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Association between levothyroxine supplementation for hypothyroidism in late pregnancy and risk of prematurity: a population-based cohort study

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Abstract

Background Hypothyroidism in pregnancy is associated with obstetrical and fetal complications, such as prematurity. However, whether its management by levothyroxine affects the risk of prematurity is not yet clear.

Methods We conducted a cohort study within the Quebec Pregnancy Cohort including pregnancies with hypothyroidism from January 1, 1998, through December 31, 2015. In primary analyses, we considered levothyroxine exposure (yes/no), total duration, mean daily dose, and cumulative dose in the 2-months period before delivery (for preterm deliveries) or before 37th weeks' gestation (for term deliveries). Secondly, levothyroxine dosage before and after the beginning of the second trimester were compared, and pregnancies were categorized in increased or constant dosage groups. Lastly, levothyroxine was also defined as a time-varying daily exposure from the 14th weeks' gestation until delivery or 37th weeks' gestation, whichever came first. Prematurity was defined as giving birth before the 37th weeks' gestation. Term pregnancies were censored at 37th weeks' gestation because they were no longer at risk of prematurity afterwards. Generalized estimating equations and Cox-proportional hazard models, adjusted for potential confounders, were used to calculate adjusted relative risks (aRRs) and hazard ratios (aHRs), respectively.

Results A total of 9489 pregnant individuals with hypothyroidism were included. Among them, 6667 (70.3%) were exposed to levothyroxine in the 2-months time-window. Adjusting for potential confounders, no association was observed between levothyroxine exposure (aRR, 0.98; 95% CI, 0.81–1.20) and the risk of prematurity compared to non-exposed. Also, no association between levothyroxine duration (> 30 days: aRR, 0.99; 95% CI, 0.81–1.21), cumulative dose (> 7125 mcg: aRR, 0.97; 95% CI, 0.73–1.27) or mean daily dose (> 125 mcg/day: aRR, 0.95; 95% CI, 0.72–1.26) and the risk of prematurity was observed, compared to non-exposure. Finally, the risk of prematurity did not vary between increased or constant dosage groups (aRR, 0.84; 95% CI, 0.67–1.05). Similarly, time-varying exposure analysis did not show any association between levothyroxine exposure and prematurity risk (aHR, 0.95; 95% CI, 0.81–1.11).

Conclusions Levothyroxine supplementation in late pregnancy among individuals with hypothyroidism was not associated with prematurity risk. Our findings support the safe use of levothyroxine during gestation and might be useful for the current guidelines.

Keywords Hypothyroidism, Pregnancy, Levothyroxine, Prematurity

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Background

Thyroid disorders represent common endocrine conditions during pregnancy affecting 1 to 5% of pregnancies [1, 2]. Hypothyroidism is characterized by an increased thyroid-stimulating hormone level with or without decreased thyroxine level [1–3]. Hormonal changes during pregnancy affect thyroid function and result in a further increase in thyroxine demand [4, 5]. Thyroid hormones are largely involved in the normal function of the major body systems, such as cardiovascular and nervous systems, and have crucial roles in the organogenesis of the fetus [6, 7]. Additionally, thyroid hormones influence trophoblast proliferation and differentiation and thus have a critical role in placental development [8]. Consequently, a deficiency in thyroid hormones may lead to obstetrical complications. Previous findings showed that hypothyroidism significantly increased the risk of obstetrical and fetal complications, such as prematurity [3, 9–12]. Indeed, the risk of prematurity can increase by 60% when hypothyroidism is not adequately treated [3]. Moreover, an American cohort study found that pregnant individuals with hypothyroidism had 34% higher risk of prematurity than those with normal thyroid function [9].

According to the World Health Organization, 13.4 million children in 2020 were born premature, defined as a delivery before the 37th weeks' gestation [13]. Prematurity is associated with serious complications in offsprings: respiratory diseases, retinopathy, and neurodevelopmental defects [13, 14]. In 2019, the prevalence of prematurity was 8.1% across Canada and 7.3% in Quebec [15].

Emerging controversies exist regarding the benefits of hypothyroidism management during pregnancy, which consists of levothyroxine supplementation [1–3]. A clinical trial by Nazarpour et al. in 2018 showed that levothyroxine reduced the risk of prematurity by 62% in pregnancies with hypothyroidism [16]. Yet, other studies failed to demonstrate an improvement of prematurity risk in pregnancies with hypothyroidism receiving levothyroxine [17–19]. Besides, a population-based study reported a 60% increase in prematurity risk associated with levothyroxine treatment during pregnancy [20]. Few other studies investigated the impact of levothyroxine on prematurity risk, but the findings were inconclusive and inconsistent. Firstly, most of the published studies were limited by small sample sizes and lack of data on the duration or dosage of levothyroxine use. Secondly, although some studies had considered multiple confounding factors, others did not appropriately account for potential confounders such as maternal comorbidities and obstetrical complications. Additionally, researchers declared that the reported increased risk of prematurity might be confounded by the disease itself; however, they could not distinguish the impact of the treatment on prematurity risk from that of the underlying condition [20, 21]. Lastly, exposures or events leading to prematurity occur commonly in the second and/or third trimester of pregnancy, and it has been demonstrated that a deficiency in thyroid hormones contributes to an inflammation which is involved in the induction of preterm delivery [22, 23]. Though, to our knowledge, the risk of prematurity associated with exposure to levothyroxine in late pregnancy has not been previously examined.

Given that hypothyroidism needs to be treated during pregnancy and that prematurity represents an important adverse pregnancy outcome, a levothyroxine supplementation may reduce the prematurity risk associated with hypothyroidism. We therefore aimed to conduct a large cohort study using real-world data to quantify the risk of prematurity associated with levothyroxine exposure in late pregnancy, its duration of exposure, cumulative dose, mean daily dose, and dosage variation, considering multiple potential confounders.

Methods

Data sources

We conducted a large cohort study within the Quebec Pregnancy Cohort (QPC), an ongoing population-based cohort, including all pregnancies between January 1, 1998, and December 31, 2015, covered by the Public Drug Insurance Plan [24]. The QPC was put in place with the linkage of three administrative, hospital, and socio-demographic databases in Quebec: Régie de l'Assurance Maladie du Québec (RAMQ) which covers medical services for all Quebec residents and pharmaceutical services for approximately 36.0% of women of reproductive age (15–45 years old) without private insurance offered by their employer, or those on welfare; the RAMQ contains demographic data, pharmaceutical prescription fillings (drug name, dosage, duration, date, and quantity) and medical services (outpatient diagnoses coded by the ninth and tenth versions of the International Classification of Diseases: ICD-9 and ICD-10, and therapeutic procedures); MedEcho which contains hospitalization data (in-hospital diagnoses (ICD-9 and ICD-10), gestational age); and l'Institut de la Statistique du Québec, which consists of the birth and death registries where we can also obtain data on gestational age, birth weight, and maternal socio-demographic data. Linkage between the databases is done using individual health care unique identifiers, anonymized for research purposes. Data of the QPC were found reliable and valid in several studies [24–26]. The first day of the last menstrual period (LMP) was identified using data on gestational age, validated by ultrasound [24, 26].

Study population

Within the QPC, we selected pregnancies with hypothyroidism, identified with a diagnosis of hypothyroidism coded by the 9th and 10th versions of the ICD and/or a prescription of levothyroxine, within the year before LMP until the end of the first trimester (Additional file 1: Table S1). Hypothyroidism diagnoses codes of the ICD-9 and ICD-10 were previously validated such as their positive predictive values were 92.8% and 93.3%, respectively, and their negative predictive values were 96.7% and 94.4%, respectively [27]. Moreover, thyroid hormone prescription fillings recorded in the QPC are highly accurate with a positive predictive value of 100% and a negative predictive value of 96% [28]. Only pregnancies that ended in a delivery and those covered by the Quebec Public Drug Plan in the 12 months before LMP and during pregnancy were included. We excluded pregnancies with multiple fetuses, as thyroid function may be more affected by multiplicity [29], and those exposed to fetotoxic drugs (Additional file 1: Table S2) throughout pregnancy, as this may increase prematurity risk [30]. Thus, pregnancies were followed from the first day of the second trimester until the delivery date (for preterm deliveries) or 37th weeks' gestation (for term deliveries), and stillbirths were censored.

Exposure definitions

In our primary analyses, the period of interest was defined as 2-months time window before delivery (for preterm deliveries) or before 37th weeks' gestation (for term deliveries); this period of interest was chosen to precisely quantify the association between late gestational exposure to levothyroxine and prematurity risk. Additionally, it allows to minimize possible immortal time bias resulting from a delay between cohort entry and treatment initiation. The gestational age and the first day of the last menstrual period (LMP), recorded and validated in the QPC, allowed us to determine gestational weeks and thus to determine the exposure status during our period of interest. In these primary analyses, exposure was first defined dichotomously as having filled at least one prescription for levothyroxine during the 2-months time-window. Then, pregnancies were categorized according to the duration of exposure (≤ 50 or $>50\%$ of the 2-months time-window), cumulative dose, and mean daily dose in the 2-months time-window. Cumulative and mean daily doses were chosen based on the cohort distribution. This categorization was considered because the duration of exposure, as well as cumulative and mean daily doses, reflect hypothyroidism severity: pregnancies exposed for longer duration and to higher dosage may represent more severe cases. Prescription fillings before the 2-months time-window but with overlapping duration were also considered. To calculate duration and doses, we removed overlaps and gaps between prescription fillings. When dosage remained constant, excess tablets resulting from overlaps were used to fill in further gaps; when dosage changed, dosage regimen ended on the day the new prescription with the change in dosage was filled. To obtain the mean daily dose, the total cumulative dose was divided by the total duration of exposure. Exposed groups of the primary analyses were compared with a reference group representing pregnancies having hypothyroidism but not receiving levothyroxine.

In our secondary analyses, as an unregulated thyroid function requires an increase in dosage to reach normality [1, 2], we compared daily doses before and after the beginning of the second trimester among individuals who were continuously exposed to levothyroxine throughout pregnancy. Subsequently, pregnancies were categorized into increased or no-change dosage groups. Indeed, pregnancies for whom the dosage was increased represent more severe cases than those who received the same dosage throughout pregnancy. Within the increased dosage group, pregnancies were further categorized based on the percentage of increase in dosage. Taking into account dosage increase and its magnitude also allows to consider more precisely the severity of hypothyroidism.

Finally, as levothyroxine exposure may vary over time, a time-varying daily levothyroxine exposure from 14th weeks' gestation until delivery (for preterm deliveries) or 37th weeks' gestation (for term deliveries) was considered, and Cox-proportional hazard models were performed [31, 32]. For this last analysis, exposure to levothyroxine (yes/no) was determined on a day-to-day basis during the second and third trimesters; the 14th weeks' starting point was chosen for the same reason: exposures leading to prematurity commonly occur during these trimesters [23].

Outcome definition

Prematurity was defined as a delivery before 37th weeks' gestation. It was determined using the gestational age at birth from the QPC, validated by ultrasound [24]. Additionally, in order for all pregnancies to be at risk of prematurity, we censored pregnancies at the time of delivery (for preterm deliveries) or at 37th weeks' gestation (for term deliveries) [31, 33].

Potential confounding factors

The following potential confounders/risk factors were considered in the 12-months before LMP until the end of the first trimester: maternal socio-demographic factors (maternal age, public drug plan coverage (welfare vs worker), place of residence (rural or urban); maternal

comorbidities identified by diagnoses or prescribed medication fillings (chronic hypertension and diabetes, depression and anxiety, other psychiatric disorders, asthma, and epilepsy); maternal utilization of healthcare resources (emergency, hospitalization, endocrinologist, general practitioner or specialist visits); maternal lifestyle: tobacco, alcohol, and other drug dependencies (used as proxies to adjust for smoking status, alcohol consumption, and illicit drug use, since lifestyles information are incomplete in the QPC) and obesity. Other potential factors were considered during pregnancy: obstetrical factors (preeclampsia or eclampsia, gestational hypertension and diabetes, placenta previa, and placental abruption) and prenatal care by obstetrician/gynecologist. The pregnancy status in the year before the LMP as this increases the risk of prematurity [34] and high dose folic acid supplementation in the 6-months before the LMP until the end of the first trimester that may be beneficial to reduce prematurity risk [35] were also included. Data on all potential confounders were obtained from the QPC databases. Diagnostic codes and/or specific drugs used to define maternal co-morbidities, lifestyle, and obstetrical complications are detailed in Additional file 1: Tables S3, S4, and S5.

Statistical analyses

To quantify prematurity risk associated with gestational levothyroxine exposure, univariate and multivariate generalized estimating equations (GEE) were modeled. Risk ratios (RR) and 95% confidence interval (CI) were calculated, taking into account potential confounders.

Our primary analyses considered: (1) exposure dichotomously (yes/no), (2) duration of exposure (≤30 or >30 days), (3) cumulative dose (≤3050, 3050–4900, 4900–7125 or >7125 mcg), and (4) mean daily dose (≤60, 60–100, 100–125 or >125 mcg/day) only in the 2-months time-window (Additional file 1: Table S6). To ensure the validity of the primary results, we therefore performed secondary analyses that considered the following exposure definitions: (1) dosage variation groups (increased or no-change) and (2) the percentage of increase in dosage after the beginning of the second trimester (≤30, 30–50 or >50%) among pregnancies for whom the dosage was increased. Our last analyses consisted of Cox-proportional hazard models and considered a time-varying daily levothyroxine exposure. All statistical analyses were performed using RStudio software version 4.3.1.

Ethics

This study was approved by the CHU Sainte-Justine's Research Ethics Committee (2010–248, 2976).

Results

Among all pregnancies included in the QPC between January 1, 1998, and December 31, 2015, 10,373 were diagnosed with hypothyroidism and/or filled a levothyroxine prescription in the year before LMP until the end of the first trimester (Fig. 1). After excluding 763 pregnancies exposed to a fetotoxic drug throughout pregnancy and 121 multiple pregnancies, 9489 met inclusion criteria and were included (Figs. 1 and 2A). While 29.7% of pregnancies were not exposed to levothyroxine in the 2-months time-window, a total of 6667 (70.3%) pregnancies were exposed (Table 1, Fig. 2A). The mean (standard deviation) maternal age of the exposed group was 29.8 (5.5) years and 510 (7.6%) premature deliveries occurred in

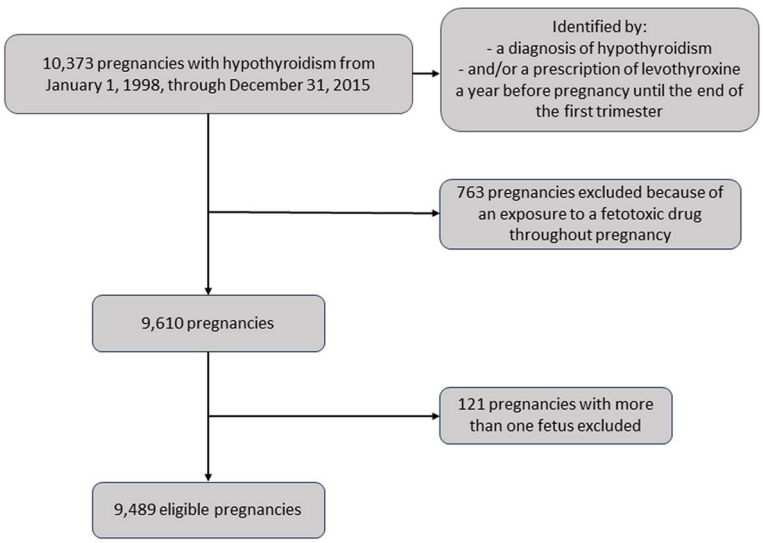

Fig. 1 Flowchart of pregnancy selection

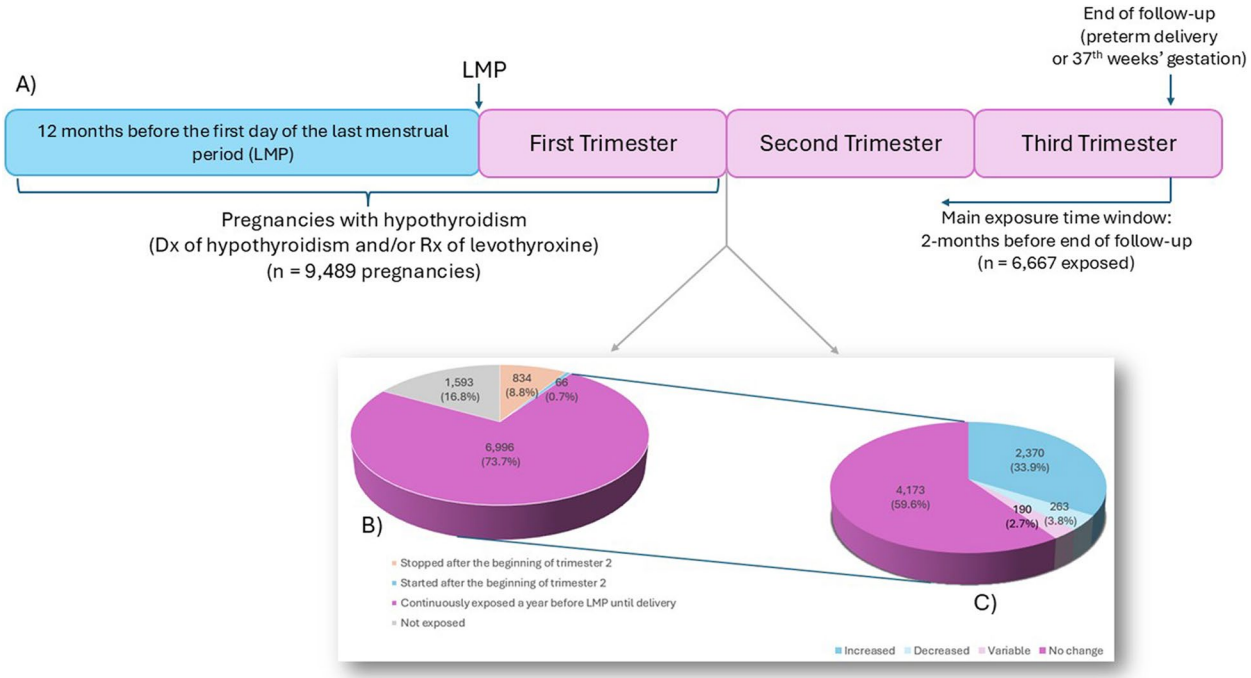

Fig. 2 **A** Identification of the study population and the main exposure time-window, **B** distribution of pregnancies based on timing of exposure to levothyroxine, and **C** distribution of pregnancies who were continuously exposed to levothyroxine a year before LMP until delivery, based on dosage variation after the 14th weeks' gestation

this group (Table 1). Overall, 65.0% of the exposed pregnancies received levothyroxine for more than 30 days of the 2-months time-window (Additional file 1: Table S7), and 19.4%, 15.8%, 17.7%, and 17.4% were respectively exposed to a cumulative dose of ≤ 3050, 3050–4900, 4900–7125, and > 7125 mcg during this period of interest (Additional file 1: Table S8). The mean daily dose of levothyroxine was above 125 mcg/day in 17.0% of the exposed pregnancies (Additional file 1: Table S9). Among the 73.7% (6996) of pregnancies who continuously received levothyroxine throughout pregnancy (Fig. 2B), the dosage was increased for 33.9% of them after the beginning of the second trimester while 59.6% (4173) had no change in dosage (Fig. 2C and Additional file 1: Tables S10, S11, S12). The percentage of increase in dosage was up to 30% in one-fifth of pregnancies (Additional file 1: Table S13).

After adjusting for potential confounders, primary analyses showed no significant association between levothyroxine use in the 2-months time-window and prematurity risk, compared with non-use (adjusted RR (aRR), 0.98; 95% CI, 0.81–1.20) (Table 2). Additionally, the risk of prematurity was unaffected by the duration of levothyroxine exposure (≤ 30 days: aRR, 0.97; 95% CI, 0.63–1.48, and > 30 days: aRR, 0.99; 95% CI, 0.81–1.21), compared with non-use. Furthermore, the risk did not vary with cumulative dose and mean daily dose: a null association was observed across all categories (Table 2). An exposure to a high cumulative dose (> 7125 mcg: aRR, 0.97; 95% CI, 0.73–1.27) and high mean daily dose (> 125 mcg/day: aRR, 0.95; 95% CI, 0.72–1.26) did not neither influence prematurity risk (Table 2).

Considering potential confounders, an increase in dosage after the beginning of the second trimester was associated with a slight decrease in prematurity risk, although this was non-statistically significant, compared with no-change dosage (aRR, 0.84; 95% CI, 0.67–1.05) (Table 3). Yet, an increase in dosage up to 30% was significantly associated with a 28% decrease in prematurity risk (aRR, 0.72; 95% CI, 0.540.96) (Table 4). Furthermore, this RR increased gradually to reach 0.93 among pregnancies for whom the percentage of increase was between 30 and 50%, and 1.11 among those who received a dosage increase exceeding 50% (Table 4).

Finally, time-varying daily levothyroxine exposure was not associated with a statistically significant risk of prematurity (Table 5) and was thus consistent with the main analyses.

Discussion

After considering potential confounders, no significant association was found between levothyroxine use during the last 2-months before delivery among preterm deliveries or before the 37th week of pregnancy among term deliveries and prematurity risk. This risk did not change

Table 1 Baseline characteristics of pregnancies

Characteristic	Levothyroxine exposure			
	Overall **N = 9489 (100.0%)**[1]	**Exposed** **N = 6667 (70.3%)**[1]	**Not Exposed** **N = 2822 (29.7%)**[1]	***p*-value**[2]
Prematurity	716 (7.5)	510 (7.6)	206 (7.3)	0.56
Delivery time (weeks of gestation)				0.20
Extremely preterm (< 28)	77 (0.8)	62 (0.9)	15 (0.5)	
Very preterm (28–32)	77 (0.8)	51 (0.8)	26 (0.9)	
Moderate to late preterm (32–37)	581 (6.1)	412 (6.2)	169 (6.0)	
Term (≥ 37)	8754 (92.3)	6142 (92.1)	2612 (92.6)	
Duration of gestation	38.7 (2.2)	38.6 (2.2)	38.7 (2.0)	0.061
Mean maternal age at LMP	29.7 (5.5)	29.8 (5.5)	29.2 (5.4)	**< 0.001**
Maternal age at LMP				**< 0.001**
< 35 years	7513 (79.2)	5215 (78.2)	2298 (81.4)	
35–39 years	1603 (16.9)	1157 (17.4)	446 (15.8)	
≥ 40 years	373 (3.9)	295 (4.4)	78 (2.8)	
Welfare recipient	2314 (24.4)	1672 (25.1)	642 (22.7)	**0.016**
Urban dweller	8204 (86.5)	5699 (85.5)	2505 (88.8)	**< 0.001**
Chronic hypertension	410 (4.3)	297 (4.5)	113 (4.0)	0.32
Chronic diabetes	659 (6.9)	502 (7.5)	157 (5.6)	**< 0.001**
Depression and anxiety	1694 (17.9)	1196 (17.9)	498 (17.6)	0.73
Other psychiatric disorders	702 (7.4)	539 (8.1)	163 (5.8)	**< 0.001**
Asthma	1728 (18.2)	1305 (19.6)	423 (15.0)	**< 0.001**
Epilepsy	265 (2.8)	205 (3.1)	60 (2.1)	**0.010**
Emergency visit and/or hospitalization	2574 (27.1)	1671 (25.1)	903 (32.0)	**< 0.001**
Endocrinologist visits	2484 (26.2)	1670 (25.0)	814 (28.8)	**< 0.001**
General practitioner visits, No				**< 0.001**
0	552 (5.8)	413 (6.2)	139 (4.9)	
1–2	1726 (18.2)	1268 (19.0)	458 (16.2)	
≥ 3	7211 (76.0)	4986 (74.8)	2225 (78.8)	
Other specialist visits, No				**< 0.001**
0	805 (8.5)	613 (9.2)	192 (6.8)	
1	1146 (12.1)	895 (13.4)	251 (8.9)	
≥ 2	7538 (79.4)	5159 (77.4)	2379 (84.3)	
Tobacco dependence	80 (0.8)	54 (0.8)	26 (0.9)	0.59
Alcohol dependence	26 (0.3)	19 (0.3)	7 (0.2)	0.75
Other drug dependence	42 (0.4)	33 (0.5)	9 (0.3)	0.24
Obesity	376 (4.0)	259 (3.9)	117 (4.1)	0.55
Preeclampsia or eclampsia	175 (1.8)	122 (1.8)	53 (1.9)	0.87
Gestational hypertension	187 (2.0)	140 (2.1)	47 (1.7)	0.16
Gestational diabetes	977 (10.3)	737 (11.1)	240 (8.5)	**< 0.001**
Placenta previa	52 (0.5)	38 (0.6)	14 (0.5)	0.66
Placental abruption	183 (1.9)	137 (2.1)	46 (1.6)	0.17
Prenatal care by obstetrician/gynecologist	7600 (80.1)	5301 (79.5)	2299 (81.5)	**0.029**
Pregnancy a year before LMP	44 (0.5)	35 (0.5)	9 (0.3)	0.18
Folic acid supplementation 6 months before LMP until the end of the first trimester	684 (7.2)	579 (8.7)	105 (3.7)	**< 0.001**

[1] *n* (%); mean (SD)

[2] Pearson's chi-squared test; Wilcoxon rank sum test

Table 2 Associations between levothyroxine exposure, duration of exposure, levothyroxine cumulative/mean daily dose, and risk of prematurity

	N	Crude RR		Adjusted RR		
Exposure	***N* = 9489**[a]	**RR**[b]	**95% CI**[b]	**RR**[c,b]	**95% CI**[b]	***p*-value**
Levothyroxine exposure	6667 (70.3%)	1.05	0.89, 1.25	0.98	0.81, 1.20	0.9
Duration of exposure (days)						
Not exposed	2822 (29.7%)	1.00	—	1.00	—	
≤ 30	503 (5.3%)	1.13	0.79, 1.60	0.97	0.63, 1.48	0.9
> 30	6164 (65.0%)	1.05	0.88, 1.24	0.99	0.81, 1.21	0.9
Levothyroxine cumulative dose (mcg)						
Not exposed	2822 (29.7%)	1.00	—	1.00	—	
≤ 3050	1839 (19.4%)	1.07	0.85, 1.34	1.02	0.78, 1.32	> 0.9
3050–4900	1500 (15.8%)	1.03	0.81, 1.31	1.00	0.76, 1.32	> 0.9
4900–7125	1677 (17.7%)	1.05	0.83, 1.32	0.96	0.74, 1.25	0.8
> 7125	1651 (17.4%)	1.05	0.82, 1.34	0.97	0.73, 1.27	0.8
Levothyroxine mean daily dose (mcg/day)						
Not exposed	2822 (29.7%)	1.00	—	1.00	—	
≤ 60	1641 (17.3%)	0.98	0.77, 1.25	0.95	0.72, 1.25	0.7
60–100	2447 (25.8%)	1.06	0.86, 1.30	1.00	0.79, 1.26	> 0.9
100–125	962 (10.1%)	1.12	0.86, 1.47	1.08	0.79, 1.47	0.6
> 125	1617 (17.0%)	1.07	0.84, 1.37	0.95	0.72, 1.26	0.7

[a] *n* (%)

[b] *RR*, risk ratio; CI, confidence interval

[c] Adjusted for: maternal age at LMP, welfare recipient, urban dweller, chronic hypertension, chronic diabetes, depression and anxiety, other psychiatric disorders, asthma, epilepsy, emergency visit and/or hospitalization, endocrinologist visits, general practitioner visits, other specialist visits, tobacco dependence, alcohol dependence, other drug dependence, obesity, preeclampsia or eclampsia, gestational hypertension, gestational diabetes, placenta previa, placental abruption, prenatal care by obstetrician/gynecologist, pregnancy 12 months before LMP, folic acid supplementation 6 months before LMP until end of first trimester

Table 3 Associations between levothyroxine dosage variation after the 14th weeks' gestation and risk of prematurity

	N	Crude RR		Adjusted RR		
Exposure	***N* = 6543**[a]	**RR**[b]	**95% CI**[b]	**RR**[c,b]	**95% CI**[b]	***p*-value**
Levothyroxine dosage variation						
No change	4173 (63.8%)	1.00	—	1.00	—	
Increased	2370 (36.2%)	0.87	0.72, 1.06	0.84	0.67, 1.05	0.13

[a] *n* (%)

[b] *RR*, risk ratio; *CI*, confidence interval

[c] Adjusted for: maternal age at LMP, welfare recipient, urban dweller, chronic hypertension, chronic diabetes, depression and anxiety, other psychiatric disorders, asthma, epilepsy, emergency visit and/or hospitalization, endocrinologist visits, general practitioner visits, other specialist visits, tobacco dependence, alcohol dependence, other drug dependence, obesity, preeclampsia or eclampsia, gestational hypertension, gestational diabetes, placenta previa, placental abruption, prenatal care by obstetrician/gynecologist, pregnancy 12 months before LMP, folic acid supplementation 6 months before LMP until end of first trimester

with longer duration of exposure, higher cumulative and mean daily doses during the 2-months time-window. Also, an increase in levothyroxine dosage after the beginning of the second trimester didn't influence prematurity risk. However, a 28% decrease in the risk was observed among pregnancies for whom the dosage was increased up to 30%.

Indeed, an uncontrolled thyroid function requires higher levothyroxine doses to reach normality and is associated with a 30 to 60% increase in prematurity risk [2, 3]. Our primary analyses showed that, compared to pregnancies with hypothyroidism who did not receive levothyroxine, probably because their thyroid function was well controlled, prematurity risk did not increase among pregnancies exposed to high doses reflecting severe cases. Though we expected an increased risk in treated pregnancies who were at higher risk, associations were consistently null. Thus, there could be a possible

Table 4 Associations between the percentage of increase in levothyroxine dosage and risk of prematurity

	N	Crude RR		Adjusted RR		
Exposure	***N*** **= 6,543**[a]	**RR**[b]	**95% CI**[b]	**RR**[c,b]	**95% CI**[b]	***p*** **-value**
Percentage of increase in levothyroxine dosage (%)						
No change	4173 (63.8%)	1.00	—	1.00	—	
≤ 30%	1429 (21.8%)	0.80	0.63, 1.02	0.72	0.54, 0.96	**0.026**
30–50%	410 (6.3%)	0.97	0.66, 1.41	0.93	0.57, 1.53	0.8
> 50%	531 (8.1%)	0.98	0.70, 1.37	1.11	0.77, 1.58	0.6

[a] *n* (%)

[b] *RR*, risk ratio; *CI*, confidence interval

[c] Adjusted for: maternal age at LMP, welfare recipient, urban dweller, chronic hypertension, chronic diabetes, depression and anxiety, other psychiatric disorders, asthma, epilepsy, emergency visit and/or hospitalizations, endocrinologist visits, general practitioner visits, other specialist visits, tobacco dependence, alcohol dependence, other drug dependence, obesity, preeclampsia or eclampsia, gestational hypertension, gestational diabetes, placenta previa, placental abruption, prenatal care by obstetrician/gynecologist, pregnancy 12 months before LMP, folic acid supplementation 6 months before LMP until end of first trimester

Table 5 Associations between time-varying daily levothyroxine exposure and risk of prematurity

	Crude HR		Adjusted HR		
Exposure	**HR**[a]	**95% CI**[a]	**HR**[b,a]	**95% CI**[a]	***p*-value**
Time-varying daily levothyroxine exposure	0.90	0.77, 1.04	0.95	0.81, 1.11	0.5

[a] *HR*, hazard ratio; *CI*, confidence interval

[b] Adjusted for: maternal age at LMP, welfare recipient, urban dweller, chronic hypertension, chronic diabetes, depression and anxiety, other psychiatric disorders, asthma, epilepsy, emergency visit and/or hospitalization, endocrinologist visits, general practitioner visits, other specialist visits, tobacco dependence, alcohol dependence, other drug dependence, obesity, preeclampsia or eclampsia, gestational hypertension, gestational diabetes, placenta previa, placental abruption, prenatal care by obstetrician/gynecologist, pregnancy 12 months before LMP, folic acid supplementation 6 months before LMP until end of first trimester

benefit of levothyroxine supplementation in preventing the augmentation of prematurity risk associated with hypothyroidism during pregnancy. However, duration and doses are proxies of the severity, and we could not tease apart the effect of hypothyroidism itself on the association. To account for severity more precisely, we considered dosage adjustment after the beginning of the second trimester as another proxy for hypothyroidism severity in our secondary analyses. Similarly, we observed that prematurity risk was not different between the increased dosage group that reflects an uncontrolled thyroid function and the no-change dosage group representing a better controlled hypothyroidism. Besides, when the magnitude of dosage increase was considered, a 28% reduction in the risk of prematurity was observed among those who received a dosage increase of 30% or less (aRR = 0.72, 95% CI: 0.54–0.96). Then, this risk tended to increase with the percentage of increase in dosage, from 0.93 for percentages between 30 and 50% up to 1.11 for percentages exceeding 50%. Pregnancies receiving a dosage increase of 30% or less are assumed to have had less severe hypothyroidism than those receiving higher dosage increases. It is therefore possible that this tendency of the RR to increase could be explained by the severity of hypothyroidism itself. Finally, findings were also consistent when we considered a time-varying daily levothyroxine exposure, showing no association with prematurity risk.

Previous studies reported that prematurity risk was similar among pregnant individuals with hypothyroidism treated with levothyroxine versus those untreated [17, 18, 36]. Yet, these studies had a small sample size and lacked precision. It was not clear whether the absence of prematurity cases among the treated group was caused by the small number of subjects included or by levothyroxine use. Moreover, a recent meta-analysis reported that levothyroxine did not influence prematurity risk but declared that existing studies lacked the statistical power needed to obtain firm conclusions [37].

Two previous prospective trials reported a significant reduction of prematurity risk associated with levothyroxine [16, 38]. In the first trial, a 70% decrease in this risk was observed among treated pregnancies that were positive to thyroid antibodies which implicate the presence of an autoimmune hypothyroid disorder, compared with those untreated [38]. Moreover, a 62% reduction in the risk was observed in the second trial among treated pregnancies having TSH concentrations > 4 mui/l but no improvement was observed among those having TSH concentrations > 2 mui/l [16]. These findings support the benefits of levothyroxine use for hypothyroidism in pregnancy especially in more severe cases. Yet, our results cannot be directly compared to those of the above-mentioned studies, most of which focused on subclinical hypothyroidism, unlike our study which included

any type of maternal hypothyroidism. Nevertheless, we conducted multiple analyses in order to control for hypothyroid severity.

In contrast, two previous population-based studies reported an increased prematurity risk associated with levothyroxine gestational exposure [20, 21]. Indeed, a cohort study by Maraka et al. showed a 60% increase in this risk among pregnant individuals having hypothyroidism and exposed to levothyroxine versus those unexposed (adjusted odds ratio (aOR), 1.60; 95% CI, 1.14–2.24) [20]. The authors suggested that this increased risk might be due to hypothyroidism itself [20]. However, no analysis was considered to control for hypothyroidism severity. A second study by Ge et al. also reported that levothyroxine was associated with a 22% increase of prematurity risk [21]. However, Ge et al. compared hypothyroid individuals with euthyroid individuals and also declared that the risk might be attributable to hypothyroidism itself [21]. To control for hypothyroid severity, Ge et al. stratified pregnancies according to cumulative doses of levothyroxine during gestation and found that an exposure to both low (less than 13,150 mcg) and high (more than 13,150 mcg) cumulative doses were associated with 21% and 23% increase in prematurity risk, respectively [21]. Yet, these groups were also compared with an euthyroid group so the effect of hypothyroidism on the estimated association cannot be eliminated. In our study, a cohort of pregnant individuals with hypothyroidism was selected to reduce indication bias. Our primary analyses considered pregnancies who did not receive levothyroxine as a reference group; these pregnancies probably had mild hypothyroidism and were at lower risk of complications than the exposed group. This could overestimate the risk among exposed pregnancies. However, results did not show any increase in the risk of prematurity in exposed pregnancies versus unexposed pregnancies, so it is unlikely that this had impacted our results. Also, as mentioned above, the risk did not vary across the categories with higher cumulative or mean daily doses, which reflect more severe cases. Unlike our study, the mentioned studies could also be subjected to exposure misclassification bias and immortal time bias. Exposure was defined as having filled one prescription (Maraka et al.) or two prescriptions (Ge et al.) for levothyroxine at any time during gestation. However, exposure was defined more precisely in our study with the primary analyses restricted to the last 2 months before delivery (preterm deliveries) or before the 37th week of gestation (term deliveries).

Thyroid hormones play a crucial role in regulating the invasion and proliferation of trophoblasts during placental development [8, 39]. Therefore, a deficiency in thyroid hormones in maternal hypothyroidism may lead to an abnormal placental development and consequently to a premature delivery. On the other hand, hypothyroidism may cause an inflammation at various times throughout pregnancy, which in turn may trigger a premature delivery [22]. Our findings showed that levothyroxine exposure in late pregnancy did not affect prematurity risk so it could be considered to normalize thyroid hormones levels in pregnancies having hypothyroidism, preventing thyroid hormones deficiency and therefore reducing prematurity risk. However, given that levothyroxine overtreatment may itself increase prematurity risk [40], further studies considering both thyroid status using laboratory tests and levothyroxine exposure are still needed to assess more precisely prematurity risk associated with gestational levothyroxine exposure based on thyroid status.

Strengths and limitations

This study used a large population-based cohort, the QPC, with accurate pharmaceutical prescription fillings. Zhao et al. found that data on prescription fillings for levothyroxine in the QPC were valid, with positive and negative predictive values of 100% and 95%, respectively [28]. Medication exposure measurements considered overlaps and gaps between prescriptions, as well as dosage variations, in order to define exposure more comprehensively. In addition, using prescription fillings is more reliable than medical prescriptions: it reduces exposure to misclassification biases and eliminates recall biases. Findings were robust to different definitions of exposure considered. Primary analyses were restricted to a 2-months time-window before delivery (for preterm deliveries) or before 37th weeks' gestation (for term deliveries) limiting potential immortal time bias [31, 41]. Also, term deliveries were censored after the beginning of the 37th weeks' gestation as they were no longer at risk afterwards [33, 42]. The gestational age in the QPC was validated by ultrasound and allowed to obtain the exact duration of gestation [26]. Thus, it was used to precisely identify prematurity and exposure timing, limiting both outcome and exposure misclassifications. The QPC also contains detailed information on potential confounders for which we adjusted all our analyses. This study was restricted to a cohort of pregnancies with hypothyroidism, minimizing indication bias. However, due to the lack of laboratory data, we could not categorize pregnancies according to TSH concentrations that indicate hypothyroidism severity. Yet, in order to control for severity, pregnancies were categorized based on cumulative doses, mean daily doses, and dosage variation. The QPC also lacks data on maternal weight and lifestyle such as smoking status, alcohol consumption, and illicit drug use. However, we used the following proxies: obesity, tobacco, alcohol,

and other drug dependencies to consider maternal lifestyle; yet, residual confounding may persist given that we adjusted for severe exposure to these substances. Also, we could not consider family history of prematurity and parity that may also affect prematurity risk. Given that our outcome is prematurity, the cohort was restricted to pregnancies who gave birth and stillbirths were censured; however, this could increase selection bias risks. Only pregnancies insured by the Public Drug Insurance Plan were included. Although previous studies showed that publicly and privately insured pregnancies have similar characteristics and co-morbidities profile, the generalizability of the study findings to privately insured pregnancies is limited despite its unaffected internal validity [43].

Conclusions

This large population-based cohort study of pregnancies with hypothyroidism showed that levothyroxine exposure in late pregnancy was safe and did not increase prematurity risk. Also, the risk didn't vary in pregnancies with unregulated thyroid function illustrated by higher dosage requirements, suggesting a possible beneficial effect of levothyroxine on prematurity risk. This is important and should be considered in revising current treatment guidelines.

Abbreviations

TSH	Thyroid-stimulating hormone
QPC	Quebec Pregnancy Cohort
RAMQ	Régie de l'Assurance Maladie du Québec
ICD-9	Nineth version of the International Classification of Diseases
ICD-10	Tenth version of the International Classification of Diseases
LMP	Last menstrual period
GEE	Generalized estimating equations
RR	Risk ratios
CI	Confidence interval
aRR	Adjusted risk ratios
aOR	Adjusted odds ratios

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03934-1.

Additional file 1: Table S1. Diagnostic codes and drugs used to define pregnancies having hypothyroidism. Table S2. List of fetotoxic medications. Table S3. Diagnostic codes and drugs used to define co-morbidities. Table S4. Diagnostic codes used to define lifestyle proxies. Table S5. Diagnostic codes used to define obstetrical complications. Table S6. Means and quantiles of the cumulative dose and mean daily dose in the 2-months time-window (2-months before delivery for preterm deliveries or before 37th weeks' gestation for term deliveries). Table S7: Characteristics of pregnancies based on levothyroxine exposure duration in the 2-months time-window. Table S8. Characteristics of pregnancies based on levothyroxine cumulative dose in the 2-months time-window. Table S9. Characteristics of pregnancies based on levothyroxine mean daily dose in the 2-months time-window. Table S10. Distribution of pregnancies based on the timing of exposure to levothyroxine. Table S11. Distribution of pregnancies based on dosage variation after the beginning of the second trimester. Table S12. Characteristics of pregnancies based on levothyroxine dosage variation after the beginning of the second trimester. Table S13. Characteristics of pregnancies based on the percentage of increase in levothyroxine dosage after the beginning of the second trimester.

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Authors' Twitter handles

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Authors' contributions

For this study, A.B. was the project supervisor, data custodian and received funding from CFI and CIHR. M.L., O.S. and A.B. contributed to the conception and design of the work. M.L. handled the databases and conducted the analyses. All authors interpreted the findings and drafted the manuscript. All authors critically reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate/publication

The acquisition of the data for the creation of the Quebec Pregnancy Cohort was approved by the Ethics Review Board of Centre Hospitalier Universaire Sainte-Justine, Montreal (reference numbers: 1740 and 2976). Additionally, the Commission d'accès à l'information authorized the linkage of databases (reference number: 1005446-S). The study was conducted in compliance with Canadian research regulations. Administrative data from the provincial health systems of Quebec were used for the study. All data were anonymized to ensure the confidentiality of individuals, and no personally identifiable information is accessible or shareable. Only aggregate data resulting from analyses will be published. Consequently, informed consent from individual participants was not required for this study.

Competing interests

The authors declare no competing interests.

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References

1. Tsakiridis I, Giouleka S, Kourtis A, Mamopoulos A, Athanasiadis A, Dagklis T. Thyroid disease in pregnancy: a descriptive review of guidelines. Obstet Gynecol Surv. 2022;77(1):45–62.
2. Thyroid Disease in Pregnancy: ACOG Practice Bulletin, Number 223. Obstet Gynecol. 2020;135(6):e261–e274. https://doi.org/10.1097/AOG.0000000000003893.
3. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis

and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017;27(3):315–89.
4. Stagnaro-Green A, Pearce E. Thyroid disorders in pregnancy. Nat Rev Endocrinol. 2012;8(11):650–8.
5. Yazbeck CF, Sullivan SD. Thyroid disorders during pregnancy. Med Clin North Am. 2012;96(2):235–56.
6. Moini J, Pereira K, Samsam M. Structures and functions of the thyroid gland. Epidemiol Thyroid Disord. 2020:21–43. https://doi.org/10.1016/B978-0-12-818500-1.00002-5.
7. Stenzel D, Huttner WB. Role of maternal thyroid hormones in the developing neocortex and during human evolution. Front Neuroanat. 2013;7:19.
8. Kilby MD, Barber K, Hobbs E, Franklyn JA. Thyroid hormone action in the placenta. Placenta. 2005;26(2–3):105–13.
9. Mannisto T, Mendola P, Grewal J, Xie Y, Chen Z, Laughon SK. Thyroid diseases and adverse pregnancy outcomes in a contemporary US cohort. J Clin Endocrinol Metab. 2013;98(7):2725–33.
10. Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, Visser WE, Visser W, de Muinck Keizer-Schrama SM, et al. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. J Clin Endocrinol Metab. 2013;98(11):4382–90.
11. Chan S, Boelaert K. Optimal management of hypothyroidism, hypothyroxinaemia and euthyroid TPO antibody positivity preconception and in pregnancy. Clin Endocrinol (Oxf). 2015;82(3):313–26.
12. Sheehan PM, Nankervis A, Araujo Junior E, Da Silva CF. Maternal thyroid disease and preterm birth: systematic review and meta-analysis. J Clin Endocrinol Metab. 2015;100(11):4325–31.
13. World Health Organization. Preterm birth. WHO; 2023. Available from: https://www.who.int/en/news-room/fact-sheets/detail/preterm-birth.
14. Crump C. An overview of adult health outcomes after preterm birth. Early Hum Dev. 2020;150: 105187.
15. Canadian Institute for Health Information. ChildBirth indicators by place of residence 2020. Available from: https://apps.cihi.ca/mstrapp/asp/Main.aspx?evt=2048001&documentID=029DB170438205AEBCC75B8673CCE822&Server=apmstrextprd_i&Project=Quick+Stats&.
16. 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. J Clin Endocrinol Metab. 2018;103(3):926–35.
17. Wang S, Teng WP, Li JX, Wang WW, Shan ZY. Effects of maternal subclinical hypothyroidism on obstetrical outcomes during early pregnancy. J Endocrinol Invest. 2012;35(3):322–5.
18. Maraka S, Singh Ospina NM, O'Keeffe DT, Rodriguez-Gutierrez R, Espinosa De Ycaza AE, Wi CI, et al. Effects of levothyroxine therapy on pregnancy outcomes in women with subclinical hypothyroidism. Thyroid. 2016;26(7):980–6.
19. 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.
20. Maraka S, Mwangi R, McCoy RG, Yao X, Sangaralingham LR, Singh Ospina NM, et al. Thyroid hormone treatment among pregnant women with subclinical hypothyroidism: US national assessment. BMJ. 2017;356:i6865.
21. Ge GM, Cheung ECL, Man KKC, Ip P, Leung WC, Li GHY, et al. Association of maternal levothyroxine use during pregnancy with offspring birth and neurodevelopmental outcomes: a population-based cohort study. BMC Med. 2022;20(1):390.
22. Johns LE, Ferguson KK, McElrath TF, Mukherjee B, Seely EW, Meeker JD. Longitudinal profiles of thyroid hormone parameters in pregnancy and associations with preterm birth. PLoS One. 2017;12(1):e0169542.
23. Mother To Baby | Fact Sheets [Internet]. Brentwood (TN): Organization of Teratology Information Specialists (OTIS); 1994-. Critical Periods of Development. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK582659/.
24. Berard A, Sheehy O. The Quebec pregnancy cohort–prevalence of medication use during gestation and pregnancy outcomes. PLoS One. 2014;9(4):e93870.
25. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidem ological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol. 1995;48:999–1009.
26. Vilain A, Otis S, Forget A, Blais L. Agreement between administrative databases and medical charts for pregnancy-related variables among asthmatic women. Pharmacoepidemiol Drug Saf. 2008;17(4):345–53.
27. Quan H, Li B, Saunders LD, Parsons GA, Nilsson CI, Alibhai A, et al. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. Health Serv Res. 2008;43(4):1424–41.
28. Zhao JP, Sheehy O, Gorgui J, Berard A. Can we rely on pharmacy claims databases to ascertain maternal use of medications during pregnancy? Birth Defects Res. 2017;109(6):423–31.
29. Dashe JS, Casey B, Wells CE, McIntire DD, Byrd EW, Leveno KJ, Cunningham FG. Thyroid-stimulating hormone in singleton and twin pregnancy: importance of gestational age-specific reference ranges. Obstet Gynecol. 2005;106(4):753–7.
30. Kulaga S, Zargarzadeh AH, Berard A. Prescriptions filled during pregnancy for drugs with the potential of fetal harm. BJOG. 2009;116(13):1788–95.
31. Matok I, Azoulay L, Yin H, Suissa S. Immortal time bias in observational studies of drug effects in pregnancy. Birth Defects Res A Clin Mol Teratol. 2014;100(9):658–62.
32. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. Ann Transl Med. 2018;6(7):121.
33. Platt RW, Hutcheon JA, Suissa S. Immortal time bias in epidemiology. Current Epidemiology Reports. 2019;6(1):23–7.
34. Schummers L, Hutcheon JA, Hernandez-Diaz S, Williams PL, Hacker MR, VanderWeele TJ, et al. Association of short interpregnancy interval with pregnancy outcomes according to maternal age. JAMA Intern Med. 2018;178(12):1661–70.
35. Li B, Zhang X, Peng X, Zhang S, Wang X, Zhu C. Folic acid and risk of preterm birth: a meta-analysis. Front Neurosci. 2019;13:1284.
36. Lepoutre T, Debieve F, Gruson D, Daumerie C. Reduction of miscarriages through universal screening and treatment of thyroid autoimmune diseases. Gynecol Obstet Invest. 2012;74(4):265–73.
37. Jiao XF, Zhang M, Chen J, Wei Q, Zeng L, Liu D, et al. The impact of levothyroxine therapy on the pregnancy, neonatal and childhood outcomes of subclinical hypothyroidism during pregnancy: an updated systematic review, meta-analysis and trial sequential analysis. Front Endocrinol (Lausanne). 2022;13:964084.
38. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majd H, Azizi F. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. Eur J Endocrinol. 2017;176(2):253–65.
39. Rao M, Zeng Z, Zhou F, Wang H, Liu J, Wang R, et al. Effect of levothyroxine supplementation on pregnancy loss and preterm birth in women with subclinical hypothyroidism and thyroid autoimmunity: a systematic review and meta-analysis. Hum Reprod Update. 2019;25(3):344–61.
40. Lemieux P, Yamamoto JM, Nerenberg KA, Metcalfe A, Chin A, Khurana R, et al. Thyroid laboratory testing and management in women on thyroid replacement before pregnancy and associated pregnancy outcomes. Thyroid. 2021;31(5):841–9.
41. Suissa S, Dell'aniello S, Vahey S, Renoux C. Time-window bias in case-control studies: statins and lung cancer. Epidemiology. 2011;22(2):228–31.
42. Chang HH, Warren JL, Darrow LA, Reich BJ, Waller LA. Assessment of critical exposure and outcome windows in time-to-event analysis with application to air pollution and preterm birth study. Biostatistics. 2015;16(3):509–21.
43. Berard A, Lacasse A. Validity of perinatal pharmacoepidemiologic studies using data from the RAMQ administrative database. Can J Clin Pharmacol. 2009;16(2):e360–9.

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