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Thyroid Stimulating Hormone Concentration and Pregnancy Outcomes during Intra-Cytoplasmic Semen Injection Cycle

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: The development in the reproductive medicine and revolution of Assisted Reproductive Technology (ART) have made significant changes in the global infertility science. There are many factors affecting the ovarian function (ovulation); thyroid disorders have made part of it.
Objective: This study aims to evaluate the prevalence of thyroid disorder and its effect on oocyte quality, implantation rate and pregnancy outcome.
Materials and Methods: This is a prospective study was conducted in the Libya National Fertility Centre. All participants were undergoing Intra-Cytoplasmic Semen Injection (ICSI). The inclusion criteria included cases with age less than 40 years and fresh embryo cycles. Cases with premature ovarian failure, endometriosis, Poly-Cytic Ovaries (PCO) and past history of ovarian surgery were excluded from the study.
Results: This study involved 627 cases. The cutoff value for Thyroid Stimulating Hormone (TSH) level (depending on the pregnancy rate, oocyte maturation and embryo quality) was 2.4 mIU/L. the participants were divided into two groups: TSH ≤2.4 mIU/L group (*n*=333) and TSH >2.4 mIU/L group (*n*=294). In the TSH ≤2.4 mIU/L group (36.69%) women achieved clinical pregnancy, while

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in the TSH >2.4 mIU/L group (31.37%) women achieved clinical pregnancy (*P*=0.038). No significant differences were observed between the two groups in pregnancy outcomes; Live Birth Rate (LBR) and abortion rate (*P*=0.052, *P*=0.258). With regard to oocyte maturation, women with TSH ≤2.4 mIU/L have a significant high chance to achieve better oocyte maturation in compare with another group (*P*=0.043).

Conclusion: The level of TSH (>2.4 mIU/L) is associated with poorer pregnancy outcome (low LBR and high miscarriage rate) and has determinantal effect on oocyte and embryo qualities. So, its recommended to prescribe the thyroxin therapy to infertile patients have TSH level (>2.4 mIU/L) before implementing ICSI cycle.

Keywords: TSH Concentration; pregnancy outcomes; intra-cytoplasmic semen injection.

ABBREVIATIONS

ART: Assisted Reproductive Technology
POI: Premature Ovarian Insufficiency
TSH: Thyroid Stimulating Hormone
COH: Controlled Ovarian S'timulation
ICSI: Intra-Cytoplasmic Semen Injection
ASRM: American Society for Reproductive Medicine
ATA: American Thyroid Association
FSH: Follicular Stimulating Hormone
LH: Lutinizing Hormone
AMH: Anti Mullarian Hormone
AFC: Antra Follicular Count
TVS: Trans-Vaginal Ultrasonography
HCG: Human Menopausal Gonadotropin
ET: Emberyo Transfer
CPR: Clinical Pregnancy Rate
ROC: Reactive Operative Curve
LBR: Live Birth Rate
ATD: Anti-Thyriod Drugs
ESCP: Endocrine Society of Clinical Practice Guideline
AACE: American Association of Clinical Endocrinologists
COS: Controlled Ovarian Stimulation
IVF: In vitro fertilization

1. INTRODUCTION

The development in the reproductive medicine and revolution of Assisted Reproductive Technology (ART) have made significant changes in the global infertility science [1,2]. The ovulatory disorder is essential issue regarding the female fertility [3]. There are many factors affecting the ovarian function (ovulation) including genetic (chromosomal), infection, polycystic ovary, iatrogenic (chemotherapy and radiotherapy), endocrine disorders (diabetes mellitus, thyroid problem, hyperprolactinemia) [4,5].

Various research revealed that the most common endocrine abnormalities interfere with the ovulation is thyroid problem which consequently ended by Premature Ovarian Insufficiency (POI) [5]. From the gynecology point view, thyroid dysfunction could carry irregularity in menstrual cycle, unovulatory cycles, POI, infertility and even if the patient conceive could carry a high miscarriage rate, low live birth rate [6,7]. The thyroid function can be monitor by some laboratory tests including the most important one is Thyroid Stimulating Hormone (TSH) and Thyroxin level; T3 and T4 [8,9].

The presentation of thyroid problem could be hypothyroidism or hyperthyroidism (Graves' disease and Hashimoto's thyroiditis) and their effect can be either by hormonal disturbance and/or cellular immunity disturbance and this is explaining the autoimmune disorder of thyroid gland [10,11,12]. The cut off level of TSH has been studied previously by many researchers in order to improve the pregnancy rate as well as the outcome. However, its upper limit is still controversial to detect its effect on oocyte quality, implantation rate, abortion rate and live birth rate [12,13,11].

The value of TSH level is critical to be detected for any women trying to conceive because the fact that, the thyroid receptors are distributed in the ovarian granulose cells and uterine endometrium which explain the physiological serum TSH level that could affect the folliculogenesis and so the Controlled Ovarian S'timulation (COH) that considered as an important step in Intra-Cytoplasmic Semen Injection (ICSI) technology [9,14,15]. In addition, the immune system might be affected by the presence of thyroid auto-antibodies. This leads to an interruption in the physiological process that takes place during pregnancy which in turn causes disturbance in the level of thyroid hormone based on the gestational age [16].

A number of studies American Society for Reproductive Medicine (ASRM) documented that

the serum level of TSH (2.5 Miu/L) is the cutoff value for improving the implantation and the pregnancy outcome after ICSI cycle [9,11,13]. However, many studies revealed that even if the TSH level above (2.5 Miu/L) can be considered normal value as it is associated with good implantation rate and pregnancy outcome [9,14]. Moreover, the existing data from ASRM recommend a routine screening for infertile patients who try to conceive as well as those whose TSH level is above (4 mIU/L) which were found to be associated with high risk of abortion. Based on that, the serum level of TSH as well as the strategy of TSH screening are still with insufficient data [2]. Furthermore, American Thyroid Association (ATA) points out that perform thyroid function test for all women prior to imparking in ICSI cycle and any recorded disturbance has to be managed accordingly [17,18,19].

This study aims to primary; detect the best TSH level before imparking in ICSI cycle which could increase the pregnancy rate and its outcome among infertile patients and secondary; evaluate the possible complications associated with TSH disturbance.

2. MATERIALS AND METHODS

This is a prospective study was conducted in Libya, National Infertility Centre Misurata. The participants in the current study underwent ICSI. The inclusion criteria included all cases with ages less than 40 years and had fresh embryo cycles. Cases with premature ovarian failure, endometriosis, polycytic ovaries and with a history of ovarian surgery were excluded from the study.

On the second day of menstrual cycle, Follicular Stimulating Hormone (FSH), Lutinizing Hormone (LH), TSH, Anti Mullarian Hormone (AMH) and Estradiol were measured by electro-chemiluminescence immunoassays and the results were reported in mIU/ml for FSH and LH but AMH by ng/ml, Whereas the Antra Follicular Count (AFC) was measured on day2 of menstrual cycle by Trans-Vaginal Ultrasonography (TVS). All the patients were performed antagonist protocol for ICSI cycle starting on the second day of menstrual cycle by start COH with administration of Human Menopausal Gonadotropin (HCG) (Menogon, Ferring, Kiel, Germany) and from day 6 of stimulation onward, the antagonist 0.25 mg of Cetrorelix was prescribed.

The ovarian responses were monitored by using TVS as well as Estradiol serum level and when three or more dominant follicle reached at least 18 mm, administration of HCG for oocyte maturation was performed. 36 hours following injection of HCG, retrieval of oocytes was carried out under general anesthesia and injected by the sperm for fertilization then Emberyo Transfer (ET) was done accordingly (day two/three emberyo or day five blastocyst). Progesterone suppositories (Cyclogest Alpharma, Barnstaple, UK) were prescribed for all cases and for a period of 18 days when the quantitative serum pregnancy test was performed. After that, the data of the pregnancy outcome were collected by contact with the participants of the study.

The primary outcomes were oocyte quality and Clinical Pregnancy Rate (CPR) (clear fetal heart activity by TVS), Whereas the secondary outcomes were miscarriage rate, Life Birth Rate LBR and ectopic pregnancy rate. The CPR, LBR and miscarriage rates were compared among the groups according to the level of TSH.

2.1 Statistical Analysis

The data from this study were statistically analyzed by using SPSS software Version 23.0 (SPSS, USA). Categorical data were described by percentages and the continuous variables were presented as mean ± standard deviation. To compare clinical characteristics and parameters between the two groups, t-test was used for continuous variables and chi-square test for nominal variables. Pregnancy rate was compared using Pearson's chi-squared or Fisher's exact test. Binary logistic regression was used for multivariate analysis of the probability of pregnancy. P value <0.05 was considered statistically significant.

3. RESULTS

This is a prospective study involved 727 cases were enrolled in the study. The cutoff value for TSH level (depending on the pregnancy rate and oocyte maturation and embryo quality) were calculated using Reactive Operative Curve (ROC) and the result was 2.4 mIU/L as TSH threshold value (Fig. 1). Then, the data divided into two groups according to TSH level, group (≤ 2.4 mIU/L) and group (> 2.4 mIU/L). The demographic data which describe the patient's profiles are presented as mean ± SD and shown in Table 1.

The oocyte maturation and embryo quality. The result is shown in Table 2. In the TSH ≤2.4 mIU/L group, (94.1%) women were mature oocytes (MII), with (P=0.043), (63.6%) women had grade A embryo, with (P=0.052), and (23.6%) women had blastocyst, with (P=0.173). In the TSH >2.4 mIU/L group, (90.8%) women were mature oocytes (MII), (65.8%) women had grade A embryo, and (21.4%) women had blastocyst.

Table 1. Descriptive data for both groups (TSH(≤ 2.4 mIU/L) and group (> 2.4 mIU/L).

variable	Group (TSH≤2.4) Mean ± SD	Group (TSH>2.4) Mean ± SD
Age	32.33 ± 2.55	33.12 ± 3.12
Infertility time (Year)	4.28 ± 2.55	4.65 ± 3.12
FSH (IU/L)	7.18 ± 2.71	6.92 ± 3.21
LH (IU/L)	4.92 ± 2.46	4.56 ± 3.21
E2(Estradiol) (PG/ML)	42.84 ± 34.45	43.44 ± 34.61
AFC	9.04 ± 5.28	8.79 ± 4.89
AMH (NG/ML)	2.68 ±1.75	3.01 ± 1.22

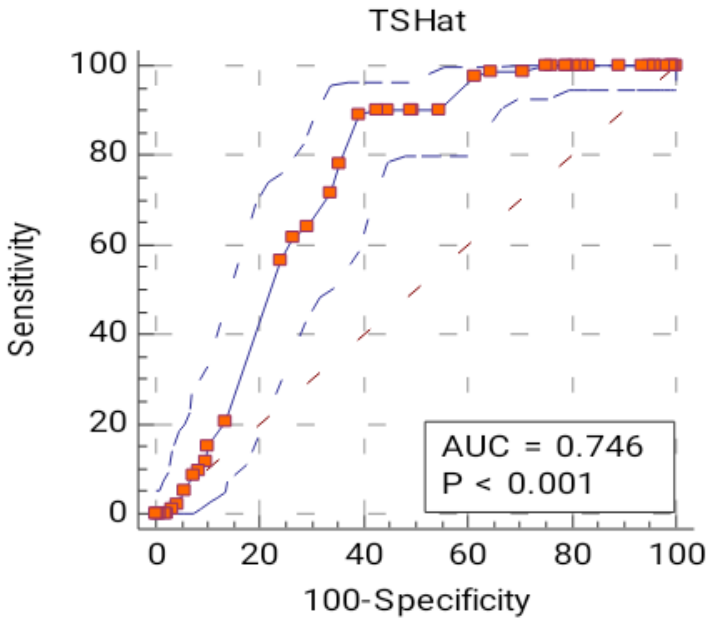

Fig. 1. ROC to measure the cut off value for TSH level (depending on the implantation rate, oocyte maturation and embryo quality) and the result was 2.6 mIU/L

Table 2. Effect of TSH level on the oocyte maturation and embryo quality

Variable	Group (TSH≤2.4) (%)	Group (TSH>2.4) (%)	P value
Mature oocyte (M II)	(93.23%)	(90.85%)	0.043
Grade A embryos	(63.69%)	(65.85%)	0.314
Blastocyst	(23.69%)	(21.48%)	0.173

Table 3. Effect of TSH level on the clinical pregnancy rate

variable	**Group (TSH≤2.4) (%)**	**Group (TSH>2.4) (%)**	P value
Clinical Pregnancy	(36.69%)	(31.37%)	0.038
Live Birth Rate	(23.28%)	(18.78%)	0.052
Abortion Rate	(31.50%)	(11.90%)	0.258

During follow-up the participants, the compare in the clinical pregnancy rate, live birth rate, miscarriage rate between the two groups was recorded. The results are shown in Table 3. In the TSH ≤2.4 mIU/L group, (36.6%) women were clinically pregnant, with (P=0.038), (23%) women had live birth rate with (P=0.052), and (13.5%) women had early pregnancy loss with (P=0.258). In the TSH >2.4 mIU/L group, (31.3%) women were clinically pregnant, (18.7%) women had live birth rate, and (11.9%) women had early pregnancy loss.

4. DISCUSSION

This large retrospective cohort study investigated the optimal TSH value (in range) used for patients before attempting conception by ICSI as well as evaluate its (TSH range) impact on pregnancy outcomes. The study has concluded that the optimal level of TSH is ≤2.4 mIU/L for euthyriod infertile patients who plane ICSI cycle in order to improve the implantation rate and Live Birth Rate (LBR) as well as reduce the abortion rate. For patients who have to receive the Anti-Thyriod Drugs (ATD) , the level of TSH has to be maximum 2.4 mIU/L on a day two of cycle of ICSI to reduce the risk of implantation failure as well as the abortion rate.

Despite the recommendation by Endocrine Society of Clinical Practice Guideline (ESCP) and ATA with American Association of Clinical Endocrinologists (AACE) recommended that during pregnancy should prescribe treatment for clinical hypothyroidism to maintain TSH level (≤ 2.5 mIU/L) during first trimester and 3.0 mIU/L during second and third trimester, however, preconception (before ICSI) recommendations regarding treatment for hypothyroidism were not available yet [20,21,22].

Moreover, Katherine et al. [23] and Lei Zhang et al. [24] recommend that the TSH level (≤2.5 mIU/L) for infertile women before attempting conception and this value will not need any further adjustment [23,24]. Y. Xu et al. [25] study large population (10266 patients) underwent In vitro fertilization (IVF)/ICSI cycles and found that the CPR, LBR and abortion rate were not statistical difference (p value >0.05) between levels of TSH among patients underwent IVF as well as ICSI cycles; however, it showed negative outcomes with regard to low birth weight infant. Furthermore, American Society for Reproductive Medicine ASRM regarding subclinical hypothyroidism in the infertile female population found that clear evidence between the increase in miscarriage rate and the TSH > 4.0 mIU/L [11].

On the other hand, there are other research revealed that the TSH level before conception has no role in the outcome of pregnancy. Coelho Neto et al. concluded that clinical pregnancy rate, ICSI outcome (live birth rates and miscarriage) were similar when TSH cut-off values were 2.5mIU/L and 4.0 mIU/L, and this was in line with other findings from various research [26,27,28]. Çalışkan et al. [29] studied the CPR and LBR among subclinical hypothyroidism infertile couple underwent ICSI cycle and found that the result did not differ from control group and the prevalence of the Subclinical hypothyroidism was 5% among sub-fertile population considered TSH cutoff value ≤ 2.5 mIU/L [9] and this was accepted prevalence in compare with results of study presented by Coelho Neto et al [28] as the prevalence was 30% at the threshold level for TSH ≤ 2.5 mIU/L.

Physiologically, the level of TSH could be changed (raised) during Controlled Ovarian Stimulation (COS) and might have negative outcomes on conception rate. Lei JIN et al [9] revealed that the CPR, LBR and abortion rate among euthyroid women had not affect with TSH level (>2.5 mIU/L) and this reject the previous hypothesis which state that receiving ATD before implement ICSI cycle in order to maintain TSH levels ≤2.5 mIU/L have no beneficial effect to improve the implantation rate and pregnancy outcomes [29]. Magri et al. [30] studied the

negative outcomes of COS among infertile patients suffer from autoimmune thyroid disease and found that effect of recombinant-FSH and serum Estradiol level on those people (ovarian response) was significantly lower in among population (≤2.5 mIU/L) [30] and this was in consistence with results of study by Çalışkan et al. [29] when comparing with the TSH level (> 4.5 mIU/L) [9]. ATA advices the use of ATD to patients during COS as well as euthyroid women with positive thyroid antibody as their positive effects higher than the risks [31].

This study is a retrospective and so it carries limitations which involved only patients underwent ICSI, Free thyroxine level and thyroid antibodies were not available in the patients" medical records. Further, it is important to suggest multi-centre large prospective cohort research in order to investigate and confirm or reject the result of this study.

5. CONCLUSION

The finding of this study were that the level of TSH (>2.4 mIU/L) is associated with poorer pregnancy outcome (low LBR and high miscarriage rate) and has determinantal effect on oocyte and embryo qualities. So, its recommended to prescribe the thyroxin therapy to infertile patients have TSH level (>2.4 mIU/L) before implementing ICSI cycle.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

The approval of the study was obtained from the Research Ethics Committee at Scientific Research and Documentation Department, Libyan National Fertility Center - Misurata, Libya (2021-10), and parental written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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