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Title:

IN A COHORT OF EUTHYROID INFERTILE WOMEN, SUBTLE VARIATIONS IN TSH ARE NOT CORRELATED WITH IMPAIRED REPRODUCTIVE OUTCOME

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Objective:

The thyroid plays a critical role in human metabolism, steroidogenesis, and development. And while treatment of thyroid abnormalities in reproductive-aged women is universally accepted, there is considerable debate in the field of endocrinology about what constitutes a normal thyroid stimulating hormone (TSH) level. The American Society for Reproductive Medicine suggests an upper threshold of 2.5 mIU/L, while the American Thyroid Association recommends 4.12 mIU/L.[1,3] There is evidence to suggest that fertility, particularly ovulatory function, implantation, and miscarriage risk, is significantly impaired by thyroid dysfunction; but, there is a limited understanding of the relationship between TSH level and artificial reproductive technologies (ART) treatment outcomes among euthyroid women. This study aimed to determine how subtle variations in TSH levels impact patient cycle outcomes following controlled ovarian stimulation (COS) for in vitro fertilization (IVF).

Design:

Retrospective cohort study

Materials and Methods:

The study included patients who underwent IVF between 2005-2018. Oocyte donation cycles were excluded from analyses. The following data were determined: patient age, gravidity, parity, day 3 serum TSH level, basal antral follicle count (BAFC), estradiol (E2) and progesterone (P4)

levels at the time of surge, cumulative gonadotropin (GND) dose, number of total oocytes and metaphase II (MII) oocytes retrieved, number of oocytes fertilized, number of blastocysts, day of blastocyst biopsy, and method of oocyte insemination (intracytoplasmic sperm injection (ICSI) versus conventional). The rates of oocyte maturity (MII), fertilization, and blastulation were determined. Patients were separated into groups based on serum TSH level: Group A=0.4-2.5 mIU/L or Group B=2.5-4.12 mIU/L. A sub-analysis of patients undergoing frozen embryo transfer (FET) with and without pre-implantation genetic testing for aneuploidy (PGT-A) was also performed. Patients with an endometrial thickness <7 mm were excluded from analysis. Clinical pregnancy rate (CPR), ongoing pregnancy rate (OPR), and clinical pregnancy loss (CPL) rate were determined. A clinical pregnancy was confirmed by sonographic evidence of a gestational sac. Data were analyzed using a Student's T-test, Chi-square, Fisher's Exact test, and multivariate logistic regression.

Results:

Data from 861 autologous IVF cycles and 358 FET cycles was included for analysis. Patients in both groups were similar in age, gravidity, parity, BAFC, surge E2 and P4, cumulative GND, type of oocyte insemination, and day of embryo biopsy for PGT-A. There were no significant differences in MII, fertilization, or blastulation rates (Table 1). However, after adjusting for confounders, blastulation was found to be significantly higher in patients with a TSH > 2.5 mIU/L (OR 1.5, 95% CI 1.2-1.7). Among patients who underwent a FET (n=370), there were no differences in CPR (58.9% vs. 63.8%, p=0.41), OPR (44.9% vs. 51.1%, p=0.30) or CPL rate (23.9% vs. 20.0%, p=0.80) between the two euthyroid groups, before and after adjusting for confounders.

Conclusions:

Pregnancy outcomes following ART treatment do not differ in euthyroid patients, even when fluctuations in TSH levels are present. Despite a higher blastulation rate in patients with a TSH >2.5 mIU/L, there were no other differences in ovarian stimulation outcomes, CPR, OPR, or CPL rate following FET between the two euthyroid groups. Given that maternal gestational hypothyroidism is associated with neurodevelopmental abnormalities of offspring, providers are encouraged to optimize maternal pre-conceptual TSH. Additionally, euthyroid patients can be reassured that while thyroid dysfunction may cause hormonal disturbances, subtle changes do not appear to impair IVF outcomes.

Support:

None

References:

1. Garber JR et al. "Clinical practice guidelines for hypothyroidism in adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association." Thyroid (22) 2012: 1200-1235.
2. Krassas G. "Thyroid disease and female reproduction." Fertil Steril (74) 2000: 1063-1070.
3. Practice Committee of the American Society for Reproductive Medicine. "Subclinical hypothyroidism in the infertile female population: a guideline." Fertil Steril, 2015.

Table 1.

Baseline Demographics and Cycle Characteristics among Euthyroid patients undergoing COS for IVF based on TSH level

	TSH 0.4-2.5 (n=599)	TSH 2.5-4.0 (n=262)	P Value
Age (y)	37.9 ± 4.5	38.0 ± 4.6	0.61
Gravidity			0.83
0	233 (44.6%)	113 (48.1%)	
1	144 (27.5%)	62 (26.4%)	
2	67 (12.8%)	27 (11.5%)	
≥3	79 (15.1%)	33 (14.0%)	
Parity			0.08
0	380 (72.5%)	181 (77.4%)	
1	110 (21.0%)	35 (15.0%)	
2	26 (5.0%)	17 (7.3%)	
≥3	8 (1.5%)	1 (0.4%)	
BAFC	10.5 ± 6.7	10.3 ± 6.7	0.75
Surge E2 (pg/mL)	1993 ± 1127	1981 ± 1119	0.90
Surge P4 (ng/mL)	0.90 ± 0.5	0.86 ± 0.40	0.36
Total GND (units)	3874 ± 1357	3885 ± 1345	0.91
Number of Oocytes Retrieved	13.2 ± 8.8	13.0 ± 8.5	0.77
Number of MIIs	10.6 ± 7.4	10.3 ± 7.1	0.61
MII Rate	81.4 ± 18.6%	82.3 ± 18.9%	0.54
Type of Insemination			0.66
- Conventional	89 (19.4%)	40 (19.5%)	

- ICSI - Split	361 (78.7%) 9 (2.0%)	163 (79.5%) 2 (1.0%)	
Number of Fertilized Oocytes	7.6 ± 5.9	7.2 ± 5.8	0.47
Fertilization Rate	69.7 ± 23.9%	69.1 ± 24.4%	0.77
Number of Blastocysts	5.8 ± 4.6	5.9 ± 5.2	0.80
Blastulation Rate	55.1 ± 34.3%	55.0 ± 35.6%	0.95
Day of Biopsy - Day 5 - Day 6 - Day 7	 130 (66.3%) 58 (29.6%) 8 (4.1%)	 49 (59.0%) 21 (37.4%) 3 (3.6%)	0.45