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Original Research

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

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Summary

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 fetomaternal 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 primigravid 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 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.

Key words: Thyroid stimulating hormone; Primigravidae; Multiparous; Miscarriage; Preterm birth; Gestational diabetes.

Introduction

Thyroid physiology changes during pregnancy and this necessitates the use of pregnancy-specific reference ranges for TSH and FT4 in order to adequately diagnose gestational thyroid disease [1]. Medici M. *et al.* [2]found that between gestational week 9 and 18, the maternal TSH reference range (2.5th to 97.5th percentile) was 0.03-4.04 mIU/liter. While guidelines of the American Thyroid Association (ATA) proposed that the upper limit of the TSH reference range should be 2.5 mIU/L in the first trimester, the upper limit of serum TSH in the first trimester was much higher than 2.5 mIU/L in Chinese pregnant women [3]. Thyroid disease is the second most common endocrine disorder affecting women of reproductive age and when untreated during pregnancy is associated with an increased risk of miscarriage, placental abruption, hypertensive disorders and growth restriction [4]. Shravani MR *et al*. [5] found in their study that 11.8% of mothers were hypothyroid of which 87% were subclinical hypothyroidism and 13% overt hypothyroidism due to adaptation of universal screening rather than targeted screening for hypothyroidism. Our aim was to find out if variations in the level of TSH in early pregnancy of women not known to have thyroid disease (euthyroid women) and without circulating anti-thyroid antibodies were linked to different feto-maternal outcomes.

Materials and Methods

This was a retrospective comparative study spanning January 2014 to December 2018. It was conducted at Jordan university hospital, a teaching referral hospital affiliated to the University of Jordan, Amman, Jordan. Pregnant patients, both primigravida and multipara who had a spontaneous singleton pregnancy with documented TSH level in the first 16 weeks' gestation were included. We excluded all patients who had known thyroid dysfunction whether on treatment or not, molar pregnancies, multiple pregnancies, presence of hyperemesis gravidarum, presence of anti-thyroid antibodies (Anti-TPO) and patients with TSH > 4.0 mIU/L or < 0.1 mIU/L. This range was used as TSH < 0.1 mIU/L indicated an undiagnosed subclinical hyperthyroidism and TSH > 4.0 indicated undiagnosed hypothy-

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roidism. In addition, there were wide variations in the TSH reference ranges. Patients' data were collected retrospectively from antenatal clinic notes, admission notes, labor ward and operative notes. Data included patients ID number, age, parity, body mass index (BMI) and TSH values in the first 16 weeks of pregnancy. The patients were divided into 2 groups according to their TSH values. Group one had TSH values between 0.1-1.99 mIU/L and group 2 had TSH values between 2-4 mIU/L. Each group was then subdivided into 2 subgroups; primigravida and multipara. (Group P1: Primigravida in group 1, Group P2: Primigravida in group 2, Group M1: Multiparous in group 1, Group M2: Multiparous in group 2).

We calculated the mean, median and range of TSH values 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, development of high blood pressure at delivery, duration of pregnancy (gestational age at delivery), preterm delivery rate, abruptio placenta, mode of delivery, birth weight and APGAR score at 1 and 5 minutes. Gestational diabetes mellitus (GDM) was diagnosed as a FBS 92-125 mg/dL or 1-hour plasma glucose level of 180 or more or 2-hour plasma glucose 153-199 mg/dL following 75-gram oral glucose load. 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 intervals 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 multiparous 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. Regarding body mass index (BMI), there was a statistically significant difference between primiparous women in group 1 and 2 (P1versus 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 primgravida 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 difference 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 developing 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 delivery. 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 values 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 difference 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 occurrence 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. Using 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 (Table 3).

Regarding fetal outcome, we excluded the miscarriage and ectopic cases. There were 37 cases with multiple gestations, 2 of which were triplets. They were also excluded from the fetal outcome statistics. There was no significant 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

Table 1. — *TSH values and maternal demographics.*

	P1	P2	M1	M2
TSH (mean ± SD) (mIU/L)	1.18 ± 0.48	2.74 ± 2.56	1.08 ± 0.48	2.66 ± 0.54
TSH (median)	1.27	2.58	1.05	2.51
TSH (range)	0.11-1.998	2.01-4.00	0.10 - 1.9954	2.0 - 4.0
Age (mean ± SD) (years)	27.4 ± 5.2	27.4 ± 5.0	32.6 ± 5.5	33.1 ± 5.3
Age (median)	27	27	32	33
Age (range)	17-47	18-40	19-48	21-45
P-value	0.48		0.11	
BMI (mean ± SD)	26.9 ± 3.9	28.0 ± 3.9	28.1 ± 4.2	28.5 ± 4.3
BMI (median)	27.3	27.3	27.3	27.3
BMI (range)	17.72-44	19.03-43.03	17.72-48.07	17.91-44.08
P-value	0.014		0.07	
*Undocumented BMI	3	1	27	4

TSH; thyroid stimulating hormone, SD; standard deviation, BMI; body mass index, P1; primigravida in group 1, M1; multipara in group 1, P2; primigravida in group 2, M2; multipara in group 2.

Table 2. — *Rates (%) of development of miscarriage, ectopic pregnancy, glucose intolerance and high BP among the 4 groups.*

	P1	P2	M1	M2
Miscarriage rate No. (%)	12 (5.26)	5 (6.41)	83 (8.4)	20 (8.77)
Odds Ratio (95% CI)	1.2 (0.4-3.6)		1.1 (0.6-1.8)	
EP rate No. (%)	0	0	22 (2.2%)	2 (0.88%)
Rate of GDM No. (%)	18 (7.9)	14 (17.9)	135 (13.6)	26 (11.4)
Odds Ratio (95% CI)	2.6 (1.2-5.4)		0.8 (0.5-1.3)	
Undocumented FBS; No. of cases	12	2	49	11
Mean FBS (mg/dL)	83.8	87.4	86.7	86.1
t-test for mean FBS	0.11		0.56	
MAP (mmHg)	84	85	85	84

P1; primigravida in group1, P2; primigravida in group 2, M1; multipara in group 1, M2; multipara in group 2, CI; confidence interval, EP; ectopic pregnancy, GDM; gestational diabetes mellitus, FBS; fasting blood sugar, MAP; mean arterial blood pressure.

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 ± 1.39 and 7.42 ± 2.14, *P* value 0.27. The mean APGAR scores at 1 minute for M1 and M2 were 7.51 ± 1.68 and 7.72 ± 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 (mean ± SD)	37.2 ± 2.3	37.2 ± 2.4	38.1 ± 2.2	38.2 ± 2
P-value		0.23		0.43
Preterm delivery No. (%), weeks	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 (prior to 34 weeks), No. (%)	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
Placental abruption cases	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 group1, 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 group1, 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
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 group1, 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 primigravidas 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 withn 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. *etal.* [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 $\leq$ 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 peroxidas; 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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