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# Prevalence and Correlation of Hypothyroidism With Pregnancy Outcomes Among Lebanese Women

**Dima Ezzeddine,[1] Diala Ezzeddine,[1] Caroline Hamadi,[1] Hussein A. Abbas,[2] Anwar Nassar,[1] May Abiad,[3] and Ghina Ghazeeri[1]**

*[1]Department of Obstetrics and Gynecology, American University of Beirut Medical Center, Beirut 1107 2020, Lebanon; [2]School of Medicine, American University of Beirut Medical Center, Beirut 1107 2020, Lebanon; and [3]Department of Biology, American University of Beirut Medical Center, Beirut 1107 2020, Lebanon*

**Purpose:** Assessment of hypothyroidism prevalence and clinical significance among pregnant women in Lebanon.

**Methods:** We performed a single-center retrospective cohort study at the American University of Beirut Medical Center. Clinical, demographic, and laboratory data were collected and analyzed using trimester-specific ranges for hypothyroidism.

**Results:** Of 920 pregnant women, 17% had hypothyroidism during gestation. A history of previous miscarriage and morbid obesity were associated with hypothyroidism during pregnancy. Pregnant women with hypothyroidism were more likely to experience a miscarriage during the first trimester [odds ratio, 2.9; 95% confidence interval, (1.13 to 7.5); $P = 0.02$] and delivery at post-term (odds ratio, 3.9; 95% confidence interval, 1.05 to 14.9; $P = 0.05$). We found no substantial correlation with preterm or premature delivery, cesarean section delivery, or gestational hypertension despite increased odds among the hypothyroidism group. No substantial differences were found with respect to the fetal outcomes between the control and hypothyroidism groups.

**Conclusions:** Hypothyroidism is prevalent in 17% of pregnant women in Lebanon and was associated with a history of miscarriage and morbid obesity. The presence of hypothyroidism correlated with miscarriage during the first trimester and with post-term delivery. Despite the lack of sufficient data supporting the efficacy of treatment of hypothyroidism during gestation, more studies should be conducted to assess the effect of hypothyroidism on gestational and fetal outcomes.



**Freeform/Key Words:** hypothyroidism, gestation, pregnancy, miscarriage

Hypothyroidism during pregnancy is associated with adverse outcomes for both the mother and the fetus. Specifically, pregnant women with hypothyroidism have a greater risk of experiencing obstetrical complications, including an increased risk of miscarriage, gestational hypertension, low birth weight, fetal distress, and intrauterine fetal death [1–4]. Furthermore, hypothyroidism has been correlated with a high risk of preterm birth and impairment of the child's neurologic development [1, 5]. However, routine screening for hypothyroidism during pregnancy remains controversial. Although some proponents have

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; ATA, American Thyroid Association; BMI, body mass index; CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine; LMP, last menstrual period; OR, odds ratio; TSH, thyroid-stimulating hormone.

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recommended it [6], the American College of Obstetricians and Gynecologists (ACOG) has recommended against routine screening for thyroid function during pregnancy owing to the lack of sufficient evidence that screening and treatment of hypothyroidism will lead to improved gestational and fetal outcomes [7]. In contrast, the American Thyroid Association (ATA) has recommended targeted high-risk case screening, which limits the laboratory screening of the thyroid-stimulating hormone (TSH) level to high-risk cases only [8]. A recent report by Nazarpour *et al.* [9] showed that using the targeted high-risk case screening checklist for thyroid disease screening during pregnancy suggested by the ATA overlooks >35% of pregnancy patients with thyroid dysfunction.

Most of the current resources used to assess the prevalence and consequences of hypothyroidism during gestation were based on Western populations. However, thyroid function is dependent on nutritional iodine intake, environmental factors, diet, body habitus, and genetic predisposition, which can vary among different populations. Hence, it is warranted to estimate the prevalence and adverse effects of thyroid dysfunction in different populations. However, only a few studies have been conducted in the Middle Eastern region where pregnancy rates are high. In a small study of 322 pregnant Jordanian women, Alkafajei *et al.* [10] found that >20% of pregnant women have subclinical hypothyroidism with younger pregnancy age a risk factor. Another study from Turkey reiterated the association between subclinical hypothyroidism and preterm delivery but did not provide prevalence data about thyroid dysfunction during pregnancy [11].

To the best of our knowledge, to date, no studies have measured the hypothyroidism rates among pregnant women in Lebanon. Furthermore, the adverse effects of hypothyroidism on gestation and neonatal health are still largely unknown. Therefore, we analyzed the thyroid profile of 920 pregnant women who are followed up at a single center in Lebanon. We also assessed the gestational and fetal outcomes in relation to maternal thyroid function.

## 1. Methods

### *A. Study Design*

We performed a single-center retrospective cohort study conducted at the American University of Beirut Medical Center from June 2014 to April 2015. Pregnant women who presented to the American University of Beirut Medical Center for obstetrical care from 1 January 2009 and 31 December 2013 and underwent TSH testing as a part of their pregnancy evaluation were included in the present study. Patients with known medical history of thyroid disease were excluded from the present study. The institutional review board of the American University of Beirut (Lebanon) provided ethical approval for the study protocol. All the study participants provided informed consent.

### *B. Data Collection*

The data from 957 pregnant women who underwent thyroid function tests from 1 January 2009 to 31 December 2013 were retrospectively collected from the electronic and paper records. The data pertaining to the personal and family history, weight changes, gestational health, and neonatal outcomes were collected and entered electronically to Excel spreadsheets for later analysis. Thirty-seven pregnant women were then removed from the study because of missing data.

### *C. Parameters*

#### C-1. Gestational weight gain

Gestational weight gain was calculated using the maternal self-reported weight at the last menstrual period (LMP) and the maternal weight at delivery. The gestational weight gain was compared with the recommended guidelines from the Institute of Medicine [12]. We also

determined the number of women who surpassed the upper limit of the Institute of Medicine recommended the range of weight gain in pregnancy for each body mass index (BMI) category.

### C-2. Neonatal outcomes

Small for gestational age and large for gestational age newborns were those having a birth weight less than the 10th percentile or greater than the 90th percentile, respectively, for their respective gestational age in weeks [13].

### C-3. Apgar score

We compared both groups using the threshold of ≤7 at 1 and 5 minutes as a predictor of adverse neonatal outcomes [14].

### C-4. Definitions and trimester-specific reference ranges

Hypothyroidism in pregnancy is defined by the presence of elevated levels of serum TSH, and it can be either overt or subclinical, depending on the free thyroxine (FT4) levels. We used the trimester-specific reference ranges suggested by the US National Academy of Clinical Biochemistry [15] and the ATA [8] when reporting the values of the thyroid test during pregnancy. Specifically, the following reference ranges were used for normal TSH levels (electrochemiluminescence immunoassay using the Elecsys system, per the manufacturer's instructions): 0.1 to 2.5 mIU/L if tested during the first trimester, 0.2 to 3.0 mIU/L for second trimester testing, and 0.3 to 3.0 mIU/L for the third trimester testing [8]. We also used the common TSH laboratory range of 0.4 to 4 mIU/L for comparison purposes.

### *D. Statistical Analysis*

Statistical analysis was performed using R software, version 2.15.1, and JMP Pro, version 12.1.0. The difference between the studied variables for those with hypothyroidism and the control cases was evaluated using the Pearson $\chi^2$ test. We calculated the odds ratios (ORs) of these studied variables and their 95% confidence intervals (CIs). We considered a $P < 0.05$ as statistically significant.

## 2. Results

### *A. Baseline Characteristics*

A total of 920 pregnant women aged 17 to 47 years were included in the present analysis. Of these 920 women, 428 (46.5%) were nulliparous. Approximately, 21% of the patients had a history of one or more miscarriages. Only 1.96% and 0.11% of pregnant women had a history of diabetes mellitus or an autoimmune disease, respectively. A family history of diabetes mellitus (18.15%) and thyroid disease (1.09%) were also reported.

All 920 participating women had TSH levels checked at 10.4 ± 6.1 weeks of gestation as a part of routine pregnancy screening. Most pregnant women tested were in their first trimester (81%), followed by the second (14%) and third (5%) trimesters. After adjustment for gestational age [8], 17.1% of women were found to have hypothyroidism during pregnancy (hypothyroid group), and 21 (2.2%) had a TSH level within the hyperthyroid range, without exhibiting any symptoms. Six patients had a TSH level >10 mIU/L. The free triiodothyronine (FT3) and FT4 levels were checked in only 5% and 4% of all patients, respectively; hence, these levels were not considered for further analysis.

The hypothyroidism group was more likely to have a history of one or more miscarriages compared with the control group (27.3% vs 19.5%; OR, 1.55; 95% CI, 1.04 to 2.3; $P = 0.035$;

Table 1). Also, the rate of morbidly obese women (BMI ≥35 kg/m$^2$) as reported at the LMP was significantly greater in the hypothyroidism group than in the control group (3.2% vs 0.9%; OR, 3.5; 95% CI, 1.1 to 11.3; $P = 0.048$; Table 1). However, no substantial difference was found between the hypothyroidism and control groups with respect to age, parity, other BMI categories, gestational diabetes, gestational hypertension, a history of diabetes or autoimmune disease, and a family history of thyroid disease or diabetes mellitus (Table 1).

We also compared the gestational complications and outcomes between the hypothyroid and control groups. We found that the women with hypothyroidism were 2.9 times more likely to experience a miscarriage during the first trimester than were the control group (OR, 2.9; 95% CI, 1.13 to 7.5; $P = 0.02$; Table 2). Similarly, pregnant women with hypothyroidism were 3.9 times more likely to experience a post-term delivery at or beyond 41 weeks of gestation than were the control group (OR, 3.9; 95% CI, 1.05 to 14.9; $P = 0.052$; Table 2). Furthermore, women diagnosed with hypothyroidism during pregnancy were more likely to experience preterm labor (14.6% vs 9.8%), deliver prematurely (12.7% vs 10.7%), undergo a cesarean section (36.3% vs 32.8%), or develop gestational hypertension (6.3% vs 4.7%) or gestational diabetes (5.1% vs 4.7%) than were the control group. However, these differences did not reach statistical significance. The hypothyroid and control groups both gained significantly more weight than the ACOG weight gain recommendations (>13 kg). However, no substantial differences were found with respect to weight gain between the two groups, irrespective of the BMI and recommended weight guidelines considered (Table 2).

We then examined whether the neonatal outcomes could vary between the hypothyroidism and control groups (Table 3). The women in the hypothyroidism group were not found to have an increased risk of having a small for gestational age newborn (12.3% vs 11.2%; $P = 0.78$). Although the number of large for gestational age newborns was 4% greater in the control group than in the hypothyroidism group (6.4% vs 2.4%), the difference not statistically significant ($P = 0.06$). We also found no correlation between the presence of hypothyroidism and the Apgar scores at 1 or 5 minutes. Only one case of intrauterine fetal death occurred in each of the groups.

Even after excluding patients with hyperthyroid activity from the control group, we found similar results for all variables between the hypothyroid and normal thyroid groups. When we compared the hypothyroid and hyperthyroid groups, we found that the hypothyroidism group had greater odds of developing gestational hypertension compared with the hypothyroidism group (OR, 4.5; 95% CI, 1.3 to 15.11; $P = 0.01$).

**Table 1. Obstetric and Medical History of Control and Hypothyroid Pregnant Women**

| Variable | Hypothyroid, n (%) | Control, n (%) | OR | 95% CI of OR | *P* Value |
|---|---|---|---|---|---|
| Women, n (%) | 157 (17.1) | 763 (82.9) | — | — | — |
| Age ≤18 y | 0 (0) | 2 (0.3) | 0 | — | 1 |
| Age ≥35 y | 25 (15.9) | 120 (15.7) | 1 | 0.6 to 1.6 | 1 |
| Nulligravidity | 75 (47.8) | 353 (46.3) | 1.1 | 0.8 to 1.5 | 0.793 |
| Multigravidity | 82 (52.2) | 410 (53.7) | 0.9 | 0.7 to 1.3 | 0.798 |
| History of miscarriage | 43 (27.4) | 149 (19.5) | 1.6 | 1 to 2.3 | 0.035[a] |
| History of DM | 0 (0) | 18 (2.4) | 0 | — | 0.061 |
| History of AI | 0 (0) | 1 (0.1) | 0 | — | 1 |
| BMI at LMP <25 kg/m$^2$ | 101 (64.3) | 518 (67.9) | 0.9 | 0.6 to 1.2 | 0.403 |
| BMI at LMP 25 to 30 kg/m$^2$ | 39 (24.8) | 193 (25.3) | 1 | 0.7 to 1.5 | 0.923 |
| BMI at LMP 30 to 35 kg/m$^2$ | 12 (7.6) | 45 (5.9) | 1.3 | 0.7 to 2.6 | 0.461 |
| BMI at LMP ≥35 kg/m$^2$ | 5 (3.2) | 7 (0.9) | 3.6 | 1.1 to 11.3 | 0.048[a] |
| Family history of TD | 2 (1.3) | 8 (1) | 1.2 | 0.3 to 5.8 | 1 |
| Family history of DM | 31 (19.7) | 136 (17.8) | 1.1 | 0.7 to 1.8 | 0.572 |

Abbreviations: AI, autoimmune disease; BMI, body mass index; DM, diabetes mellitus; LMP, last menstrual period; TD, thyroid disease.
[a]Statistically significant.

**Table 2. Gestational Complications and Outcomes Between Hypothyroid and Control Groups**

| Variable | Hypothyroid, n (%) | Control, n (%) | OR | 95% CI of OR | *P* Value |
|---|---|---|---|---|---|
| Miscarriage during first trimester | 7 (4.5) | 12 (1.6) | 2.92 | 1.1 to 7.5 | 0.020[a] |
| Miscarriage during second trimester | 0 (0) | 2 (0.3) | 0 | — | 1 |
| Preterm labor | 23 (14.6) | 75 (9.8) | 1.57 | 1 to 2.6 | 0.078 |
| Preterm birth | 20 (12.7) | 82 (10.7) | 1.21 | 0.7 to 2 | 0.464 |
| Cesarian section | 57 (36.3) | 251 (32.9) | 1.16 | 0.8 to 1.7 | 0.447 |
| Post-term delivery (≥41 wk) | 4 (2.5) | 5 (0.7) | 3.96 | 1.1 to 14.9 | 0.052 |
| Gestational diabetes | 8 (5.1) | 36 (4.7) | 1.1 | 0.5 to 2.4 | 1 |
| Gestational hypertension | 10 (6.4) | 36 (4.7) | 1.4 | 0.7 to 2.8 | 0.404 |
| BMI <18.5 kg/m$^2$ and >18.14-kg weight gain | 0 (0) | 8 (1.04) | 0.0 | — | — |
| BMI 18.5 to 25 kg/m$^2$ and >15.87-kg weight gain | 37 (23.6) | 169 (22.1) | 1.08 | 0.7 to 1.6 | 0.748 |
| BMI 25 to 30 kg/m$^2$ and >11.3-kg weight gain | 23 (14.6) | 108 (14.2) | 1.04 | 0.6 to 1.7 | 0.881 |
| BMI ≥30 kg/m$^2$ and >9-kg weight gain | 8 (5.1) | 36 (4.7) | 1.08 | 0.5 to 2.4 | 1 |

[a]Statistically significant.

## 3. Discussion

Considerable changes occur in the thyroid hormone physiology and thyroid gland anatomy during pregnancy [7, 16]. Specifically, the thyroid gland of the pregnant woman is characterized by glandular hyperplasia, increased vascularity, and an approximately 30% increased volume, despite a normal echo structure [17, 18]. Furthermore, thyroid function test changes can occur because of estrogen-mediated increases in thyroid-binding globulin and a decline in iodide because of increased renal clearance and placental loss [16]. These physiologic and anatomic changes can lead to a high suspicion of thyroid abnormalities during pregnancy and might lead to increase in screening frequency.

Hypothyroidism during pregnancy has been associated with adverse outcomes in both the mother and the fetus. In the present study, we assessed the rate of hypothyroidism among 920 pregnant women presenting for general obstetric care in Lebanon. The present comprehensive study also assessed the adverse gestational and fetal outcomes attributed to hypothyroidism. We found that >17% of pregnant women have TSH levels indicative of hypothyroidism after adjustment for trimester-specific ranges. These results are comparable to those from a study conducted in Jordan, where 20.8% of women were considered to have hypothyroidism during pregnancy [10]. However, these rates are significantly higher than those from the Western population, in which the hypothyroidism rate varies from 2% to 10% [16, 19–21]. Our greater prevalence in Lebanon could be attributed to inherent genetic characteristics or environmental factors that were not assessed in the present study. The lack of other studies in the Middle East hindered our evaluation of the prevalence compared with other regional countries. Significantly fewer patients had hyperthyroidism than hypothyroidism in our patient population.

In the present study, we used TSH levels to assess thyroid function. Thus, we could not distinguish between overt and subclinical hypothyroidism, because data on FT4 and FT3

**Table 3. Neonatal Outcomes in Hypothyroid and Control Groups**

| Outcome | Hypothyroid, n (%) | Control, n (%) | OR | 95% CI of OR | *P* Value |
|---|---|---|---|---|---|
| Birth weight <10th percentile | 20 (12.3) | 86 (11.2) | 1.11 | 0.7 to 1.9 | 0.776 |
| Birth weight >90th percentile | 4 (2.5) | 49 (6.4) | 0.37 | 0.1 to 1 | 0.062 |
| Apgar score at 1 min ≤7 | 6 (3.7) | 29 (3.8) | 0.98 | 0.4 to 2.4 | 1 |
| Apgar score at 5 min ≤7 | 1 (0.6) | 6 (0.8) | 0.79 | 0.1 to 6.6 | 1 |
| Intrauterine fetal death | 1 (0.6) | 1 (0.1) | 4.88 | 0.3 to 78.5 | 0.297 |

were lacking. Nevertheless, the ACOG has reported that TSH should be considered the best predictor of thyroid disease during pregnancy [7]. Furthermore, the ACOG guidelines noted that no evidence is available to identify and treat subclinical hypothyroidism during pregnancy [22]. Identifying and treating pregnant women with overt hypothyroidism could minimize the risk of adverse outcomes [16, 23, 24]. However, a recent study showed that treating subclinical hypothyroidism or hypothyroxinemia in pregnant patients did not improve pregnancy and neonatal outcomes [25].

We found that previous miscarriages and a BMI $>35$ kg/m$^2$ at the LMP were both significantly associated with hypothyroidism during pregnancy. Furthermore, pregnant women with hypothyroidism were more likely to miscarry during their first trimester, similar to the findings from previous studies [2, 23]. This warrants screening for hypothyroidism in pregnant women with a BMI $>35$ kg/m$^2$ or a history of miscarriage. However, the significance of treating women with hypothyroidism during pregnancy remains controversial. It is possible that an elevated BMI could affect the TSH levels and, hence, the measurement of thyroid antibodies would be valuable in severely obese patients [26]. This study reports a correlation between late-term delivery ($\geq$41 gestational weeks) and hypothyroidism. The pathophysiology of how hypothyroidism could be associated with post-term delivery is unclear. It is possible that hypothyroidism could depress uterine muscle contractions, especially because thyroid disease can be associated with muscle weakness. It is also possible that hormonal imbalances resulting from hypothyroidism could contribute to post-term delivery. Hypothyroidism was found in the present study to be weakly associated with preterm labor, preterm delivery, and cesarean section. Although these associations did not reach the statistical significance threshold, they should not be neglected owing to the serious burden that preterm and cesarean deliveries entail. Our results suggest that maternal hypothyroidism has a limited effect on fetal outcomes as assessed by fetal size, Apgar scores, and intrauterine fetal death. Further research is needed to confirm these findings and to examine the role of thyroid hormones in the initiation of labor.

All the groups experienced weight gain that exceeded the ACOG recommendations for BMI-specific ranges. This could have been related to the common belief among Lebanese pregnant women that increased caloric intake during pregnancy is encouraged for healthier fetal development. Although the weight gain in pregnancy did not correlate with hypothyroidism *per se*, it sheds lights on the importance of increasing awareness about adequate weight gain during pregnancy.

The strengths of the present study include the relatively large population, the standardized testing used, and the inclusion of different reproductive age groups (age range, 17 to 47 years). Furthermore, all 920 patients included in the present study were followed up regularly and until term in the clinics, allowing for full documentation of pregnancy complications and outcomes. Finally, in our analysis, we considered trimester-specific ranges, allowing for accurate representation of thyroid function as recommended by the ATA [8]. However, our study failed to distinguish overt from subclinical hypothyroidism as discussed, which perhaps could have affected some of our results. Furthermore, we did not measure thyroid autoantibodies as a part of the evaluation for thyroid disease.

In conclusion, the findings from the present study underscore the prevalence of hypothyroidism among pregnant women in Lebanon. Specifically, women with a BMI $>35$ kg/m$^2$ and those who experienced a miscarriage might have a greater risk of developing hypothyroidism and ultimately miscarry in their subsequent pregnancies. Hence, more studies are required to assess thyroid function during pregnancy and should include screening for FT4 and FT3, especially for patients with an abnormal TSH level.

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Address all correspondence to: Ghina Ghazeeri, MD, Department of Clinical Obstetrics and Gynecology, American University of Beirut Medical Center, PO Box 11-0236, Riad El-Solh, Beirut 1107 2020, Lebanon. E-mail: gg02@aub.edu.lb.

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