

Live birth rate after intrauterine insemination is not different between women with lower quartile versus higher quartile normal range thyroid stimulating hormone levels

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STUDY QUESTION: Does lower quartile normal range thyroid stimulating hormone (TSH) compared to higher quartile normal range in women without thyroid hormone substitution affect live birth rate after a complete IUI treatment series?

SUMMARY ANSWER: Lower quartile normal range TSH, in women without thyroid hormone substitution, does not affect live birth rate after a complete intrauterine insemination treatment series compared to higher quartile normal range TSH.

WHAT IS KNOWN ALREADY: TSH is historically seen as the most sensitive test for thyroid function. Its distribution is right-skewed. Whether the preconceptional upper reference TSH values in subfertile women should be 2.5 or 4.5 mIU/L is under debate. Studies have shown that IUI patients treated with levothyroxine for TSH levels above 2.5 mIU/L show higher pregnancy rates. However, no adverse outcome is associated with untreated high normal TSH levels studied in first IUI cycles. Thyroid peroxidase antibodies have also impaired outcomes in some studies whereas others have shown an effect only in combination with high normal TSH levels. As a subgroup, patients with unexplained infertility showed increased levels of TSH. This article adds to the value of TSH evaluation and fertility outcome in four quartiles and in the context of a completed IUI treatment modus of a maximum of six inseminations.

STUDY DESIGN, SIZE, DURATION: This is a retrospective cohort study in 909 women undergoing 3588 IUI cycles starting treatment between the first of January 2008 and the first of March 2012.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women aged 22–45 years with TSH 0.3–4.5 mIU/L without thyroid hormone substitution were included at Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands, an Iodine-sufficient area. The primary endpoint was live birth. Clinical pregnancy, pregnancy loss and ongoing pregnancy were secondary endpoints. Logistic regression was used with the natural logarithm of TSH as a continuous predictor. Chi-square tests and logistic regression were used to compare groups of patients based on TSH values in four quartile TSH groups (0.3–1.21 mIU/L; 1.22–1.75 mIU/L; 1.76–2.34 mIU/L; 2.35–4.5 mIU/L) on basic characteristics and on the endpoints while adjusting for confounders.

MAIN RESULTS AND THE ROLE OF CHANCE: Analysis with the natural logarithm of TSH as a continuous variable showed no association with live birth, pregnancy chance or pregnancy loss. There were no differences in any of the outcomes across the quartile TSH level

ranges after regression analysis before and after adjusting for age, BMI, use of alcohol, tobacco, use or gonadotrophins, sperm count, diminished ovarian reserve, unexplained infertility and primary or secondary subfertility.

The distribution of primary and secondary subfertility and smoking characteristics were remarkably different across the four groups, with proportionally the lowest prevalence of primary subfertility and the highest rate of smoking in the lowest TSH group (0.3–1.20 mIU/L).

LIMITATIONS, REASONS FOR CAUTION: Unknown values of free thyroxine and thyroid peroxidase antibodies, as well as the retrospective character of the study, limit the clinical interpretability.

WIDER IMPLICATIONS OF THE FINDINGS: TSH in the highest quartile range (2.35–4.5 mIU/L) in subfertile women preceding IUI is not associated with a lower live birth rate or rate of clinical and ongoing pregnancy, or with loss of pregnancies, compared to subfertile women with TSH in the lower three quartile groups after complete intrauterine insemination treatment.

STUDY FUNDING/COMPETING INTEREST(S): The department of Obstetrics and Gynaecology, division of Reproductive Medicine, and of Internal Medicine, division of Endocrinology provided support. There are no competing interests.

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Key words: thyroid stimulating hormone / intrauterine insemination / live birth rate / pregnancy loss / upper reference level

WHAT DOES THIS MEAN FOR PATIENTS?

In general it is assumed that poor thyroid functioning is associated with a lower chance of pregnancy and a less optimal child health outcome.

It is unknown whether, within normal range TSH values, a distinction can be made between lower quartile normal and higher normal quartile TSH values and chances of fertility outcome. For that reason, we investigated in couples undergoing IUI for fertility treatment whether lower or higher normal TSH values affect chances of pregnancy and live birth rate. In our study, we evaluated 909 patients and 3588 cycles. We did not find any differences in each of these outcome parameters between the four normal range groups. Women who had not been pregnant previously showed higher TSH levels.

A simple and obvious conclusion based on these observations is that within the normal range of TSH, no disadvantage can be expected on aforementioned parameters, but it might be useful to investigate subgroups such as women with thyroid antibodies and/ or those who are trying to conceive for the first time.

Introduction

Because of the strong associations of hypothyroidism with subfertility, the definition of euthyroidism in subfertile women is a present-day topic of debate, with the upper reference level of thyroid stimulating hormone (TSH) as one of the issues, being 4.5 mIU/L according to the American Society for Reproductive Medicine ([Practice Committee of the American Society for Reproductive, 2015](#)), but considered to be 2.5 mIU/L for subfertile women according to the American Thyroid Association ([Alexander *et al.*, 2017](#)). The prevalence of (subclinical) hypothyroidism in women of reproductive age varies from 2 to 4%, largely in the presence of Thyroid Autoimmunity (TAI). In women treated with ART, the prevalence of TSH in the range of 2.5–4.5 mIU/L is higher than in the general population: 20–26% compared to 5% ([Reh *et al.*, 2010](#); [Michalakis *et al.*, 2011](#)). Some advocate that TSH values >2.5 mIU/L in subfertile women could indicate insufficient capacity for basic reproductive functions such as oocyte quality, ovulation, fertilization and implantation ([Karmon *et al.*, 2016](#)).

Reports on the TSH upper reference level in IUI—populations differ; comparisons of low (0.3–2.49 mIU/L) and high (2.5–4.5 mIU/L) normal levels of TSH have shown no adverse first cycle IUI outcome for women with high normal TSH levels ([Karmon *et al.*, 2015](#); [Unuane *et al.*, 2017](#); [Tuncay *et al.*, 2018](#)). However, treatment with levothyroxine of women with high normal TSH levels before IUI showed higher pregnancy rates after multivariate analysis ([Jatzko *et al.*, 2014](#)). Studies

evaluating the presence or absence of thyroid autoantibodies, independent of TSH levels and without levothyroxine treatment, did not show any difference in fertility outcome in IUI ([Unuane *et al.*, 2017](#)) as well as after randomization for treatment with levothyroxine in IVF/ICSI ([Wang *et al.*, 2017](#)).

By comparing interquartile TSH levels and pregnancy outcomes in subfertile women in a retrospective IUI cohort, we aimed to identify potential subgroups of subfertile women with high normal TSH who might benefit from supplementation of thyroid hormone.

While previous studies evaluated TSH value associations with only the first cycle IUI outcome, we evaluated effects on a complete IUI treatment mode to a maximum of six cycles as in agreement with the Dutch Guidelines ([NVOG, 2015](#)).

Materials and Methods

Study population and participants

All subfertile women who started IUI in the Amsterdam UMC, Vrije Universiteit Amsterdam in the Netherlands between January 2008 and March 2012 with a follow up until 2013, were retrospectively reviewed. Data were obtained from paper and electronic patient files and, in case of ongoing pregnancy, via a routine patient questionnaire.

Inclusion criteria were: eligible for intrauterine insemination, i.e. ovulating women between 18 and 43 years old, one or two patent tubes

visualized by hysterosalpingography, partner with a washed semen count $> 3 \times 10^6$, and a TSH value measured preceding the first insemination. Spontaneous ovulating women (>10 ovulations a year) should have pursued pregnancy for at least 2 years prior to starting therapy.

Exclusion criteria were: TSH out of reference value (<0.3 and > 4.5 mIU/L; $n = 57$), a history of thyroid dysfunction or thyroid hormone substitution ($n = 52$), use of donor semen ($n = 5$), or complete retrograde ejaculation ($n = 2$). Cycles were excluded if there was no insemination (various, non- thyroid-related reasons $n = 17$) or if the semen count was $< 0.5 \times 10^6$ ($n = 68$).

Anovulatory women (WHO II) underwent all IUI cycles with gonadotrophin stimulation by hMG (Menopur[®], Ferring) with hCG (Pregnyl[®], Merck Sharp & Dohme) for triggering final maturation and timing of insemination. The first three IUI treatments of women with indications other than anovulation were in natural cycles, while the following cycles to a maximum of another three, were with hMG and hCG.

The outcomes were live birth per patient (Harbin Consensus Conference Workshop, 2014), clinical pregnancy rate per patient (intrauterine pregnancy at 6–8 weeks), pregnancy loss per clinical pregnancy (loss of a clinical pregnancy < 12 weeks), and ongoing pregnancy rate per patient (vital pregnancy > 12 weeks).

For patient characteristics, TSH values as well as data on BMI and on tobacco and alcohol use nearest to and preceding the first cycle of IUI treatment were used for analysis. For semen and endometrium categories, the values of the first treatment were used. A third generation TSH assay (ECLIA Roche[®] Cobas 8000) was used, with a reference range of 0.3–4.5 mIU/L.

We defined four interquartile groups with different TSH value ranges for the purpose of uncovering possible u-shaped associations of TSH and pregnancy outcomes, such that described between thyroid hormones and the IQ levels of the child (Korevaar *et al.*, 2016).

Statistical analysis

SPSS 22 was used for statistical analysis, with patient as the unit of analysis. Demographic and baseline characteristics were compared between groups using one-way ANOVA, Kruskal–Wallis ANOVA and chi-square test. Live birth rate, clinical and ongoing pregnancy and pregnancy loss were determined for the patients' first six cycles of IUI or fewer cycles in case the first ongoing pregnancy was achieved earlier.

Logistic regression was used with the natural logarithm of TSH as a continuous predictor. The first model contained only a linear term. In a second analysis, a quadratic term was added to account for a non-linear relationship. In a final analysis, patients were categorized based on TSH levels, using the quartiles of the distribution (0.3–1.21 mIU/L; 1.22–1.75 mIU/L; 1.76–2.34 mIU/L; 2.35–4.5 mIU/L). Differences in pregnancy outcomes were tested using logistic regression analysis with pregnancy outcome as the dependent variable and TSH group as predictor.

Adjusted analyses were performed in which we corrected for: age, BMI, use of alcohol and tobacco (Knudsen *et al.*, 2005; Hornstein, 2016), use of gonadotrophins, semen count, presence of diminished ovarian reserve defined as FSH > 10 IU/L with an ovulating cycle, presence of unexplained subfertility, and primary or secondary subfertility. Categories were as follows: BMI $< 20.9/21.0–28.9/29–34.9/>35$ kg/m² (van der Steeg *et al.*, 2008); use of alcohol: no alcohol (0 units a week)/ moderate (1–8 units a week)/ heavy (>8 units a week) (Rachdaoui and Sarkar, 2013; Health Council of the N, 2015; Donald *et al.*, 2018); use of tobacco yes/no (Wiersinga, 2013); use of gonadotrophin yes/no, washed semen count $0.5–2.9 \times 10^6/3–4.9 \times 10^6/5–29.9 \times 10^6/30–50 \times 10^6$, diminished ovarian reserve yes/no, unexplained subfertility yes/no and primary/secondary subfertility.

Odds ratios were reported as effect–size together with their 95% CI and *P*-values. With the given group size of 920 patients, a pairwise comparison between the four groups with an alpha of 0.05 and a beta of 0.2 allowed proportions of $> 7.25\%$ to be distinguished.

Ethical approval

This study has been formally exempted from ethical approval granted by the Institutional Review Board of the VU University Medical Centre (reference 2013.83, dated 25 March 2013).

Results

Basic characteristics

There were 909 women who met the inclusion criteria. A total of 3588 cycles until first ongoing pregnancy, with a maximum of six insemination cycles per patient, were analysed. The interquartile groups were: group I, TSH 0.30–1.21 mIU/L, $n = 228$; group II, TSH 1.22–1.75 mIU/L, $n = 228$; group III TSH 1.76–2.34 mIU/L, $n = 231$; and group IV TSH = 2.35–4.5 mIU/L, $n = 233$. Baseline data (Table 1) show that in group I (TSH 0.30–1.21 mIU/L) prevalence of primary subfertility was lower and more women were smoking than in the higher quartile groups. The median number of cycles per patient was 3 in group I, and 4 in groups II, III and IV.

Outcome parameters

Analysis of the natural logarithm of TSH as a continuous predictor showed no association with live birth, clinical pregnancy or pregnancy loss ($P = 0.37$, $P = 0.99$ and $P = 0.51$, respectively). When a quadratic term was added, this also was found to be not significant ($P = 0.81$, $P = 0.63$ and $P = 0.67$).

Using logistic regression with group IV as reference (TSH value 2.35–4.5 mIU/L), the odds ratios for live birth rate, clinical and ongoing pregnancy, with crude data and after adjusting for age, BMI, use of alcohol, tobacco, use of gonadotrophins, sperm count, presence of diminished ovarian reserve, presence of unexplained infertility and primary or secondary subfertility, showed no statistical differences across the TSH quartile ranges (Table 2).

Discussion

In the current study, there was no association of fertility outcome in terms of live birth rate, clinical or ongoing pregnancy or pregnancy loss, when comparing lower TSH quartiles to higher TSH quartiles within the normal reference range after a series of IUI. This persisted after adjustment for age, BMI, use of alcohol, tobacco, use of gonadotrophins, sperm count, diminished ovarian reserve, unexplained infertility and primary or secondary subfertility. The distribution however of primary and secondary subfertility was remarkably different across the quartile groups, with fewer primary subfertile women in the lowest TSH group. It agrees with the higher TSH levels in women with predominantly primary unexplained infertility that Orouji Jokar found (Orouji Jokar *et al.*, 2018). This might indicate that primary subfertility is associated with higher TSH levels. Furthermore, there were significantly more smokers among women with the lowest TSH. This agrees with the notion that smoking decreases TSH levels (Wiersinga, 2013).

Table 1 Patient characteristics of IUI patients in interquartile TSH groups.

	TSH (0.30–1.21 mIU/L) <i>n</i> = 228 (24.8%) 847 cycles	TSH (1.22–1.75 mIU/L) <i>n</i> = 228 (24.8%) 890 cycles	TSH (1.76–2.34 mIU/L) <i>n</i> = 231 (25.1%) 925 cycles	TSH (2.35–4.50 mIU/L) <i>n</i> = 233 (25.3%) 926 cycles	P
TSH (mIU/L) (median, IQR)	0.94 (0.73–1.08)	1.47 (1.36–1.60)	2.0 (1.86–2.14)	2.85 (2.57–3.38)	
Number of days of TSH measurement prior to first IUI (days) (median, IQR)	220 (140–364)	212 (137–314)	227 (150–373)	235 (142–370)	0.156*
Age (years) (mean, SD)	35.5 (4.2)	35.3 (4.4)	35.5 (4.1)	35.8 (4.0)	0.663**
BMI					0.207
<20.9	59 (27.2%)	69 (32.1%)	70 (31.7%)	59 (26.9%)	
21.0–28.9	125 (57.6%)	117 (54.4%)	130 (58.8%)	128 (58.4%)	
29–34.9	26 (12.0%)	22 (10.2%)	15 (6.8%)	17 (7.8%)	
>35	7 (3.2%)	7 (3.3%)	6 (2.7%)	15 (6.8%)	
Missing	11	13	10	14	
Alcohol use					0.501
No alcohol	86 (38.1%)	83 (36.7%)	82 (36.1%)	78 (34.5%)	
1–7	116 (51.3%)	130 (57.5%)	128 (56.4%)	132 (58.4%)	
>7 units/w	24 (10.6%)	13 (5.8%)	17 (7.5%)	16 (7.1%)	
missing	2	2	4	7	
Smoking					0.004
Not smoking	163 (71.5%)	181 (79.4%)	194 (84%)	193 (82.8%)	
Smoking	65 (28.5%)	47 (20.6%)	37 (16%)	40 (17.2%)	
Subfertility					0.050
Primary	114 (50%)	125 (54.8%)	145 (62.8%)	128 (54.9%)	
Secondary	114 (50%)	103 (45.2%)	86 (37.2%)	105 (45.1%)	
Subfertility diagnosis					
Tubal factor	17 (7.5%)	22 (9.6%)	13 (5.6%)	16 (6.9%)	0.417
Endometriosis I–II	15 (6.6%)	22 (9.6%)	15 (6.5%)	10 (4.3%)	0.150
PCOS ^a	13 (5.7%)	17 (7.5%)	9 (3.9%)	21 (9.0%)	0.135
DOR ^b	21 (9.2%)	15 (6.6%)	19 (8.2%)	14 (6.0%)	0.539
Male factor	55 (24.1%)	62 (27.2%)	49 (21.5%)	57 (24.5%)	0.523
Unexplained	89 (39.0%)	91 (39.9%)	113 (48.9%)	100 (42.9%)	0.131
Cervical factor	22 (9.6%)	17 (7.9%)	21 (9.1%)	22 (9.4%)	0.916
Other ^c	7 (3.1%)	9 (3.9%)	4 (1.7%)	4 (1.7%)	0.358
Cycles (number) (mean, SD)	3 (2–6)	4 (2–6)	4 (3–6)	4 (2–6)	0.256*
Mild stimulation first cycle	61 (26.8%)	67 (29.4%)	58 (25.1%)	62 (26.6%)	0.766
Sperm count					0.895
0.5–2.99 × 10 ⁶	17 (7.5%)	24 (10.5%)	24 (10.4%)	16 (6.9%)	
3–4.99 × 10 ⁶	20 (8.8%)	25 (11.0%)	24 (10.4%)	24 (10.3%)	
5–29.99 × 10 ⁶	115 (50.4%)	104 (45.6%)	108 (46.8%)	114 (48.9%)	
≥30 × 10 ⁶	76 (33.3%)	75 (32.9%)	75 (32.5%)	79 (33.9%)	
Endometrial thickness					0.469
<7 mm	35 (15.5%)	30 (13.5%)	39 (17.5%)	42 (18.6%)	
≥7 mm	191 (84.5%)	193 (86.5%)	184 (82.5%)	184 (81.4%)	
Missing	2	5	8	7	

*Kruskall Wallis, **ANOVA.

^aPCOS, polycystic ovary syndrome.^bDOR, diminished ovarian reserve, defined as ovulatory cycles with FSH > 10 U/L.^cOther, congenital uterus anomaly, Asherman's syndrome.

Table II Pregnancy outcomes after IUI compared within interquartile TSH groups (n, (%), odds ratio's with 95% CI).

Number of patients	Group I TSH 0.30–1.21 mIU/L n = 228 (24.8%)	Group II TSH 1.22–1.75 mIU/L n = 228 (24.8%)	Group III TSH 1.76–2.34 mIU/L n = 231 (25.1%)	Group IV TSH 2.35–4.50 mIU/L n = 233 (25.3%)	Group IV as reference			P	Group IV as reference ^a			P
					Crude OR (95% CI)				Adjusted OR (95% CI)			
					I vs IV	II vs IV	III vs IV		I vs IV	II vs IV	III vs IV	
Clinical pregnancy per patient	88 (38.6%)	77 (33.8%)	75 (32.5%)	90 (38.6%)	0.999 (0.686–1.453)	0.810 (0.554–1.186)	0.764 (0.522–1.118)	0.376	0.955 (0.640–1.425)	0.766 (0.510–1.148)	0.813 (0.543–1.217)	0.515
Pregnancy loss	15 (17%)	15 (19.5%)	19 (25%)	21 (23%)	0.675 (0.341–1.338)	0.675 (0.341–1.338)	1.860 (0.452–1.635)	0.600	0.845 (0.411–1.736)	0.870 (0.425–1.782)	0.992 (0.493–1.994)	0.954
Ongoing pregnancy per patient	75 (32.9%)	67 (29.4%)	61 (26.4%)	71 (30.5%)	1.118 (0.755–1.656)	0.950 (0.637–1.415)	0.819 (0.546–1.227)	0.498	0.993 (0.653–1.512)	0.832 (0.544–1.273)	0.846 (0.552–1.295)	0.736
Live birth per patient	63 (27.6%)	58 (25.4%)	57 (24.7%)	69 (29.6%)	0.908 (0.606–1.360)	0.811 (0.538–1.222)	0.779 (0.516–1.174)	0.623	0.807 (0.524–1.243)	0.701 (0.453–1.086)	0.793 (0.514–1.223)	0.466
TOP ^b	1	3	1	0								
Pregnancy loss > 12 w	3	4	0	1								
Missing birth data	7	2	3	1								

^aAdjusted for confounding factors age, BMI, use of alcohol, tobacco or gonadotrophins, sperm count, diminished ovarian reserve, unexplained infertility and primary/secondary subfertility.

^bTOP, termination of pregnancy.

Ongoing pregnancy per patient and pregnancy loss do not add up to Clinical pregnancy because some patients did achieve an ongoing pregnancy after a pregnancy loss.

The normal range distribution of TSH levels in our study agrees with that reported in other studies of subfertile women, with $\pm 80\%$ of them having a TSH value below 2.5 mIU/L (Reh et al., 2010; Michalakis et al., 2011; Karmon et al., 2015; Unuane et al., 2017).

The American Thyroid Association considers it reasonable to recommend treatment with levothyroxine if TSH is > 2.5 mIU/L preceding pregnancy in subfertile women, and both the American Thyroid Association and the American Society for Reproductive Medicine recommend to consider treatment if TPO antibodies are positive (Practice Committee of the American Society for Reproductive, 2015; Alexander et al., 2017). This would suggest that TPO antibody screening is as important as TSH screening (Korevaar et al., 2017b), particularly in subfertile women. TPO antibody positivity affects $\sim 38\%$ of subfertile women with TSH > 2.5 mIU/L (Chai et al., 2014; He et al., 2016). Treatment of TPO antibody positive pregnant women with levothyroxine has been reported to decrease the risk of preterm delivery with a number needed to treat of 5.9 (Negro et al., 2007; Nazarpour et al., 2017), which could be explained by an impaired thyroidal response to hCG in TPO antibody positive women (Korevaar et al., 2017a) in early pregnancy. On the other hand TPO antibody positivity in IUI patients showed no negative effects on pregnancy or miscarriage rate with TSH 0.1–5.0 mIU/L (Unuane et al., 2017). In line with this, a prospective study from China in euthyroid IVF/ICSI patients with presence of TPO antibodies, showed no benefit of treatment with levothyroxine (started maximally 6 weeks before oocyte retrieval) on the miscarriage rate (Wang et al., 2017). In both studies however patients with TPO antibody positivity and with TSH > 2.5 mIU/L were not studied separately. Based on this and on our findings, we suggest that future studies account for primary or secondary subfertility and absence or presence of TPO antibodies.

Aside from the possibility that pregnancy outcomes after IUI may be different in subfertile women with TSH > 2.5 mIU/L in presence of TPO antibodies, this is the fourth single centre study showing that high normal range TSH is not associated with adverse pregnancy effects following IUI, and there seems to be no rationale for lowering the upper limits of TSH in general in subfertile women undergoing IUI.

Authors' roles

C.R.v.D.-D. and E.W.C.M.v.D. designed the study. C.R.v.D.-D. sought ethical approval. C.R.v.D.-D., S.H., L.v.d.K. and E.V. collected the data. R.S. supervised the collection of the data. E.W.C.M.v.D. supervised the research and writing process. P.M.v.d.V. and C.R.v.D.-D. performed the statistical analysis. R.P. was involved in interpretation of the data. C.B.L. was the supervisor of the study and of critical analysis, interpretation and presentation of the study.

All authors gave full input to the final draft of the article.

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Conflict of interest

None of the authors had any conflict of interest.

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