The impact of levothyroxine exposure on delivery outcome in hypothyroid pregnant women (PETAL study): A five-year retrospective cohort study

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Abstract

Background: Hypothyroidism affects 3% of pregnant women, and to date, no studies have addressed the impact levothyroxine-treated hypothyroidism on delivery outcome.

Methods: This retrospective cohort study was conducted among 750 women with a singleton pregnancy who gave birth between 2015 and 2019. Delivery modes were compared between 250 hypothyroid women exposed to levothyroxine and 500 euthyroid control women. The aim of this study was to determine the impact of levothyroxine exposure on delivery outcome.

Results: Multiple logistic regression showed no significant association between exposure to levothyroxine and the overall rate of caesarean delivery (aOR 1.1; 95% CI 0.8 to 1.6). Mean TSH concentrations were significantly higher throughout the pregnancy in hypothyroid women despite levothyroxine treatment. Maternal and neonatal outcomes in both groups were not different.

Conclusion: Hypothyroidism treated with levothyroxine during pregnancy according to local guidelines is not a significant risk factor for caesarean delivery.

Keywords
Perinatal outcome, hypothyroidism, levothyroxine, caesarean delivery, uterine contractions, pregnancy

Date Received: 25 June 2021; accepted: 15 November 2021

Introduction

Hypothyroidism affects between 2% and 5% of pregnant women.1 Thyroid hormone deficiency is known to cause adverse effects on pregnancy that impact the delivery outcome, such as pre-eclampsia, placenta abruption, and prematurity.1,2 Some studies have also demonstrated a possible association with dystocia and fetal malpresentation leading to caesarean deliveries (CD), and this was explained by the possible thyroid hormonal influence on myometrial cell contraction and relaxation.3,4 Turunen et al. supported this finding while observing an increased CD rate for hypothyroid pregnant women (21.2%) compared to euthyroid pregnant women (15.7%).5 They also observed a persistent significant risk association between CD and hypothyroidism treated with levothyroxine (OR 1.1, 95% CI 1.1–1.2) compared to euthyroidism. This finding supposes a slight attenuating effect of levothyroxine over the impact of hypothyroidism on uterine contractility and vaginal delivery prognosis, although the thyroid function nor the prescribed doses of levothyroxine were not considered in this study.5

CD have increased from 18.0% to 28.8% over the last 25 years in Canada, with similar increases in other countries.5,6 Both emergency and elective CD are associated with increased maternal morbidity and mortality secondary to post-partum hemorrhage, infection, thromboembolic events8–10 and substantial costs for the health-care system.1 Besides fetal distress, dystocia is the main indication for CD.5

There is a paucity of data about the effect of levothyroxine treatment on the delivery mode of women diagnosed with overt or subclinical hypothyroidism. Our team showed in previous studies a possible dose-dependent effect of levothyroxine on the uterine contractility pattern. For instance, we demonstrated decreased contraction frequency and increased amplitude and duration of contractions in the myometrium biopsies from hypothyroid women who were treated with levothyroxine throughout their pregnancy, and who had an elective CD.11 We conducted a second study where the same altered contraction pattern was observed in hypothyroid female rats that were supposedly over-supplemented with levothyroxine, although their thyroid function was not verified.12 Therefore, exposure to an inappropriate dosage of levothyroxine may possibly affect the uterine contraction efficiency in peripartum.

The objective of this retrospective cohort study was to evaluate the association between hypothyroidism treated with levothyroxine (according
Methods

Design and participants

We conducted a retrospective cohort study with matched groups at the Centre Hospitalier Universitaire de Sherbrooke (CHUS) in Quebec, Canada. Our population included all women with a singleton pregnancy who delivered at the CHUS after 24 weeks of gestation. Women with multiple gestation were excluded. A database of all deliveries from 2015 to 2019 was created by our archives’ info-center, presenting extracted data from medical records including the CHUS record number, date of delivery, maternal age, gestational age at delivery and parity. The ICD code for unspecified endocrine disorder (E34.9) was also extracted for each woman in the database where applicable. Records presenting this code included diagnoses of overt and subclinical hypothyroidism. Diagnosis was made by a medical physician either before the current pregnancy or at the first trimester of pregnancy through the hypothyroidism universal screening program, in presence of TSH serum concentrations above 3.5 mUI/L and clinical presentation.

Starting from the most recent delivery of 2019, each record associated with the E34.9 ICD code was reviewed by the first author (DO) to verify a diagnosis of hypothyroidism and treatment with levothyroxine. Through a convenient sampling method, the first 250 women found to have confirmed diagnosis of clinical or subclinical hypothyroidism (according to the local clinical guidelines) and a confirmed treatment with levothyroxine were selected and then assigned to the hypothyroid levothyroxine-exposed group.

For each selected hypothyroid woman exposed to levothyroxine, two control euthyroid women (without an E34.9 ICD code) were matched according to maternal age, parity and gestational age at delivery. These characteristics influence the delivery mode and were also used to match groups in previous studies assessing the delivery outcome. The control group consisted of 500 euthyroid pregnant women not exposed to levothyroxine.

Each woman could only be included once. For hypothyroid women, only their most recent pregnancy was included in the levothyroxine-exposed group.

| Table 1. Maternal, gestational, and neonatal cohort characteristics. | Levothyroxine-exposed group (n = 250) | Control group (n = 500) | p value |
| --- | --- | --- | --- |
| **Maternal characteristics** | | | |
| Maternal age (years) | 29.77 ± 4.62 | 29.77 ± 4.62 | 1.00 |
| Parity | 0.78 ± 0.95 | 0.78 ± 0.95 | 1.00 |
| Primiparous | 50.4% | 50.4% | 1.00 |
| **Pre-pregnancy conditions** | | | |
| BMI (kg/m²) | 27.38 ± 7.23 | 26.00 ± 6.18 | **0.02** |
| Obesity (> 30 kg/m²) | 29.2% | 22.8% | 0.06 |
| Diabetes (type I or type II) | 2.0% | 0.4% | **0.04** |
| Hypertension | 3.6% | 1.2% | **0.03** |
| Preexisting hypothyroidism | 64.4% | 0.8% | <**0.001** |
| Other medical conditions | 15.6% | 23.6% | **0.01** |
| **Gestational characteristics** | | | |
| TPL | 1.2% | 0.8% | 0.69 |
| PPROM | 0.4% | 1.0% | 0.67 |
| Abruptio placenta | 1.6% | 1.6% | 1.00 |
| Gestational diabetes | 14.0% | 12.2% | 0.49 |
| Gestational HTN | 6.8% | 5.8% | 0.59 |
| Pre-eclampsia | 2.0% | 3.2% | 0.35 |
| IUGR | 1.6% | 3.2% | 0.20 |
| Placental anomaly | 0.8% | 1.0% | 1.00 |
| Oligohydramnios | 0.4% | 1.6% | 0.29 |
| Polyhydramnios | 1.2% | 1.0% | 1.00 |
| Chorioamnionitis | 1.2% | 4.0% | **0.04** |
| **Neonatal characteristics** | | | |
| Gestational age (weeks) | 38.85 ± 1.31 | 38.85 ± 1.31 | 1.00 |
| Prematurity (<37 weeks) | 3.2% | 3.2% | 1.00 |
| Term (≥37, <40 weeks) | 62.4% | 62.4% | 1.00 |
| Post-term (≥40 weeks) | 34.4% | 34.4% | 1.00 |
| Birth weight (g) | 3333.02 ± 455.78 | 3316.79 ± 492.00 | 0.66 |
| Umbilical cord blood pH | 7.24 ± 0.07 | 7.21 ± 0.23 | 0.17 |
| APGAR score <7 at 5 min | 4.0% | 3.6% | 0.79 |
| NCU transfer | 10.4% | 9.6% | 0.73 |
| Stillbirth | 0.0% | 0.2% | 1.00 |

Data is presented as mean ± standard deviation or proportion, as appropriate.

p values were calculated from Student t-test or Mann–Whitney U test for continuous variables, and from χ² test or Fisher’s exact test for dichotomous variables.

BMI: body mass index; HTN: hypertension; TPL: threatened preterm labor; PPROM: premature preterm rupture of membranes; IUGR: intra-uterine growth retardation; PPH: post-partum hemorrhage; NCU: neonatal care unit (including intermediate and intensive neonatal care). Placental anomaly included: placenta previa (n = 2), placenta accreta (n = 1) grade 3 placenta (n = 2), hypertrophic placenta (n = 1).

Results in bold represent statistically significant results.

to local clinical guidelines) and delivery outcome, while comparing hypothyroid pregnant women to euthyroid pregnant women, matched according to age, parity and gestational age at delivery as per previous studies.
assessing this outcome, including maternal, gestational, obstetric and neonatal characteristics that may influence the delivery mode. The secondary outcomes were (1) rates of assisted vaginal delivery (VAD) in relation with exposure to levothyroxine, (2) indications for CD and VAD, and (3) maternal and neonatal morbidity and mortality.

To determine the potential effect of levothyroxine exposure on delivery outcome, the operative delivery indications were categorized as “uterine muscle dysfunction related” indications or unrelated indications. Based on our initial hypothesis, the former category included dystocia and fetal malpresentation, in addition to uterine atony and maternal exhaustion as direct and indirect contributing factors to dystocia. Previous history of CD due to the potential impact of tissue scarring on uterine muscle function is also included in this category, as well as post-term pregnancy and failure of induced vaginal delivery, representing other signs of uterine muscle rigidity and decreased sensitivity to uterotonic agents.

In comparison, the unrelated indications included fetal distress, the most frequent indication of operative delivery unrelated to the uterine function. We also collected all available TSH concentration values throughout all trimesters of pregnancy for each participant. Since universal screening for hypothyroidism in the first trimester was implemented at the CHUS before 2015, all women had at least one TSH concentration measurement in the first trimester of pregnancy. Hypothyroid women were all followed with serial TSH concentration measurements and treated with adjusted dosage of levothyroxine according to the local hypothyroidism in pregnancy protocol used uniformly by all health care professionals in our center, targeting a TSH value under 3.5 mIU/L. Euthyroid women had routine TSH measurement in the first trimester and only occasionally thereafter, according to clinical indications.

The project was approved by the CRUSSS de l’Estrie-CHUS research ethics committee with a delegated consent process (exempt from requiring individual consent (2017–1764)).

### Statistical analysis

A previous local data review done by the Department of Obstetrics and Gynecology of Université de Sherbrooke showed an increased CD delivery rate in hypothyroid women treated with levothyroxine, estimating a possible effect size of 20% when compared to non-hypothyroid women not exposed to levothyroxine. Based on this information, the size of the levothyroxine-exposed group and the control group have been established respectively as 250 and 500 women, for a power of 80% and an alpha level of 5%.

Statistical analysis was performed using IBM SPSS Statistics 27.0. Descriptive analysis was presented as frequencies and proportions for categorical variables, and as mean and standard deviations for continuous numerical variables. Differences between groups were evaluated with chi-square test or Fisher’s exact test for categorical variables, and with Student t test or Mann Whitney U test for continuous numeric variables. The risk association between levothyroxine exposure during pregnancy and delivery mode was assessed by simple and multivariable logistic regression models including variables with statistically or clinically significant associations. No regression model selection procedure was used. Significant confounding variables with p<0.05 in univariable analysis were all included in the multivariable model. TSH values during the pregnancy were not considered in the model as a marker of adequate dosage of levothyroxine; exposure alone to levothyroxine was considered in hypothyroid women in this model. Confidence intervals for non-adjusted and adjusted odds ratios were calculated with an alpha level of 5%.

### Results

Between January 2015 and December 2019, 13 923 deliveries occurred at the CHUS. Among these women, 66.8% had a spontaneous vaginal

### Table 2. Indications for each operative delivery mode, including overall, elective and emergency caesarean delivery, and assisted vaginal delivery.

| Indication                          | Levothyroxine-exposed group | Control group |
|------------------------------------|-----------------------------|--------------|
| Overall caesarean delivery         |                             |              |
| Possible uterine muscle dysfunction|                             |              |
| Dystocia                           | 16 (23.9)                   | 18 (14.5)    | 0.106 |
| Uterine atony                      | 0 (0.0)                     | 9 (7.3)      | 0.028 |
| Abnormal fetal presentation        | 0 (0.0)                     | 0 (0.0)      | 1.000 |
| Maternal exhaustion                | 0 (0.0)                     | 11 (9.0)     | 0.059 |
| Post-term pregnancy                | 1 (1.5)                     | 11 (8.1)     | 0.059 |
| Failed vaginal delivery            | 1 (1.5)                     | 9 (6.5)      | 0.059 |
| Previous CD                        | 23 (34.3)                   | 36 (29.0)    | 0.450 |
| Fetal distress                     | 15 (22.4)                   | 40 (32.3)    | 0.151 |
| Elective caesarean delivery        |                             |              |
| Possible uterine muscle dysfunction|                             |              |
| Dystocia                           | 25 (73.5)                   | 60 (82.2)    | 0.302 |
| Uterine atony                      | 0 (0.0)                     | 8 (11.0)     | 0.053 |
| Abnormal fetal presentation        | 6 (17.6)                    | 6 (8.2)      | 0.191 |
| Maternal exhaustion                | 1 (2.9)                     | 12 (15.1)    | 0.098 |
| Post-term pregnancy                | 1 (2.9)                     | 7 (9.6)      | 0.431 |
| Failed vaginal delivery            | 1 (2.9)                     | 5 (6.8)      | 0.662 |
| Previous CD                        | 22 (66.7)                   | 31 (40.8)    | 0.585 |
| Fetal distress                     | 34 (13.6)                   | 73 (26.4)    | 0.018 |

p values were calculated from χ² test or Fisher’s exact test for dichotomous variables. CD: caesarean delivery; VAD: vaginal delivery; previous CD: previous history of caesarean delivery. Results in bold represent statistically significant results.
Results in bold represent statistically significant results.

delivery \((n = 9302)\), 24.6% had a CD \((n = 3424)\), and 8.6% had an VAD \((n = 1197)\). We excluded 289 women for multiple gestation and 63 women for delivery before 24 weeks of gestation. A total of 3081 women had more than one delivery during this period, which represented repetitive medical records. Of the remaining 10 490 records, 750 women were selected according to inclusion criteria.

Descriptive statistics regarding maternal, gestational, and neonatal characteristics are presented in Table 1. There was no difference between groups regarding the matching variables. Of the women exposed to levothyroxine, 64.4% had a diagnosis of hypothyroidism prior to pregnancy. Also, women exposed to levothyroxine showed a significantly higher body mass index (BMI) at the beginning of the pregnancy \((27.38 \text{vs. 26.00 kg/m}^2, p = 0.02)\), although the proportion of obese women was similar \((29.2\% \text{vs. 22.8\%,} p = 0.06)\). Women exposed to levothyroxine had higher rates of diabetes, hypertension and hypothyroidism prior to the pregnancy. In contrast, control women were significantly more affected by other medical conditions not related to thyroid function \((23.6\% \text{vs. 15.6\%,} p = 0.01)\), asthma and other cardiopulmonary conditions being the most frequent in this group. Chorioamnionitis was significantly more frequent in the control group \((4.0\% \text{vs. 1.2\%,} p = 0.04)\), and there were otherwise no significant differences between groups regarding gestational characteristics. There were also no significant differences between groups in terms of neonatal characteristics.

The prevalence of the operative delivery modes and their respective indications are depicted in Table 2. No difference was observed in the prevalence of overall CD in the levothyroxine-exposed group \((26.8\% \text{vs. 24.8\%,} p = 0.553)\), compared to the control group. When analyzing the indications of overall CD rate, uterine atony was more frequent in the control group compared with the levothyroxine-exposed group \((7.3\% \text{vs. 0.0\%,} p = 0.028)\). Otherwise, there was no difference between groups regarding any of the operative delivery indications, whether related or unrelated to possible uterine muscle dysfunction.

TABLE 3. Univariable logistic regression analysis to establish the risk association between exposure to levothyroxine during pregnancy and the delivery mode.

| Variables                      | Overall CD aOR (CI) | Elective CD aOR (CI) | Emergency CD aOR (CI) | VAD aOR (CI) |
|-------------------------------|---------------------|----------------------|-----------------------|--------------|
| Levothyroxine exposure        | 1.1 (0.8–1.6)       | 1.3 (0.8–2.2)        | 0.9 (0.6–1.4)         | 0.9 (0.5–1.5) |
| Prematurity                   | 1.6 (1.1–2.3)       | 7.9 (3.4–18.4)       | 0.7 (0.4–1.0)         | 0.7 (0.4–1.2) |
| Post-term delivery            | 1.7 (0.7–4.2)       | 8.4 (2.2–32.2)       | 0.5 (0.1–1.8)         | 0.7 (0.2–2.4) |
| AMA                           | 1.2 (0.8–1.8)       | 1.5 (0.8–2.6)        | 1.0 (0.5–1.8)         | 1.3 (0.7–2.3) |
| Multiparity                   | 0.6 (0.4–0.8)       | 3.2 (1.9–5.4)        | 0.1 (0.1–0.2)         | 0.2 (0.1–0.4) |
| Preexisting diabetes          | 4.0 (0.9–17.9)      | 1.3 (0.2–11.1)       | 4.6 (1.0–20.9)        | ---          |
| Preterm HTN                   | 1.5 (0.5–4.4)       | 2.0 (0.6–7.3)        | 0.9 (0.2–4.1)         | 0.7 (0.1–5.2) |
| Obesity                       | 1.8 (1.2–2.6)       | 1.7 (1.0–2.8)        | 1.6 (1.0–2.4)         | 0.7 (0.4–1.3) |
| TPT                           | 0.5 (0.1–4.1)       | ---                  | 1.0 (0.1–8.4)         | ---          |
| PPROM                         | 0.6 (0.1–5.0)       | ---                  | 1.2 (0.1–10.4)        | ---          |
| Abruptio placenta             | 0.3 (0.0–2.0)       | 0.7 (0.1–5.6)        | 0.0 (0.0–)            | 0.9 (0.1–6.7) |
| Gestational diabetes          | 1.0 (0.6–1.6)       | 0.9 (0.5–1.8)        | 1.0 (0.6–1.9)         | 0.7 (0.3–1.6) |
| Gestational HTN               | 1.6 (0.9–3.0)       | 1.0 (0.4–2.5)        | 2.0 (0.9–4.0)         | 1.5 (0.6–3.5) |
| Pre-eclampsia                 | 1.5 (0.6–3.7)       | 1.3 (0.4–4.6)        | 1.4 (0.5–4.3)         | 1.0 (0.2–4.3) |
| Oligohydramnios               | 3.6 (0.9–14.1)      | 1.2 (0.1–10.7)       | 4.6 (1.1–20.2)        | 1.1 (0.1–9.6) |
| Polyhydramnios                | 1.8 (0.4–7.5)       | ---                  | 3.7 (0.9–15.6)        | ---          |
| Abnormal placenta             | 1.1 (0.2–6.1)       | 0.8 (0.1–7.1)        | 1.3 (0.1–12.6)        | 4.4 (0.7–27.9) |
| Chorioamnionitis              | 3.2 (1.3–7.7)       | 1.00 (1.0–7.9)       | 3.1 (1.3–7.6)         | 1.6 (0.5–4.5) |

CD: caesarean delivery; aOR: adjusted odds ratio; CI: confidence intervals; AMA: advanced maternal age (≥ 35 years old); HTN: hypertension; TPT: threatened preterm labor; PPROM: preterm premature rupture of membranes.

Abnormal placenta included: placenta previa \((n = 2)\), placenta accreta \((n = 1)\), grade 3 placenta \((n = 2)\), hypertrophic placenta \((n = 1)\).

Table 4. Multivariable logistic regression model to establish the risk association between exposure to levothyroxine during pregnancy and the delivery mode.

| Significant variables            | Overall CD aOR (CI) | Elective CD aOR (CI) | Emergency CD aOR (CI) | VAD aOR (CI) |
|---------------------------------|---------------------|----------------------|-----------------------|--------------|
| Levothyroxine exposure          | 1.1 (0.8–1.6)       | 1.3 (0.8–2.2)        | 1.0 (0.6–1.5)         | 0.9 (0.5–1.6) |
| Prematurity                     | 1.7 (1.1–2.4)       | 8.1 (3.5–19.1)       | 0.7 (0.4–1.1)         | 0.7 (0.4–1.3) |
| Post-term delivery              | 1.6 (0.6–4.1)       | 12.3 (3.0–50.8)      | 0.5 (0.1–1.8)         | 0.6 (0.1–2.6) |
| AMA                             | 1.2 (0.8–2.0)       | 1.1 (0.6–2.0)        | 1.5 (0.8–2.8)         | 2.1 (1.0–4.2) |
| Multiparity                     | 0.6 (0.4–0.9)       | 3.4 (2.0–5.9)        | 0.1 (0.1–0.2)         | 0.2 (0.1–0.4) |
| Preexisting diabetes            | 3.7 (0.8–16.9)      | 0.8 (0.1–8.4)        | 6.4 (1.1–37.3)        | ---          |
| Obesity                         | 1.7 (1.2–2.5)       | 1.6 (1.0–2.7)        | 1.6 (1.0–2.7)         | 0.7 (0.3–1.2) |
| Oligohydramnios                 | 3.6 (0.9–14.1)      | 1.2 (0.1–10.7)       | 4.6 (1.1–20.2)        | 1.1 (0.1–9.6) |
| Abnormal placenta               | 1.1 (0.2–6.1)       | 0.8 (0.1–7.1)        | 1.3 (0.1–12.6)        | 4.4 (0.7–27.9) |
| Chorioamnionitis                | 3.2 (1.3–7.7)       | 1.00 (1.0–7.9)       | 3.1 (1.3–7.6)         | 1.6 (0.5–4.5) |

CD: caesarean delivery; aOR: adjusted odds ratio; CI: confidence intervals; AMA: advanced maternal age (≥ 35 years old). Abnormal placenta included: placenta previa \((n = 2)\), placenta accreta \((n = 1)\), grade 3 placenta \((n = 2)\), hypertrophic placenta \((n = 1)\).
The association between exposure to levothyroxine and delivery outcome was evaluated with a univariable logistic regression model, presented in Table 3. Variables with a statistically significant association with overall CD rate in the univariable analysis were then analyzed in the multivariable model (Table 4), along with other clinically-significant or protective factors. Controls were significantly more affected by other medical conditions unrelated to their thyroid function, which is likely explained by random occurrence. Otherwise, groups were comparable. Therefore, there was no difference in terms of maternal and fetal morbidity and mortality related to levothyroxine exposure.

The potential effects of the underlying hypothyroid condition should be considered while analyzing our results, as they might not represent the effect of levothyroxine alone. Based on the results our team previously demonstrated in fundamental research, we could presume a possible additional effect of levothyroxine due to overtreatment in hypothyroid pregnant women of our population. Some clinical studies also documented an increased risk of CD and labor induction with hyperthyroidism, where women are exposed to high thyroxine serum concentrations due to a pathological overstimulation of thyroid hormone production. Therefore, a prolonged uterine quiescent phase in late pregnancy could be hypothesized as a cause of fetal breech presentation, in addition to an inefficient uterine contraction pattern induced by a high thyroxine concentration state, resulting in an increase of overall CD rate. However, our study cannot support this hypothesis as the prescribed dosage, the women’s adherence to levothyroxine therapy and their thyroid function could not be assessed for all patients due to missing data. More studies are then needed to explore the effect of inappropriately treated hypothyroidism on delivery outcome.

Our results have also shown significantly higher TSH serum concentrations at each trimester of pregnancy in hypothyroid women compared to control women, despite their levothyroxine treatment. The TSH concentration value distribution was also analyzed, to compare the thyroid function status in both groups. According to these results, at least 25% of women from the exposed group were treated with an insufficient dosage of levothyroxine in the first trimester of pregnancy, as their 75th percentile TSH concentration value was above the targeted threshold for hypothyroidism to be controlled. This finding suggests potential underdosing of levothyroxine in at least 25% of hypothyroid women who were treated as recommended by the local guidelines, which could have influenced the outcomes observed in our study that differ with our initial hypothesis. However, whether this difference has a clinical impact is uncertain, and the missing data regarding the thyroid function of most of the euthyroid women in our study limits our interpretation.

Our study presented several limitations, the foremost being our sample size. Other studies investigating the impact of thyroid hormone variations and thyroid diseases on perinatal outcome were conducted with larger samples, often population-wide. For instance, Turunen et al. observed, in their population-based cohort including 16 364 hypothyroid pregnant women, a risk association between hypothyroidism treated with levothyroxine and CD with a significant odds ratio of 1.13 (95% CI 1.06 to 1.21). Several studies have observed a significantly increased prevalence of breech presentation and dystocia as indications for CD in

### Table 5. TSH serum concentration value distribution for each trimester of pregnancy.

| TSH serum concentration (mIU/L) | Levothyroxine-exposed group | Control group | p value |
|--------------------------------|-----------------------------|---------------|--------|
| Pre-pregnancy                   |                             |               |        |
| n = available data              | 188                         | 349           |        |
| Mean ± SD                       | 3.94 ± 11.13                | 1.73 ± 0.84   | <0.001 |
| Median (range)                  | 2.20 (115.99)               | 1.67 (5.78)   |        |
| 75th percentile                 | 3.39                        | 2.16          |        |
| 1st trimester                   |                             |               |        |
| n = available data              | 229                         | 470           |        |
| Mean ± SD                       | 4.02 ± 9.71                 | 1.48 ± 0.79   | <0.001 |
| Median (range)                  | 3.14 (145.00)               | 1.37 (3.50)   |        |
| 75th percentile                 | 4.30                        | 1.96          |        |
| 2nd trimester                   |                             |               |        |
| n = available data              | 200                         | 70            |        |
| Mean ± SD                       | 2.56 ± 2.91                 | 1.40 ± 0.82   | <0.001 |
| Median (range)                  | 2.10 (37.80)                | 1.19 (3.40)   |        |
| 75th percentile                 | 3.03                        | 1.98          |        |
| 3rd trimester                   |                             |               |        |
| n = available data              | 168                         | 30            |        |
| Mean ± SD                       | 2.76 ± 9.81                 | 1.26 ± 0.76   | 0.002  |
| Median (range)                  | 1.68 (127.90)               | 1.16 (3.00)   |        |
| 75th percentile                 | 2.48                        | 1.80          |        |

p values were calculated from Mann–Whitney U test for continuous variables. TSH: thyroid stimulating hormone; SD: standard deviation; T1, T2, and T3: first, second, and third trimester of pregnancy.

Discussion

In our study, we found no significant evidence regarding the previously-hypothesized risk association between levothyroxine exposure during pregnancy and overall CD rates. There was no significant association between exposure to levothyroxine and VAD. Our results also show no difference between groups concerning the specific indications of operative delivery, related or not to possible uterine muscle dysfunction, except for uterine atony in the overall CD rate. We observed that women exposed to levothyroxine were significantly less affected with uterine atony compared to control women, which could be explained as a possible less-exhausting uterine contraction activity when exposed to levothyroxine due to an absolute decreased number of contractions. As noticed in previous fundamental research, levothyroxine was shown indeed to decrease uterine contraction frequency. Hence, contrasting with our initial hypothesis, levothyroxine treatment may possibly decrease the occurrence of some uterine dysfunction related to underlying hypothyroidism. However, whether exposure to levothyroxine in pregnancy is a proper protective factor for uterine atony during labor needs further study.

Women exposed to levothyroxine were significantly more affected by pre-existing diabetes and hypertension, and tended to have a higher BMI at the beginning of the pregnancy, which could be related to their underlying hypothyroid condition that is known to be associated with metabolic and cardiovascular diseases, in addition to weight gain. Control women were significantly more affected by other medical conditions unrelated to their thyroid function, which is likely explained by random occurrence. Otherwise, groups were comparable. Therefore, there was no difference in terms of maternal and fetal morbidity and mortality related to levothyroxine exposure.

The 75th percentile value of TSH concentration was above 3.5 mIU/L in the levothyroxine-exposed group, meaning that the thyroid function of at least 25% of these hypothyroid women was not optimal. Respectively in the second and third trimesters of pregnancy, 70.0% and 45.5% of the exposed women presenting a TSH above the 75th percentile were also considered to have a suboptimal thyroid function. All the women from the control group had a TSH concentration value in the normal range throughout their pregnancy.

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women diagnosed with hypothyroidism (without specifying their treatment status). These tendencies are not significant in our study. Hence, a lack of power due to an overestimated effect size in the sample size calculation might explain our results. However, the 250 levothyroxine-exposed hypothyroid women were selected among 3182 eligible women, between the delivery dates of the first and the last selected women for this group, representing a prevalence of 7.9% of hypothyroidism during this period, which is slightly greater than the estimated hypothyroidism prevalence in the population. Moreover, obtaining such non-significant results in a smaller sample causes us to question the clinical significance of the effect of levothyroxine and of hypothyroidism on a perinatal outcome that is known to be only significant in very large samples. More studies are needed to answer this question.

Another limitation is our control group. The ideal control group would have been hypothyroid women not treated with levothyroxine. We believe that euthyroid women represented the most appropriate control group in terms of ethical and clinical issues, as the absence of levothyroxine treatment in hypothyroid pregnant women can lead to significant obstetric, neurologic and intellectual sequelae for the future newborn, particularly in the case of clinical hypothyroidism. Also, our study presents results that seem to contradict previous fundamental research suggesting both hypothyroidism and exposure to high-dosages of levothyroxine as risk factors for operative delivery, due to altered uterine muscle function. The inclusion of adequately and inadequately-treated hypothyroid women in the levothyroxine-exposed group might have influenced our results, and this lack of information limits the analysis of our study.

Finally, selection bias and information bias while collecting data from medical records were additional limitations of our study, as some information might not have been documented and as participants were not randomly selected.

Conclusion

Rates of CD did not differ between our cohort of hypothyroid women treated with levothyroxine and a selected and matched population of euthyroid women. These results are discordant with existing fundamental and clinical findings on the subject. Additional studies must be carried out with larger samples to determine the clinical significance of the previously-described levothyroxine effect on obstetric outcome, while paying particular attention to hypothyroid women who are not treated appropriately with levothyroxine during their pregnancy.

Acknowledgments

We would like to thank Audrey Hamel-Thibault for logistic assistance, Samuel Lemaire-Paquette for statistical support and Ju-Hong Lee for medical record access.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from the CIUSSS de l’Estrie-CHUS research ethics committee (2017–1764).

Informed consent

This study was exempt from informed consent by its retrospective nature.

Guarantor

Dr Jean-Charles Pasquier.

Contribution

Dr Jean-Charles Pasquier and Dr Diana Oprea researched literature, and Dr Jean-Charles Pasquier conceived the study. Dr Diana Oprea was also involved in protocol development, gaining ethical approval, patient selection, and data analysis. Dr Nadine Sauvé contributed to protocol adjustments, data analysis, and interpretation of results. Dr Diana Oprea wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved its final version.

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