Original Article

Relationship between Maternal Serum Thyroid-Stimulating Hormone and *in vitro* Fertilisation-Conceived Pregnancy Outcomes

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Abstract

Background: Thyroid dysfunction impairs female fertility and pregnancy outcome. Optimal preconception and gestational TSH level is still debatable in IVF-conceived pregnancies. **Aims:** To explore the relationships of IVF success and pregnancy outcomes with maternal serum levels of TSH (at both preconception and 12-week IVF-conceived pregnancy). Also, to confirm or refute the recommended TSH level ≤2.5μIU/mL. **Study Setting and Design:** Retrospective cohort. **Material and Methods:** 158 IVF-conceived pregnant women and 117 age-matched controls non-pregnant (≤39years, BMI 18.5-38kg/m2) were recruited. Preconception and 12-week IVF-conceived pregnancy serum samples were analysed for reproductive hormones, fasting glucose, insulin and TSH levels. Data of pregnant women at 28 weeks for GDM screening (75-gram OGTT) and up until delivery were included. **Statistical Analysis:** Binary logistic regression used to predict association between preconception TSH levels and IVF success, and pregnancy outcomes. Association of delta change of hormones was determined with linear regression. Significance level $P \leq 0.05$ with 95% confidence interval (CI). **Results:** Overall, median (IQR) age was 32(6)years, BMI 25.4(6.9) kg/m2, HbA1c 5.2(0.52)% and TSH 1.82(1.4)μIU/mL. There was no significant association between preconception TSH level and IVF success rate. During the first trimester of IVF-conceived pregnancy, delta change in TSH level was associated with that of progesterone (P=0.03). 12-week gestation TSH level did not predict adverse pregnancy outcomes (i.e. onset of GDM, delivery type and premature delivery); but a higher TSH level predicted earlier delivery in weeks. There was a higher risk of delivery by caesarean section when TSH>2.5μIU/mL. **Conclusion:** Variation of maternal TSH within normal range (0.4-4.0μIU/mL) at preconception and 12-week gestation has no predictive effect on IVF success and pregnancy outcomes in IVF-pregnancy. Our data provide no support for a recommended preconception TSH level ≤2.5μIU/mL in IVF-conceived pregnancy, but rather promote a preconception TSH level within normal range.

Keywords: *Gestational hypothyroidism, in vitro fertilisation, in vitro fertilisation-pregnancy, pregnancy, thyroid disease, thyroid-stimulating hormone*

Introduction

Thyroid dysfunction impairs menstrual cyclicity, female fertility and pregnancy outcome and is classified as the second most common endocrine disorder in women of reproductive age.[1,2]

The maternal thyroid gland undergoes metabolic and haemodynamic adaptations during pregnancy.[3] In the early stages of pregnancy, the foetus relies upon

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maternal thyroxine. After 10 weeks of gestation, both maternal and foetal thyroid hormones are necessary to support both increased maternal requirements and foetal neurological development.[2,4] During pregnancy, the synthesis of thyroid hormones (T3: triiodothyronine and T4: thyroxine) increases by about 50% as an effect of oestrogen.[5] Furthermore, placental human chorionic gonadotropin (hCG) hormone influences the serum levels of thyroid-stimulating hormone (TSH), given the molecular and receptor homology of hCG and TSH.[3,6] The serum hCG level peaks around week 10 of gestation, which results in a low-normal serum TSH level during the first trimester and occasionally hyperthyroidism.[7]

Exogenous female reproductive hormones can also alter thyroid function in a similar way to that in pregnancy.[8] Compared to a naturally conceived pregnancy, *in vitro* fertilisation (IVF) results in maternal supra-physiological levels of oestrogen that in turn stimulates endogenous thyroid hormone synthesis and may also influence the serum levels of TSH.[5,9] Furthermore, the administration of gonadotropin-releasing hormone (GnRH) during IVF may further have an impact on endogenous thyroid hormone production.[10] Impaired thyroid function predicts poor IVF fertilisation outcome, promoting an important role for thyroxine in oocyte physiology and maturation.[11]

While thyroid dysfunction treatment is commonly approved, TSH cutoff is still debated. In addition, the acceptance and validity of a maternal preconception serum TSH range of 0.4–4.0 μIU/mL are still questionable with IVF therapy. The American Society for Reproductive Medicine and the Endocrine Society recommends a preconception and early gestation maternal serum TSH level ≤2.5 μIU/mL (including for IVF-conceived pregnancies),[12,13] while the American Thyroid Association suggests a upper reference limit of 4.0 μIU/mL.[7] Numerous studies have suggested that preconception TSH >2.5 μIU/mL associates with worse IVF success rate and predisposes to adverse pregnancy outcomes including preeclampsia, recurrent pregnancy loss, post-partum haemorrhage, preterm birth, placental abruption, lower gestational age and birth weight.[14,15] There was also a significant association between increased prevalence of caesarean section in general (emergency and elective) and preconception TSH >2.5 μIU/mL.[16] Conversely, other studies refute a maternal preconception serum TSH cutoff of 2.5 μIU/mL but rather support a serum TSH level simply within the normal range.[17,18] There is hence limited contradicting results on IVF outcomes in euthyroid women.

Thyroid hormones also influence glucose metabolism through multiple mechanisms that include the reduction of insulin half-life, promotion of hepatic glucose output and glycogenolysis.[19] Furthermore, both hypo-and hyperthyroidism impair insulin sensitivity. Therefore, through such mechanisms, thyroid dysfunction may influence the development of gestational diabetes mellitus (GDM).[20] In one study, it was shown that in early pregnancy, serum levels of thyroid hormones were lower in women who later develop GDM compared to non-GDM women.[21]

Our aim was to explore the possible relationship of IVF success and pregnancy outcomes with maternal serum levels of TSH at both preconception and 12 weeks of IVF-conceived pregnancy. We also assessed the validity of the recommended maternal serum TSH cutoff of 2.5 μIU/mL in IVF-conceived pregnancies.

Materials and Methods

Subjects and procedure

This retrospective cohort study was conducted between January 2018 and September 2019. All women aged 18–39 years of age, who underwent their first IVF cycle, body mass index (BMI) range of 18.5–38 kg/m^2 and with no history of DM or thyroid dysfunction nor taking any diabetes or thyroid-related treatments (defined by a serum TSH level outside of the normal range of 0.4–4.0 μIU/mL) were included in the study.

Participants' anthropometric measures (weight and height) and medical history questionnaires were also recorded. Women presented with any chronic medical condition (such as hepatic, respiratory or cardiovascular disease) and who received therapies that may influence glucose homeostasis and thyroid profile (such as growth hormones and steroids) were excluded. The sample size calculation was based on the original study representing pregnant and non-pregnant with IVF therapy (Coussa *et al*., 2020). Change in endocrine parameters was the primary outcomes of the study, and which were expected to occur earlier in IVF-conceived pregnancy as an effect of exogenous hormones. In order to detect a moderate difference (standardised difference = 0.5), with 80% power, 0.05 significance level, a sample size of 96 clinically confirmed pregnant women was required. IVF pregnancy success rate is about 30% and this declines with age (SART, 2017); 275 participants were hence recruited at baseline.

The study included two phases: at first, cases were women with a clinically confirmed pregnancy (pregnant group), and their matched control group represented those who did not become pregnant (non-pregnant group). From 12 weeks of gestation up until delivery (study phase two), cases became those pregnant women who experienced adverse maternal and/or foetal

outcomes (such as GDM, low birth weight, premature delivery, etc.), while their matched control group did not. The study was designed and complied with the code of ethics within the Declaration of Helsinki. Ethical approvals were obtained from local Scientific Research Ethics Committee (11/2017_09) and from the Medical Research Department at the Ministry of Health (HCQ-190-18). Participants' consented on their first (baseline) visit to the fertility clinic (preconception stage, 1st day of IVF) for using their data anonymously for research purposes.

In vitro fertilisation intervention

All women underwent the controlled ovarian stimulation IVF/intracytoplasmic sperm injection treatment with a GnRH antagonist protocol. Daily recombinant follicle-stimulating hormone was administered for 12 days. GnRH antagonist injection was administered daily (0.25 mg) starting from day 5 of stimulation. Follicle growth (size and number) was monitored with frequent ultrasound and blood tests. Final maturation triggering injection with recombinant hCG (250 μg) was administered when at least three follicles had a diameter of ≥18 mm. Egg retrieval was scheduled 36 h later, and embryos were transferred on day 5. Progesterone (oral tablet: 10 mg three times/day, injection: 50 mg/day and vaginal pessaries: 400 mg twice/day) and oestrogen therapies (oral tablet: 2 mg three times/day) were then initiated and continued until 12 weeks of pregnancy. The first pregnancy test was scheduled 10 days after embryo transfer with measurement of serum beta-hCG (β-HCG) and the first pregnancy ultrasound was conducted 4 weeks following positive B-hCG to detect foetal heartbeat. In the first phase of the study, clinically confirmed pregnancy was based on a positive serum β-HCG test and a gestational sac observed on ultrasound. Non-pregnant women (control group) presented a negative β-HCG test or there was no visible gestational sac.[22] Biochemical and ectopic pregnancies were not included in the nonpregnant group data. Biochemical pregnancy represents a pregnancy confirmed by a positive β-HCG but no visible sac is detected on ultrasound; and in an ectopic pregnancy, the embryo abnormally implants outside the uterus.[22] With all cases of negative β-HCG, ectopic or biochemical pregnancies, all reproductive therapies were discontinued at this stage; while clinically confirmed pregnant women were required to continue taking their reproductive therapies (oestrogen and progesterone) for the first trimester (until around week 12 of pregnancy).

Outcome measures

Retrieved data include fasting blood samples at baseline and at 12 weeks of IVF therapy for all subjects. Female reproductive hormones (oestrogen and progesterone), insulin and TSH were measured with electrochemiluminescence immunoassay ECLIA, using Cobas E immunoassay analysers (Roche Diagnostics, Indianapolis, USA). Plasma glucose was measured by the enzymatic reference method with hexokinase-glucose-6-phosphate dehydrogenase. At 4 weeks following initiation of IVF hormonal therapy, a β-HCG test was performed to confirm pregnancy status. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as follows: (fasting plasma insulin x fasting plasma glucose)/405.[23] GDM screening was conducted at 28 weeks of gestation with the 2-h 75-g oral glucose tolerance test (OGTT). Diagnostic GDM levels suggested by the International Association of Diabetes and Pregnancy Study Groups were applied and included the following plasma glucose levels: 95 mg/dL (5.3 mmol/L) fasting; 180 mg/dL (10 mmol/L) at 1 h and 153 mg/dL (8.5 mmol/L) at 2 h post-OGTT.[24]

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 21.0 for Windows (Chicago, IL, USA). Data were non-normally distributed (identified with Shapiro − Wilk test) and presented as median and interquartile range (IQR). Baseline anthropometrics and biochemical data for each of the two subgroups (pregnant vs. non-pregnant) were compared using the (non-parametric) Mann–Whitney U test for two independent samples. Binary logistic regression was used to predict the existence of an association between preconception TSH levels and IVF outcome (successful vs. failed pregnancy). The association between serum TSH >2.5 μIU/mL and IVF outcome was tested using Fisher's exact test.

In the pregnant subgroup, the association of delta change (preconception to 12-week gestation) in TSH levels (dependent variable) with change in anthropometrics and other biochemical data (independent variables) was determined with linear regression multivariate analysis. Predicting onset of GDM with maternal anthropometrics and endocrine biomarkers was determined with binary logistic regression, and adjusted for age and 12-week gestation BMI. Similarly, predictors of type of delivery (vaginal or caesarean section) and early delivery in weeks (i.e., premature delivery) were assessed using binary logistic regression and adjusted for age. Chi-square and Fisher's exact tests were used to assess the validity of documented early gestation TSH cutoff of 2.5 μIU/mL with pregnancy outcomes (categorical): preconception and gestational BMI, type of pregnancy (singleton or twins), GDM,

delivery type, premature delivery (<37 weeks)[25] and low birth rate (LBW) (<2.5 kg).[26] The significance level was set at $P \leq 0.05$ with 95% confidence interval (CI).

Results

In total, data from 275 participants were included in the study with 158 clinically confirmed pregnant women (57%) and 117 non-pregnant (43%). Biochemical and ectopic pregnancies (n = 10) were excluded. The pregnant group comprised 105 singleton (66%) and 53 multiple (34%). In singleton pregnancies, the mean birth weight was 2.8 (0.58) kg and in multiple pregnancies, birth weights were 2.3 (0.51) kg and 2.2 (0.56) kg for the first and second babies, respectively (data not shown in tables). Ethnicity of participants was: 53% Gulf nationals, 20% from Far East, 15% Middle Eastern, 8% Europeans and 4% with African origins.

In vitro fertilization success rate

Preconception anthropometrics, hormonal and biochemical parameters did not differ between pregnant and non-pregnant women [Table 1]. Overall, participants had a median (IQR) age of 32 (6) years, BMI of 25.4 (6.9) kg/m^2, HbA1c of 5.2 (0.52) % and TSH of 1.82 (1.4) µIU/mL. Preconception TSH level did not differ between pregnant and non-pregnant women. At 12 weeks, TSH level differed significantly between pregnant and non-pregnant women ($P < 0.001$), related to the significant reduction in TSH level in the pregnant group ($P < 0.001$).

There was no association between preconception serum TSH level and the pregnancy outcome of IVF ($P = 0.37$), tested by binary regression (results are not shown in tables). In addition, 39% of women (n = 275) had a preconception serum TSH >2.5 µIU/mL, and for all women, TSH level remained ≤4.0 µIU/mL during early pregnancy. IVF success rate was independent of this TSH cutoff of 2.5 µIU/mL ($P = 0.23$).

Pregnancy outcomes

In pregnancy, the association of delta change in TSH level from preconception to 12-week gestation compared with delta change in other parameters is presented in Table 2. Delta change in TSH level between preconception and 12-week gestation was only signifcantly associated with delta change in serum progesterone level (B = 0.008; 95% CI = [0.001, 0.02]; $P = 0.03$), and no correlation was found with change in oestrogen and b-HCG levels.

The associations of 12-week gestation maternal TSH level and pregnancy outcomes are summarized in Table 3. Regression analysis revealed that 12-week TSH level predicted the onset of GDM (B = 0.37; 95% CI = 0.01, 0.73; $P = 0.04$) and delivery in weeks B = −0.06; 95% CI = −0.11, 0.008; $P = 0.02$) but not LBW and delivery type. The higher the 12-week TSH level of the mother was, the earlier the delivery in weeks (prematurely), even after adjusting for maternal age and 12-week gestation BMI (B = −0.05; 95% CI = −0.10, −0.004; $P = 0.03$). When adjusting for age and 12-week-BMI, 12-week TSH level was no longer a significant predictor of onset of GDM.

Table 1: Comparison of Anthropometrics, Hormonal and Endocrine Parameters of IVF-conceived pregnant and non-pregnant women at Baseline and 12 Weeks of IVF Treatment

Variables	Baseline		[a]*P*	12 Weeks		[a]*P*	[b]*P*	
	Pregnant (*n*=158)	Non-pregnant (*n*=117)		Pregnant (*n*=158)	Non-pregnant (*n*=117)		Pregnant (*n*=158)	Non-pregnant (*n*=117)
Age (years)	32.0 (7.0)	32.5 (7.00)	0.32					
Weight (kg)	65.5 (18.95)	64.0 (13.97)	0.58	66.9 (15.9)	64.7 (15.05)	0.21	<0.001	0.003
Body mass index (kg/m^2)	24.8 (7.30)	25.55 (6.15)	0.62	25.7 (6.90)	25.75 (5.73)	0.86	<0.001	0.002
Female Hormones								
FSH (IU/L)	6.46 (2.51)	6.65 (2.47)	0.25					
LH (IU/L)	5.99 (3.16)	5.75 (2.70)	0.39					
Ratio FSH/LH	1.10 (0.60)	1.10 (0.50)	0.14					
Estrogen (pg/mL)	41.9 (24.2)	41.04 (19.15)	0.41	*412.15 (857.10)	*220.5 (197.90)	<0.001	<0.001	<0.001
Progesterone (ng/mL)	0.23 (0.23)	0.24 (0.20)	0.84	*41.07 (37.61)	*20.96 (23.95)	<0.001	<0.001	<0.001
Endocrine								
Fasting glucose (mg/dL)	86.15 (8.0)	86.04 (10.0)	0.73	82.19 (7.19)	87.62 (8.34)	<0.001	<0.001	<0.001
Fasting insulin (µIU/mL)	8.84 (6.81)	8.72 (6.41)	0.93	9.45 (6.95)	9.37 (5.4)	0.86	0.23	0.008
HbA1c (%)	5.3 (0.58)	5.2 (0.50)	0.77	5.08 (0.53)	5.19 (0.47)	0.003	<0.001	0.16
HOMA-IR	1.95 (1.52)	1.9 (1.50)	0.99	2.00 (1.60)	2.1 (1.5)	0.17	0.75	0.003
TSH (µIU/mL)	1.71 (1.29)	1.95 (1.46)	0.34	1.36 (1.10)	1.8 (1.05)	<0.001	<0.001	0.17

Data presented in median and interquartile range (IQR; IQR=Q3-Q1); *Levels at 4 weeks; [a]*P*<0.05 vs. pregnancy by independent test; [b]*P*<0.05 vs. at 12 weeks within subgroups by two-related-samples test; FSH: follicle-stimulating hormone; LH: luteinizing hormone; HbA1c: glycated haemoglobin A1c; HOMA-IR: homeostatic model assessment of insulin resistance

The correlations of pregnancy outcomes with 12-week TSH cutoff of 2.5 μIU/mL are summarized in Table 4. Early gestation TSH level is associated with preconception and 12-week gestation BMI (respectively, $P = 0.001$ and $P = 0.03$). Delivery type is also associated with early gestation TSH level ($P = 0.02$), and caesarean section accounted for 65% in the overall pregnant group. The risk of caesarean section is significantly higher when early gestation TSH >2.5 μIU/mL (odds ratio = 0.22; 95% CI = 0.06,0.79; $P = 0.02$). Number and gender of babies, onset of GDM, miscarriage (mid-gestation; $n = 15$), premature delivery and LBW were all independent to an early gestation TSH >2.5 μIU/mL.

Discussion

In this study, we show an evidence from one of the most highly phenotyped studies on IVF-conceived pregnancies to date, that maternal serum TSH level (within normal range) at preconception does not predict the success of IVF, nor pregnancy outcomes during the ensuing pregnancy (including onset of GDM). The prevalence of GDM in the studied participants was similar to that reported in spontaneously conceived pregnancies and to the latest statistics, which is about 30%.[27]

Overall, the median age of participants was below the high-risk age group of 35 years, TSH level was within normal preconception range (0.4–4 μIU/mL) and BMI classified within the overweight category (24.9–29.9 kg/m^2), the latter increasing the risk of an adverse pregnancy outcome.[28] Our data on IVF-pregnancy success rate based on preconception TSH levels are consistent with those from other studies.[5,18] Other studies, however, report that although oocyte number, maturation and fertilisation inversely correlate with TSH level, IVF-pregnancy outcome does not.[11] We did not explore the effects of maternal serum TSH level on IVF-related oocytes data.

Drop in 12-week TSH level in pregnancy is consistent with previous studies reporting 20%–50% suppression, a pregnancy effect;[29] while TSH level did not change in the non-pregnant group. Overall, TSH levels remained within the normal range. Unlike previous studies associating changes in TSH level with the sharp increase in oestrogen and b-HCG concentrations,[5,6] particularly in twin pregnancies,[30] change in TSH was likely correlated with change in progesterone level in our study.[31] We are unable to explain the lack of association between TSH and b-HCG, especially that the latter peaks during the first trimester; further studies should explore this association.

Early gestation maternal TSH level (based on a threshold of 2.5 μIU/mL) was not associated with the type of pregnancy (single or twins), while higher preconception and gestational BMI were associated with serum TSH > 2.5 μIU/mL level, emphasising the well-known correlation between maternal thyroid function and BMI.[32] In relation to pregnancy outcomes, early gestation serum TSH levels outside of the normal range associate with increased risk of developing GDM, due to decreased insulin sensitivity.[19] Variations in serum TSH between preconception and 12-week gestation did not associate with any change in maternal fasting plasma glucose, serum insulin levels or HOMA-IR-based insulin sensitivity. In addition, 12-week gestation serum TSH level was a poor predictor of onset of GDM when adjusted for age and 12-week gestation BMI. Given that maternal serum TSH level remained within the normal range,[33] this may have affected the power to show any association between maternal serum TSH levels and glucose homeostasis. The onset of GDM was likely associated with maternal characteristics (advanced

Table 2: Association of delta change in serum thyroid-stimulating hormone level at 12 weeks gestation with delta changes in anthropometrics and other biochemical parameters using linear regression analysis

Variables	*B*	95% CI	*P*
BMI	0.04	−0.07-0.14	0.49
Glucose	0.02	−0.002-0.03	0.09
Insulin	0.002	−0.03-0.03	0.90
Estrogen	−0.00005	−0.0002-0.0001	0.65
Progesterone	0.008	0.001-0.02	0.03
B-HCG	0.0001	0.0001-0.001	0.28

CI=Confidence interval, B-HCG=Beta-human chorionic gonadotropin, BMI=Body mass index

Table 3: 12 weeks' gestation maternal thyroid-stimulating hormone levels (dependent variable) predicting pregnancy outcomes, adjusted for age and 12 weeks gestation body mass index using linear logistic regression (*n*=158)

Variables	Unajusted analysis			Adjusted analysis		
	B	95% CI	*P*	OR	95% CI	*P*
GDM	0.37	0.01-0.73	0.04	0.21	−0.17-0.60	0.28
LBW	−0.13	−0.48-0.23	0.49	−0.08	−0.44-0.27	0.65
Premature delivery	−0.06	−0.11-0.008	0.02	−0.05	−0.10-−0.004	0.03
Delivery type	0.1	−0.21-0.40	0.53	0.06	−0.25-0.37	0.71

OR=Odds ratio, CI=Confidence interval, GDM=Gestational diabetes mellitus, LBW=Low birth weight

Table 4: Association of anthropometrics and pregnancy outcomes with early gestation thyroid-stimulating hormone >2.5 µIU/mL

Variables	TSH ≤2.5 (*n*=136), *n* (%)	TSH >2.5 (*n*=22), *n* (%)	*P*
Preconception-BMI (kg/m^2)			
<18.5	5 (3.7)	0	0.001**
18.5-24.9	70 (51.5)	4 (18.2)	
25-30	37 (27.2)	7 (31.8)	
30-35	19 (14.0)	11 (50.0)	
>35	5 (3.7)	0	
12 weeks BMI (kg/m^2)			
<18.5	2 (1.5)	0	0.03**
18.5-24.9	63 (46.3)	4 (18.2)	
25-30	44 (32.4)	8 (36.4)	
30-35	19 (14.0)	9 (40.9)	
>35	8 (5.9)	1 (4.5)	
Pregnancy type			
Single	89 (65.4)	14 (63.6)	0.87**
Twin	47 (34.6)	8 (36.4)	
Gender of baby			
Male	63 (46.3)	7 (31.8)	0.41**
Female	50 (36.8)	11 (50.0)	
Mix	23 (16.9)	4 (18.2)	
GDM			
Yes	26 (19.1)	8 (36.4)	0.09*
No	110 (80.9)	14 (63.6)	
Delivery type			
Vaginal	56 (41.5)	3 (13.6)	0.02*,¥
Cesarean	79 (58.5)	19 (86.4)	
Premature delivery (weeks)			
<37	69 (50.7)	13 (59.1)	0.50*
≥37	67 (49.3)	9 (40.9)	
LBW (kg)			
<2.5	35 (25.7)	9 (40.9)	0.20*
≥2.5	101 (74.3)	13 (59.1)	

P<0.05 versus TSH >2.5 µIU/mL, by *Fisher's exact test, **Chi-square test, ¥OR=0.22; 95% CI=0.06-0.79; *P*=0.02. TSH=Thyroid-stimulating hormone, GDM=Gestational diabetes mellitus, LBW=Low birth weight, CI=Confidence interval, BMI=Body mass index, OR=Odds ratio

age and higher gestational weight) rather than TSH level related. Furthermore, our data do not support an association between gestational serum TSH level >2.5 µIU/mL with an increased risk of developing GDM, miscarriage, preterm delivery and LBW.[14,16]

In agreement with similar studies,[34] type of delivery was associated with 12-week pregnancy TSH level, with a significant higher risk of caesarean section when TSH >2.5 µIU/mL. However, linear regression did not show any predictive relation between TSH level (within normal range) and type of delivery, but it did with premature delivery. Consequently, higher early gestation maternal TSH level predicts earlier delivery in weeks (i.e., premature, <37 weeks), even after adjusting for age and 12-week BMI. It is important to note that although an association was found between TSH level and premature delivery, it cannot be confirmed that premature delivery is dependent on the TSH cutoff of 2.5, as other non-endocrine factors may have interfered (non-TSH level related). In addition, delivery by caesarean section was more common among participants of this study and which can be associated with different factors. Advanced maternal age (≥35 years) relates to a higher rate of a caesarean delivery, possibly explained by the physician and pregnant women concerns over pregnancy outcome in older age;[35,36] our study reported similar results. Furthermore, while caesarean section is more common in multiple pregnancies, it is not considered as an indication.[37] The pathophysiological mechanism involved in thyroid function in relation to the type of delivery needs to be further elucidated. The participants may have therefore presented other obstetric conditions that promoted choice of caesarean section, including abnormal presentation of foetus, failure to progress to a vaginal delivery, repeated caesarean and cord prolapse.[37] Another important factor is related to the fact that IVF-conceived pregnancy is considered as a "high-risk" intervention with increased risk for pregnancy-related complications[38] (including caesarean section) compared to spontaneously conceived pregnancies. Women may consider IVF-conceived pregnancy as 'precious' after many years of infertility, and electively chose to have a caesarean section to prevent perceived complications from a vaginal delivery and not necessarily because of medical necessity.[39] In this study, given that most deliveries were by caesarean section, the timing of delivery may be clinically irrelevant in relation to TSH level as the treating physician usually chooses it. In sum, in contrast with previous studies conducted on spontaneously conceived pregnancies,[40] TSH level of participants was within normal range and did not associate with obstetric outcomes in IVF-conceived pregnancy. In addition, given that different factors may be related with premature delivery and caesarean section, the association of raised TSH levels remains inconclusive. Further studies assessing other factors of premature delivery and caesarean section in relation to gestational TSH level may be needed.

Our study does have some limitations. Several important markers of IVF success and outcomes were not assessed in the study and these include infertility diagnosis, parity and ovarian reserve, and embryo quality. Measurement of TSH level alone is not a sufficient diagnostic parameter of thyroid dysfunction;

instead T4 and T3 hormones should also be tested to confirm subclinical or overt hypo-or hyperthyroidism diagnosis.[30] In addition, assessing other contributing factors to thyroid dysfunction may have been useful, including iodine insufficiency (estimated by urinary iodine) and thyroid autoimmunity (measurement of anti-thyroid antibodies).[6] Measurement of serum TSH levels later in pregnancy may have allowed a more accurate assessment of its effect on pregnancy-related outcomes. Finally, the normal reference range for serum TSH may vary between different ethnicities.[5] However, we only used one standard TSH reference range, which is recommended by the American Thyroid Association.

Conclusions

We show no predictive effect of maternal preconception and early gestation serum TSH level within the normal range on IVF success and pregnancy outcomes, except premature delivery with higher levels. During early gestation, strictly controlled TSH level to ≤2.5 μIU/mL was a poor predictor of IVF success rate and adverse pregnancy outcomes. As per the current guidelines, we hence highlight the importance of attaining and maintaining a maternal serum TSH level within the normal range from preconception to at least throughout the first trimester, rather than choosing a controversial cutoff of serum TSH level.

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Data availability statement

Data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Conflicts of interest

There are no conflicts of interest.

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