Thyroid stimulating hormone (TSH) level variations in early pregnancy and feto-maternal outcome; retrospective study

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Introduction

Thyroid disease is the second most common endocrine disorder affecting women of reproductive age. The debate continues which TSH levels need to be considered as a reflection of subclinical hypothyroidism in pregnancy. Our aim was to find out if variations in the level of thyroid stimulating hormone (TSH) in early pregnancy of women not known to have thyroid disease or anti-thyroid antibodies were linked to different feto-maternal outcomes. Materials and Methods: Retrospective comparative study that compared group 1 (TSH level 0.1-1.99 mIU/L) and group 2 (TSH level 2.0-4 mIU/L). Each group was further subdivided into primigravidae and multipara with a total of 1527 pregnant women included in the study. Results: The body mass index (BMI), was statistically higher in primiparous women in group 2 (P2) than primiparous in group 1 (P1), (mean BMI 28.0 vs. 26.9, respectively, P value 0.014). The odds ratio of miscarriage in the primigravidae in group 2 was 1.24. This was not statistically significant (95% confidence interval; 0.42-3.63). The miscarriage rate was not also statistically different between multipara (odds ratio 1.04, 95% CI 0.6-1.7). For the primigravida groups, the odds of developing gestational diabetes mellitus was significantly higher in group 2 than in group 1 (Odds Ratio = 2.6, 95% CI 1.2-5.4). This was not seen in multiparous women. This difference could be explained by the higher BMI in group 2. There was a significant difference in the mean arterial blood pressure in multipara between the 2 groups. Although the values of the mean blood pressure (85 and 84 mmHg) were close, the P-value of the t-test performed was 0.007 possibly due to the difference in variance and sample size of each group. There were no statistical difference in the mean gestational age at delivery, preterm birth, mode of delivery and birth weight of term and preterm deliveries. Conclusions: In singleton pregnancies of women without thyroid dysfunction and with negative anti-thyroid antibodies, variations of the TSH level in early pregnancy up to 4.0 mIU/L were not associated with a significant difference in most of the feto-maternal outcomes. TSH values between 2.0-4.0 mIU/L were found to be associated with gestational diabetes in primigravid women and higher mean arterial blood pressure in multiparous women.

Key words: Thyroid stimulating hormone; Primigravidae; Multiparous; Miscarriage; Preterm birth; Gestational diabetes.
The oddsofhavingahistoryofectopicpregnancyforgroup
However, there were 22 cases in M1 and 2 cases in M2.
there were no cases reported in the primigravida patients.
3.63 and 0.6-1.7) (Table 2). Regarding ectopic pregnancy,
differences between the groups as related to maternal age.
Regardingbodymassindex(BMI),therewasastatistically
significantdifferencebetweenprimiparouswomengroup
(P1, P2, M1 and M2). Therewerenostatisticallysignificant
differences between the groups as related to maternal age.

We calculated the mean, median and range of TSH val-
ues in each subgroup. The feto-maternal outcome was then
compared between the 2 groups. We studied miscarriage
rate, ectopic pregnancy rate, maternal blood sugar values
(Fasting blood sugar (FBS), glucose tolerance test (GTT),
HbA1c or a combination) between 26 and 34 weeks, deve-
lopment of high blood pressure at delivery, duration of preg-
nancy (gestational age at delivery), preterm delivery rate,
abruptio placentae, mode of delivery, birth weight and AP-
GAR score at 1 and 5 minutes. Gestational diabetes mellitus
(GDM) was diagnosed as a FBS 92-125 mg/dL or 1-hour
plasmaglucoselevelof180ormoreor2-hourplasmaglu-
cose153-199mg/dLfollowing75-gramoralglucoseload.
The study obtained the approval of the institutional review
board (IRB) at Jordan University Hospital (JUH) number
179/2019 dated 17/4/2019.

The statistical analysis was performed with the Data
Toolkit in Excel (Microsoft, Redmond, WA, USA) using
descriptive analysis. Relative risk and 95% confidence in-
tervals were also calculated to compare variables. P values
were considered significant at < 0.05. The obtained data
were examined using a frequency table and are presented as
frequency, percentage and mean.

Results

After exclusions, the final number of patients included
in our study was 1,527. There were 228 primiparous in
Group 1 (P1) and 78 in group 2 (P2). There were 993 mul-
tiparous women in group 1 (M1) and 228 in group 2 (M2).
The median TSH Values were 1.27, 2.58, 1.05, and 2.51 in
P1, P2, M1 and M2. There were no statistically significant
differences between the groups as related to maternal age.
Regardingbody mass index (BMI), there was a statistically
significant difference between primiparous women in group
1 and 2 (P1 versus P2) with mean BMI 26.9 and 28.0 in P1
and P2 P value 0.014. There was no significant difference
in mean BMI between M1 and M2 (Table 1).

The miscarriage rate was not statistically significantly
different between P1 and P2 or M1 and M2. (95% CI 0.42-
3.63 and 0.6-1.7) (Table 2). Regarding ectopic pregnancy,
there were no cases reported in the primigravida patients.
However, there were 22 cases in M1 and 2 cases in M2.
The odds of having a history of ectopic pregnancy for group
M1 was 2.6 times that of group M2. However, this dif-
ference was not statistically significant (Table 2). There
was no statistical difference between the mean fasting blood
sugar (FBS) or HbA1c in early pregnancy between groups
P1 and P2 or between M1 and M2 (P-values 0.11 and 0.56)
(Table 2). For the primigravida groups, the odds of de-
veloping GDM is significantly higher in group P2 than in
group P1 (OR = 2.6, 95% CI 1.2-5.4). This was not seen
in multiparous women. We compared the different groups
regarding the development of high blood pressure at deliv-
ery. There was no statistical difference in the mean arterial
pressure (MAP) between groups P1 and P2 (P-value 0.25)
(Table 2). However, there was a significant difference in
the MAP between groups M1 and M2. Although the val-
ues of the MAP (85 and 84) were close, the P-value of the
t-test performed was 0.007 possibly due to the difference in
variance and sample size of each group (Table 2).

Using student’s t-test, there was no significant differ-
ence between the mean gestational age (GA) at delivery
between groups P1 and P2 or groups M1 and M2 (Table
3). There was no significant difference between the occur-
rence of preterm (24 to 37 weeks) delivery or very preterm
rate (before 34 weeks) between groups P1 and P2 or groups
M1 and M2 (Table 3). We also calculated the average GA
for patients who delivered preterm and very preterm. Using
the t-test, there was no significant difference between the
mean GA between P1 and P2 or M1 and M2. There were 4
cases of placental abruption, which were not enough cases
to calculate significant differences in occurrence (2 cases in
P1, no cases in P2, one case in each of M1 and M2). The
rates of each mode of delivery vaginal delivery (VD) and
cesarean section (C/S) were also determined and were not
found to be significantly different between the groups. Us-
ing Odds Ratio, the difference in proportions between P1
and P2 regarding mode of delivery (C/S: VD ratios) were
not significant. The same result applied to M1 vs. M2 (Ta-
ble 3).

Regarding fetal outcome, we excluded the miscarriage
and ectopic cases. There were 37 cases with multiple ges-
tations, 2 of which were triplets. They were also excluded
from the fetal outcome statistics. There was no signifi-
cant difference between mean birth weight at term between
groups P1 and P2 and between M1 and M2 (Table 4).

Regarding the mean preterm birth weight, there was no
significant statistical difference between groups P1 and P2
or between M1 and M2 (Table 5).

For term deliveries, there was no significant difference
found between P1/P2 and M1/M2 regarding APGAR scores
at 1 minute. The mean APGAR scores at 1 minute for P1
and P2 respectively were 7.8 ± 0.77 and 7.95 ± 0.22, P
value 0.14. The mean APGAR scores at 1 minute for M1
and M2 respectively were 7.93 ± 0.53 and 7.9 ± 0.55, P
value 0.22. There were no significant differences regarding
APGAR scores at 5 minutes between the 2 groups (P values
were 0.23 and 0.35 for primigravidas and multipara).

We also studied the average improvement of APGAR
score (the change from 1 minute to 5 minute), which was observed to be 1.07 for P1, 1.04 for P2 (statistically not significant, $P$-value 0.23). For M1 and M2, the average improvement was 1.05 and 1.08 (statistically not significant difference, $P$-value 0.14).

There was also no significant difference found between P1/P2 and M1/M2 regarding the mean APGAR scores at 1 and 5 minutes for preterm deliveries. The mean APGAR scores at 1 minute for P1 and P2 in preterm deliveries were $7.76 \pm 1.39$ and $7.42 \pm 2.14$, $P$ value 0.27. The mean APGAR scores at 1 minute for M1 and M2 were $7.51 \pm 1.68$ and $7.72 \pm 1.42$, $P$ value 0.26. There were no significant differences regarding APGAR scores at 5 minutes between the 2 groups as related to preterm deliveries ($P$ values were 0.3 and 0.34 for primigravidas and multipara).

**Discussion**

We hypothesized that variations in the levels of TSH in early pregnancy could influence the feto-maternal outcome. We exclusively compared the effects of the variations in the level of TSH in the first 16 weeks on the feto-maternal outcome. Delitala AP et al. [6] reviewed the literature and found that subclinical hyperthyroidism and the vast majority of transient gestational hyperthyroidism were usually asymptomatic with no need for pharmacologic treatment. We selected a range from 0.1-4 mIU/L. Wei Q et al. [7] found that TSH reference intervals [percentile 2.5-percentile 97.5 (P(2.5)-P(97.5))] were 0.08-3.29 mU/L and 0.59-4.22 mU/L in the first and second trimesters, respectively. Li C et al. [3] used laboratory reference range of 0.14-4.87 mIU/L. The TSH values in our patients were in the first trimester and early second trimester (up to 16 weeks’ gestation). Shen FX et al. [8] found that in thyroid antibody negative pregnant women, the normal TSH level was 0.16-3.78 mIU/L and 0.34-3.51 mIU/L in the first and second trimester. We chose to investigate TSH level only without T3 and T4 as both FT4 and FT3 levels were uniform throughout gestation [3, 9]. To decrease the effects of parity on the development of GDM, high BP and birth weight, we compared different TSH levels within primigravidas alone.
Table 3. — GA at delivery, preterm delivery rate, placental abruption, mode of delivery.

|                        | P1          | P2          | M1          | M2          |
|------------------------|-------------|-------------|-------------|-------------|
| GA at delivery (weeks) | 37.2 ± 2.3  | 37.2 ± 2.4  | 38.1 ± 2.2  | 38.2 ± 2    |
| P-value                | 0.23        | 0.43        | 0.32        | 0.24        |
| Preterm delivery (%)   | 34 (14.9)   | 14 (17.9)   | 170 (17.1)  | 32 (14)     |
| OR (95% CI)            | 0.8 (0.4-1.6)| 1.3 (0.8-1.9)|            |             |
| Very preterm delivery  | 6 (2.6)     | 2 (2.6)     | 30 (3.0)    | 5 (2.2)     |
| Mean preterm GA (weeks)| 34.6        | 35          | 35          | 35.2        |
| P-value                | 0.26        | 0.42        | 0.26        | 0.42        |
| Placental abruption    | 2           | 0           | 1           | 1           |
| VD, No. (%)            | 141 (62.1)  | 54 (71.1)   | 460 (49.5)  | 117 (55.2)  |
| C/S, No. (%)           | 86 (37.9)   | 22 (28.9)   | 469 (50.5)  | 95 (44.8)   |
| OR (95% CI)            | 1.5 (0.9-2.7)| 1.3 (0.9-1.7)|            |             |

GA; gestational age, measured in weeks. Mode of delivery rates are excluding all miscarriage cases (121 total). SD; standard deviation, OR; odds ratio, CI; confidence interval, VD; vaginal delivery, C/S; cesarean section, P1; primigravida in group 1, P2; primigravida in group 2, M1; multipara in group 1, M2; multipara in group 2.

Table 4. — Average term birthweight (in kg).

| BW (Range) In Kg | Mean BW (kg) ± SD | P-value |
|------------------|-------------------|---------|
| P1               | 1.79-4.20         | 3.05 ± 0.48 | 0.39 |
| P2               | 2.37-3.92         | 3.10 ± 0.44 |       |
| M1               | 1.8-4.55          | 3.16 ± 0.49 | 0.27 |
| M2               | 2.22-4.39         | 3.13 ± 0.46 |       |

BW; birth weight, Kg; kilogram, SD; standard deviation, P1; primigravida in group 1, P2; primigravida in group 2, M1; multipara in group 1, M2; multipara in group 2.

Table 5. — Average preterm birthweight (in kg).

| BW (Range) In Kg | Mean BW (kg) ± SD | P-value |
|------------------|-------------------|---------|
| P1               | 0.9-3.6           | 2.5 ± 0.4 |       |
| P2               | 2.0-3.54          | 2.49 ± 0.4|       |
| M1               | 0.67-3.9          | 2.7 ± 0.5 |       |
| M2               | 1.9-3.72          | 2.7 ± 0.4 |       |

BW; birth weight, Kg; kilogram, SD; standard deviation, P1; primigravida in group 1, P2; primigravida in group 2, M1; multipara in group 1, M2; multipara in group 2.

and similarly different TSH levels within multipara alone.

The BMI in our patients were not significantly different between the multipara. This was an important feature since high BMI is associated with higher risk of developing GDM and pre-eclampsia [10]. However, there was a statistically significant difference between the primiparous groups (higher BMI in P2). This could at least partially explain the higher risk of developing GDM in P2. The difference in BMI in primiparous women was not reflected in any difference in the MAP.

Maternal age was not significantly different in our groups of patients. This eliminates the possible effects of maternal age on the development of GDM or pre-eclampsia [11, 12].

The miscarriage rate was not different between the 2 groups in the multiparous women. Although the odds ratio for miscarriage was higher in group 2 than group 1 primigravida women, this difference was not statistically significant. This signified that with TSH levels up to 4 mIU/L in the first 16 weeks, there was no increase in the miscarriage rate. Liu H. et al. [13], found that women with subclinical hypothyroidism (SCH) and thyroid auto-immunity (TAI) were at an increased risk of miscarriage and women with a combination of SCH and TAI were found to have the highest risk. Zhang Y et al. [14] in a systematic review and meta-analysis found that SCH patients with TAI have a higher prevalence of miscarriage, while isolated SCH patients also have a higher miscarriage rate than euthyroid women. Their patients’ TSH levels were less than 10.0 mIU/L.

In our patients, only primigravida in group 2 had a significantly higher risk of developing GDM than group 1. The higher level of TSH and/or higher BMI might have contributed to this. The significant increase in MAP in multipara of group 2, although minimal, was likely due to difference in variance and sample size.

Medici M et al. [15] found that hypothyroidism and hypothyroxinemia were not associated with hypertensive disorders and that within the normal range, the high-normal FT4 levels were associated with an increased risk of hypertensive disorders. They also found that these associations were seen for a mild variation in thyroid function within the normal range.

Our study did not show a difference between group 1 and 2 regarding overall mean gestational age at delivery, preterm and very preterm delivery, average gestational age in preterm and very preterm deliveries and mode of delivery. These findings implicated that a change of TSH level
from 0.1 mIU/L to 4.0 mIU/L was not reflected in a different outcome of the variables studied. Subclinical hypothyroidism was found to be associated with significant preterm birth and low birthweight [16].

Our patients were negative for anti-thyroid antibodies. This could play a role in the absence of significant differences in fetal outcomes. Van den Boogaard E. et al. [17] found in the meta-analyses that the presence of thyroid antibodies was associated with preterm birth (OR 1.9, 95% CI 1.1-3.5). Behroozi-Lak T. et al. [18] concluded that hypothyroidism had an insignificant effect on preterm delivery rates, but anti-thyroid peroxidase antibodies (Anti-TPO) in the serum significantly increased the effect on early preterm deliveries and could be regarded as a risk factor. Meena M. et al. [19] found that euthyroid women with Anti-TPO positive antibodies had a high prevalence of preterm delivery. The variation within the normal range of TSH in our study was not reflected in differences in birthweight. Our finding contradicted the finding by Medici M. et al. [20] as they studied mothers with normal-range FT4 and TSH levels and found that higher maternal FT4 levels were associated with lower birth weight. They concluded that mild variation in thyroid function within the normal range can have important fetal consequences.

The mode of delivery in our patients was not affected by the variations in TSH levels. Behme RM et al. [21] found that in late preterm infants, despite many infants having a low total T4, there was no association between total T4 levels, respiratory support or mode of delivery. This was explained by the fact that variations in TSH levels did not cause significant obstetric changes (birth weight, gestational age at delivery, preterm birth rate) that could be reflected in different rates of mode of delivery.

The APGAR scores of both term and preterm newborns and the rate of improvement from 1 to 5 minutes were not different between groups 1 and 2. These findings were consistent with those of Rosario PW et al. [22] as they found that there was no difference in obstetric or neonatal outcomes when women with TSH ≤ 0.1, between 0.1 and 2.5, and between 2.5 and 4 mIU/L were compared. The upper limit of TSH level in our patients was 4.0 mIU/L. In untreated subclinical hypothyroidism where TSH levels were more than 5.0 mIU/L even with negative Anti-TPO antibody, the outcome was different. Cakmak BD et al. [23] found that in untreated antibody negative subclinical hypothyroidism there was an increased pregnancy loss, impaired glucose tolerance, hypertensive disorders of pregnancy, neonatal intensive care admission, placenta previa and cesarean delivery.

In contrast, Yamamoto JM et al. [24] in a systematic review and meta-analysis of randomized controlled trials found no benefit of therapy on obstetric, neonatal, childhood intelligent quotient (IQ) or neurodevelopmental outcomes and they concluded that currently, there was no evidence to support the treatment of subclinical hypothyroidism diagnosed in pregnancy. Moreover, the role of subclinical hypothyroidism and thyroid autoimmunity on assisted reproductive technology (ART) success rate was recently found to be controversial [25]. Our patients did not receive treatment with Levo-thyroxine. Velasco I et al. [26] found that there was mismatch between guideline recommendations and the use of levo-thyroxine in clinical settings and the disparity of criteria between scientific societies from different medical specialties. They recommended that agreements between both endocrinologists and obstetricians be reached. Despite the wide sample size of our study, the results were limited by its retrospective design.

Conclusions

In singleton pregnancies of women without thyroid dysfunction and with negative anti-thyroid antibodies, variations of the TSH level in early pregnancy up to 4.0 mIU/L were not associated with a significant difference in most of the fetomaternal outcomes. TSH values between 2.0-4.0 mIU/L were found to be associated with gestational diabetes in primigravid women and higher mean arterial blood pressure in multiparous women.

Trial Registration

ClinicalTrials.gov, ID: NCT04565873. Registered on September 25, 2020.

List of Abbreviations

TSH, thyroid stimulating hormone; mIU/L, milli-international unit per litre; BMI, body mass index; GTT, glucose tolerance test; FBS, fasting blood sugar; Anti-TPO, anti-thyroid antibodies; IRB, institutional review board; JUH, Jordan university hospital; GDM, gestational diabetes mellitus; EP, ectopic pregnancy; Anti-TPO, anti-thyroid peroxidases; P1, primigravida in group 1; P2, primigravida in group 2; M1, multipara in group 1; M2, multipara in group 2; SD, standard deviation; OD, odds ratio; CI, confidence interval; MAP, mean arterial pressure; TAI, thyroid autoimmunity; SCH, subclinical hypothyroidism; ART, assisted reproductive technology; ATA, American Thyroid Association.

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Conflict of Interest

All authors declare no conflicting interests.

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