM: 18.2% vs. 13.3%; gestational HTN: 5.9% vs. 2.8%; Preeclampsia: 1.2 vs. 0.9; preterm delivery: 4.7% vs. 4.2%; placenta previa: 1.2% vs. 0.4; placenta abruption: 0.9% vs. 0.8%	LBW: 3.2 vs. 2.7; Macrosomia: 9 vs. 5.8; SGA: 3.8 vs. 4.4; LGA:18.4 vs. 13.1	**gestational HTN**: **RR: 2.21 (1.28–3.82)*** **Macrosomia**: **RR: 1.64 (1.01–2.67)***

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, body mass index, and study site.

ð Adjusted for cohort, maternal age, country of origin, employed during pregnancy, maternal and paternal height, maternal body mass index, 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

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

Details of the quality assessment of studies included are presented in supplementary table 2. This assessment showed that 11 studies were classified as being of high quality (6, 14, 15, 20–27) and four had moderate quality (11, 16, 28, 29). In addition, cohort studies had a low risk of bias for selection of exposed and non-exposed cohorts, assessment of exposure, presence of outcome of interest at start of study, outcome assessment, and adequacy of follow up of cohorts; however, approximately 30% had a problem risk of bias in the domain of control of prognostic variables, 13% in existence of outcome at start of study and 7% in outcome evaluation (Supplementary Fig. 1).

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

Diagnostic criteria used in studies included were quite variable and heterogeneous. In this respect, in terms of TSH, 8 studies used population-derived 2.5th – 97.5th (6, 14, 20, 21, 24, 25, 27, 28) percentiles as the TSH reference interval for diagnosis and 3 studies used the population-derived of 5th – 95th percentiles (22, 23, 26). 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, 29). Regarding fT4, the cut point of fT4 also varied between studies. Three studies applied the population-derived ⩽10th percentile (15, 25, 29), Three studies used the population-derived ⩽5th percentile (22, 23, 26) and also Eight studies used the population-derived ⩽2.5th percentile (6, 11, 14, 20, 21, 24, 27, 28), and one study used the three criteria of the population-derived ⩽10th and ⩽5th percentiles as the fT4 cut point and also total T4 < 7.8 ng/dL for diagnosis of IMH (16).

Feto-maternal Outcomes

The association between IMH and feto-maternal outcomes, investigated by 14 studies (6, 11, 14–16, 20–26, 28, 29), had wide variations in amplitude of findings between studies included in this review. Regard this association, 11 studies examined the risk of preterm birth among women with IMH (6, 11, 14–16, 20–22, 25, 26, 28). The prevalence of preterm birth among women with IMH ranged between 2.3%-10.3%, although 90.9% of the studies included found no significant association between preterm birth and IMH, a prospective population-based cohort study with large sample size from Netherlands reported that maternal hypothyroxinemia 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). However, one study reported that IMH in the first trimester was associated with preterm labor (OR: 1.62, 95% CI: 1.00–2.62) without increasing the risk of preterm birth (20) and one (21) of four studies (6, 20, 21, 28) 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)

Of publications included, 6 evaluated the risk of GDM among women with hypothyroxinemia in first and second trimesters of pregnancy (6, 11, 16, 20, 23, 28) and reported that prevalence of GDM varied between 0-18.2% and 1-14.7% in women with and without IMH; of these studies, 4 found no association (6, 11, 16, 23), 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, 28).

Nine studies investigated the association of maternal IMH and gestational HTN, preeclampsia and eclampsia (6, 11, 14, 16, 20, 23–25, 28). 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). Of 8 studies (6, 11, 14, 16, 20, 23, 25, 28) that assessed the association between maternal IMH and placenta abruption, all except one (28), showed no association between IMH and placenta abruption. Two studies assessed the risk of breech presentation in mothers with IMH (6, 29) and one (29) 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).

Moreover, there were no associations between maternal IMH and other adverse feto-maternal outcomes, including cesarean Sect. (14), miscarriage (6, 20, 26), placenta previa (11, 20, 25), maternal weight gain ⩾20 kg (23), fetal deaths (26), fetal loss (16, 25, 26) or IUGR (28) among studies included.

Neonatal Outcomes

Among studies included, 6 examined the association between IMH and macrosomia (6, 11, 14, 20, 26, 28); 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) (27) and significant higher birthweight (22) in the first half of pregnancy. Six studies assessed the risk of SGA among women diagnosed with IMH (11, 15, 22, 25–27), and Of just one (26) 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) (26).

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, 25, 26), perinatal mortality and neonatal death (14, 16, 20, 25, 26), or neurodevelopmental disturbances (26).

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 showes 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, 31). 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 (32–35), obesity leading to increased peripheral deiodination (36–40), iron deficiency due to reduced activity of the heme-dependent thyroid (41–44), peroxidase antibodies (21) and pro/antiangiogenic factors (45) 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 not only directly, through anabolic effects on fetal metabolism and induce fetal oxygen consumption, but also, indirectly by controlling the bioavailability and effectiveness of insulin-like growth factors and catecholamines, which both have important effect of fetal growth and development (46). In addition, higher insulin resistance index was reported in euthyroid pregnant women with low fT4 levels, which may potentially associate with to GDM (47, 48), 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 (49, 50). Moreover, higher BMI has been reported in pregnant women with IMH in many studies (27, 36, 51–53) which may lead to decreased thyroid function capacity (53). 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 (54, 55) 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 (29).

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 defection being based on normal maternal TSH in conjunction with FT4 in the lower 5th or 10th percentile of the reference range (56), 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 (57, 58) as well as TPOAb-positivity (59–61) 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 two published meta-analysis that evaluated the risk of preterm birth in women diagnosed with IMH (62, 63); interestingly, these two meta-analyses also had conflicting findings too. However, a single study suggested 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. This systematic review was able to evaluate only what was reported in studies included, not what may in fact have been done. 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 (64).

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. 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 common disorder on pregnancy complications.

List Of Abbreviations

IMH Isolated Maternal hypothyroxinemia

T3 Triiodothyronine

T4 Thyroxine

fT4 free thyroxine

TSH Thyroid-stimulating hormone

TPOAb Thyroid peroxidase antibody

PROSPERO Prospective Register of Systematic Reviews

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PIH Pregnancy Induced Hypertension

GDM Gestational diabetes

LBW Low birth weight

PROM Premature rupture of membrane

IUGR Intra uterine growth restriction

SGA Small for gestational age

RDS Respiratory distress syndrome

NICU Newborn, or Neonatal, Intensive Care Unit

RCTs Randomized controlled trials

NRS Non-randomized trials

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

This manuscript does not report personal data such as individual details; therefore, consent for publication is not applicable.

Availability of data and materials

Data will be available upon request of the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SN was involved in study design, search in databases, studies selection, data analysis, manuscript drafting, and submitting manuscript.

FRT was involved in study design, data analysis, manuscript drafting and critical discussions.

SBG contributed in data analysis, and critical discussion, execution and manuscript drafting.

All authors have read and approved the final version of the manuscript.

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References

1. Cignini P, Cafà EV, Giorlandino C, Capriglione S, Spata A, Dugo N. Thyroid physiology and common diseases in pregnancy: review of literature. Journal of prenatal medicine. 2012;6(4):64.
2. Korevaar TI, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nature Reviews Endocrinology. 2017;13(10):610.
3. Moleti M, Trimarchi F, Vermiglio F. Thyroid physiology in pregnancy. Endocr Pract. 2014;20(6):589–96.
4. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Minooee S, Rahmati M, et al. Effects of levothyroxine on pregnant women with subclinical hypothyroidism, negative for thyroid peroxidase antibodies. The Journal of Clinical Endocrinology Metabolism. 2017;103(3):926–35.
5. Nazarpour S, Tehrani FR, Amiri M, Yarandi RB, Azizi F. Levothyroxine treatment and pregnancy outcomes in women with subclinical hypothyroidism: a systematic review and meta-analysis. Archives of gynecology and obstetrics. 2019:1–15.
6. Gong X, Liu A, Li Y, Sun H, Li C, Yu X, et al. The impact of isolated maternal hypothyroxinemia during the first and second trimester of gestation on pregnancy outcomes: an intervention and prospective cohort study in China. J Endocrinol Investig. 2019;42(5):599–607.
7. Furnica RM, Lazarus JH, Gruson D, Daumerie C. Update on a new controversy in endocrinology: isolated maternal hypothyroxinemia. J Endocrinol Investig. 2015;38(2):117–23.
8. Zhang X, Li C, Mao J, Wang W, Xie X, Peng S, et al. Gestation-specific changes in maternal thyroglobulin during pregnancy and lactation in an iodine-sufficient region in China: a longitudinal study. Clin Endocrinol. 2017;86(2):229–35.
9. Dosiou C, Medici M. Management of endocrine disease: isolated maternal hypothyroxinemia during pregnancy: knowns and unknowns. European journal of endocrinology. 2017;176(1):R21–38.
10. van Mil NH, Steegers-Theunissen RP, Bongers-Schokking JJ, Marroun HE, Ghassabian A, Hofman A, et al. Maternal hypothyroxinemia during pregnancy and growth of the fetal and infant head. Reproductive Sciences. 2012;19(12):1315–22.
11. Su X, Zhao Y, Cao Z, Yang Y, Duan T, Hua J. Association between isolated hypothyroxinaemia in early pregnancy and perinatal outcomes. Endocrine connections. 2019;1(aop).
12. Finken MJ, van Eijsden M, Loomans EM, Vrijkotte TG, Rotteveel J. Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5-to 6-year-old offspring. The Journal of Clinical Endocrinology Metabolism. 2013;98(4):1417–26.
13. Román GC, Ghassabian A, Bongers-Schokking JJ, Jaddoe VW, Hofman A, De Rijke YB, et al. Association of gestational maternal hypothyroxinemia and increased autism risk. Ann Neurol. 2013;74(5):733–42.
14. Casey BM, Dashe JS, Spong CY, McIntire DD, Leveno KJ, Cunningham GF. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. Obstetrics Gynecology. 2007;109(5):1129–35.
15. Hamm MP, Cherry NM, Martin JW, Bamforth F, Burstyn I. The impact of isolated maternal hypothyroxinemia on perinatal morbidity. Journal of Obstetrics Gynaecology Canada. 2009;31(11):1015–21.
16. Rosario PW, Oliveira LFF, Calsolari MR. Maternal hypothyroxinemia in the first trimester of gestation and association with obstetric and neonatal outcomes and iron deficiency: a prospective Brazilian study. Archives of endocrinology metabolism. 2018;62(3):332–6.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264–9.
18. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2009. Available in March 2016.
19. Higgins JP, Green S. Cochrane handbook for systematic reviews of inter–ventions. Vol. 4. New York: Wiley; 2011.
20. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF, et al. Maternal thyroid hypofunction and pregnancy outcome. Obstetrics gynecology. 2008;112(1):85.
21. Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, Visser WE, Visser W, de M Keizer-Schrama. SM, et al. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. The Journal of Clinical Endocrinology Metabolism. 2013;98(11):4382–90.

22. León G, Murcia M, Rebagliato M, Álvarez-Pedrerol M, Castilla AM, Basterrechea M, et al. Maternal Thyroid Dysfunction during Gestation, Preterm Delivery, and Birthweight. The Infancia y Medio Ambiente Cohort, S pain. Paediatr Perinat Epidemiol. 2015;29(2):113–22.
23. Mannisto T, Vaarasmaki M, Pouta A, Hartikainen A-L, Ruokonen A, Surcel H-M, et al. Thyroid dysfunction and autoantibodies during pregnancy as predictive factors of pregnancy complications and maternal morbidity in later life. The Journal of Clinical Endocrinology Metabolism. 2010;95(3):1084–94.
24. Medici M, Korevaar TI, Schalekamp-Timmermans S, Gaillard R, de Rijke YB, Visser WE, et al. Maternal early-pregnancy thyroid function is associated with subsequent hypertensive disorders of pregnancy: the generation R study. The Journal of Clinical Endocrinology Metabolism. 2014;99(12):E2591-E8.
25. Ong GS, Hadlow NC, Brown SJ, Lim EM, Walsh JP. Does the thyroid-stimulating hormone measured concurrently with first trimester biochemical screening tests predict adverse pregnancy outcomes occurring after 20 weeks gestation? The Journal of Clinical Endocrinology Metabolism. 2014;99(12):E2668-E72.
26. Su P-Y, Huang K, Hao J-H, Xu Y-Q, Yan S-Q, Li T, et al. Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective population-based cohort study in China. The Journal of Clinical Endocrinology Metabolism. 2011;96(10):3234–41.
27. Zhu Yd, Han Y, Huang K, Zhu Bb Y, Sq, Ge X, et al. The impact of isolated maternal hypothyroxinaemia on the incidence of large-for-gestational-age infants: the Ma'anshan Birth Cohort study. BJOG: An International Journal of Obstetrics Gynaecology. 2018;125(9):1118–25.
28. Breathnach FM, Donnelly J, Cooley SM, Geary M, Malone FD. Subclinical hypothyroidism as a risk factor for placental abruption: Evidence from a low-risk primigravid population. Aust N Z J Obstet Gynaecol. 2013;53(6):553–60.
29. Pop VJ, Brouwers EP, Wijnen H, Oei G, Essed GG, Vader HL. Low concentrations of maternal thyroxin during early gestation: a risk factor of breech presentation? BJOG: An International Journal of Obstetrics Gynaecology. 2004;111(9):925–30.
30. Medici M, Timmermans S, Visser W, de M Keizer-Schrama, Jaddoe SM, Hofman VW. A, et al. Maternal thyroid hormone parameters during early pregnancy and birth weight: the Generation R Study. The Journal of Clinical Endocrinology Metabolism. 2013;98(1):59–66.
31. Vermiglio F, Lo Presti V, Argentina GS, Finocchiaro M, Gullo D, Squatrito S, et al. Maternal hypothyroxinaemia during the first half of gestation in an iodine deficient area with endemic cretinism and related disorders. Clin Endocrinol. 1995;42(4):409–15.
32. Ghassabian A, Pierotti L, Basterrechea M, Chatzi L, Estarlich M, Fernández-Somoano A, et al. Association of exposure to ambient air pollution with thyroid function during pregnancy. JAMA network open. 2019;2(10):e1912902-e.
33. Zhao Y, Cao Z, Li H, Su X, Yang Y, Liu C, et al. Air pollution exposure in association with maternal thyroid function during early pregnancy. J Hazard Mater. 2019;367:188–93.
34. Pearce EN, Braverman LE. Environmental pollutants and the thyroid. Best practice & research Clinical endocrinology & metabolism. 2009;23(6):801–13.
35. Chevrier J, Eskenazi B, Holland N, Bradman A, Barr DB. Effects of exposure to polychlorinated biphenyls and organochlorine pesticides on thyroid function during pregnancy. Am J Epidemiol. 2008;168(3):298–310.
36. Han C, Li C, Mao J, Wang W, Xie X, Zhou W, et al. High body mass index is an indicator of maternal hypothyroidism, hypothyroxinemia, and thyroid-peroxidase antibody positivity during early pregnancy. BioMed research international. 2015;2015.
37. Kahr MK, Antony KM, DelBeccaro M, Hu M, Aagaard KM, Suter MA. Increasing maternal obesity is associated with alterations in both maternal and neonatal thyroid hormone levels. Clin Endocrinol. 2016;84(4):551–7.
38. Roti E, Minelli R, Salvi M. Thyroid hormone metabolism in obesity. International Journal of Obesity & Related Metabolic Disorders. 2000;24.
39. Biondi B. Thyroid and obesity: an intriguing relationship. Oxford University Press; 2010.
40. Gowachirapant S, Melse-Boonstra A, Winichagoon P, Zimmermann MB. Overweight increases risk of first trimester hypothyroxinaemia in iodine-deficient pregnant women. Matern Child Nutr. 2014;10(1):61–71.
41. Maldonado-Araque C, Valdés S, Lago-Sampedro A, Lillo-Muñoz JA, Garcia-Fuentes E, Perez-Valero V, et al. Iron deficiency is associated with Hypothyroxinemia and Hypotriiodothyroninemia in the Spanish general adult population: Di@ bet. es study. Scientific reports. 2018;8(1):6571.
42. Teng X, Shan Z, Li C, Yu X, Mao J, Wang W, et al. Iron deficiency may predict greater risk for hypothyroxinemia: a retrospective cohort study of pregnant women in China. Thyroid. 2018;28(8):968–75.
43. Yu X, Shan Z, Li C, Mao J, Wang W, Xie X, et al. Iron deficiency, an independent risk factor for isolated hypothyroxinemia in pregnant and nonpregnant women of childbearing age in China. The Journal of Clinical Endocrinology Metabolism. 2015;100(4):1594–601.
44. Zimmermann MB, Burgi H, Hurrell RF. Iron deficiency predicts poor maternal thyroid status during pregnancy. The Journal of Clinical Endocrinology Metabolism. 2007;92(9):3436–40.
45. Korevaar TI, Steegers EA, de Rijke YB, Visser WE, Jaddoe VW, Visser TJ, et al. Placental angiogenic factors are associated with maternal thyroid function and modify hCG-mediated FT4 stimulation. The Journal of Clinical Endocrinology Metabolism. 2015;100(10):E1328-E34.
46. Forhead AJ, Fowden AL. Thyroid hormones in fetal growth and prepartum maturation. J Endocrinol. 2014;221(3):R87–103.
47. Bassols J, Prats-Puig A, Soriano-Rodríguez P, García-González MM, Reid J, Martínez-Pascual M, et al. Lower free thyroxin associates with a less favorable metabolic phenotype in healthy pregnant women. The Journal of Clinical Endocrinology Metabolism. 2011;96(12):3717–23.
48. Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. The Journal of Clinical Endocrinology Metabolism. 2006;92(2):491–6.

49. Duntas LH, Orgiazzi J, Brabant G. The interface between thyroid and diabetes mellitus. Clin Endocrinol. 2011;75(1):1–9.
50. Männistö T, Vääräsmäki M, Pouta A, Hartikainen A-L, Ruokonen A, Surcel H-M, et al. Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. The Journal of Clinical Endocrinology Metabolism. 2009;94(3):772–9.
51. Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, et al. Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. N Engl J Med. 2017;376(9):815–25.
52. Furnica RM, Gruson D, Lazarus JH, Maiter D, Bernard P, Daumerie C. First trimester isolated maternal hypothyroxinaemia: adverse maternal metabolic profile and impact on the obstetrical outcome. Clin Endocrinol. 2017;86(4):576–83.
53. Korevaar TI, de Rijke YB, Chaker L, Medici M, Jaddoe VW, Steegers EA, et al. Stimulation of thyroid function by human chorionic gonadotropin during pregnancy: a risk factor for thyroid disease and a mechanism for known risk factors. Thyroid. 2017;27(3):440–50.
54. Thornton S, Baldwin P, Harris P, Harding F, Davison J, Baylis P, et al. The role of arginine vasopressin in human labour: functional studies, fetal production and localisation of V1a receptor mRNA. BJOG: an international journal of obstetrics gynaecology. 2002;109(1):57–62.
55. Ciosek J, Drobnik J. VASOPRESSIN AND OXYTOCIN RELEASE. Journal of physiology pharmacology. 2004;55(2):423–41.
56. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21(10):1081–125.
57. Charoenratana C, Leelapat P, Traisrisilp K, Tongsong T. Maternal iodine insufficiency and adverse pregnancy outcomes. Matern Child Nutr. 2016;12(4):680–7.
58. Chen R, Li Q, Cui W, Wang X, Gao Q, Zhong C, et al. Maternal Iodine Insufficiency and Excess Are Associated with Adverse Effects on Fetal Growth: A Prospective Cohort Study in Wuhan, China. J Nutr. 2018;148(11):1814–20.
59. Meena A, Nagar P. Pregnancy outcome in euthyroid women with anti-thyroid peroxidase antibodies. The Journal of Obstetrics Gynecology of India. 2016;66(3):160–5.
60. Chen X, Jin B, Xia J, Tao X, Huang X, Sun L, et al. Effects of thyroid peroxidase antibody on maternal and neonatal outcomes in pregnant women in an iodine-sufficient area in China. International journal of endocrinology. 2016;2016.
61. Rajput R, Yadav T, Seth S, Nanda S. Prevalence of thyroid peroxidase antibody and pregnancy outcome in euthyroid autoimmune positive pregnant women from a tertiary care center in Haryana. Indian journal of endocrinology metabolism. 2017;21(4):577.
62. Nasirkandy MP, Badfar G, Shohani M, Rahmati S, YektaKooshali MH, Abbasalizadeh S, et al. The relation of maternal hypothyroidism and hypothyroxinemia during pregnancy on preterm birth: An updated systematic review and meta-analysis. International Journal of Reproductive BioMedicine. 2017;15(9):543.
63. Sheehan PM, Nankervis A, Araujo Júnior E, Da Silva Costa F. Maternal thyroid disease and preterm birth: systematic review and meta-analysis. The Journal of Clinical Endocrinology Metabolism. 2015;100(11):4325–31.
64. Morrison A, Moulton K, Clark M, Polisena J, Fiander M, Mierzwinski-Urban M, et al. English-language restriction when conducting systematic review-based meta-analyses: systematic review of published studies. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009. pp. 1–17.

Figures

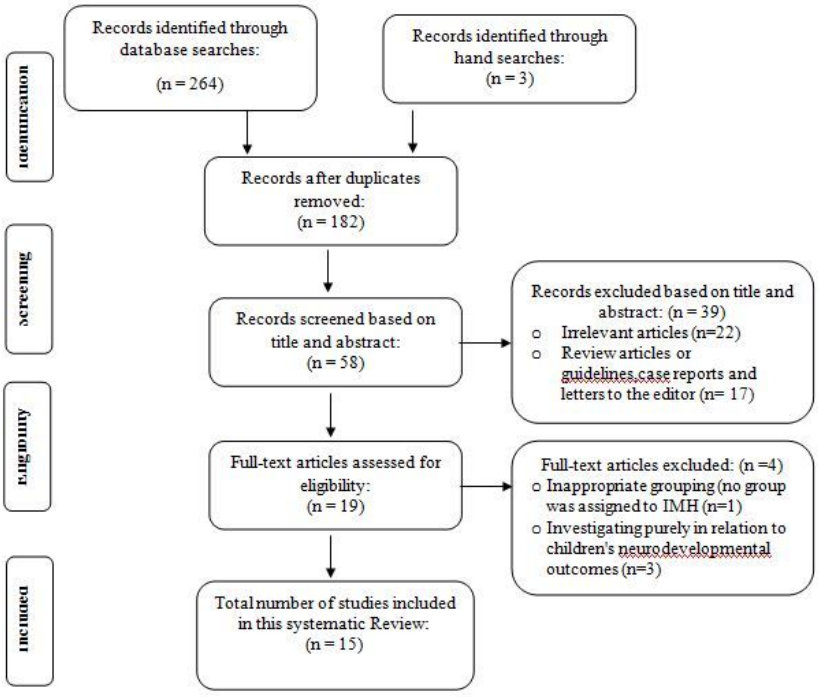

Figure 1

Flow chart of the literature search for the systematic review.

Supplementary Files

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