



# Thyroxine Supplementation Improve Intrauterine Insemination Outcome in patients with subclinical Hypothyroidism

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## Abstract

### Background

Subclinical hypothyroidism (SCH) is thyroid disorder affecting 4%-8% of reproductive age women. It may contribute to increased risk of infertility and adverse early and late pregnancy problems. Previous studies on effect of SCH on infertility treatment consequence, and pregnancy end result still controversial. The aim of this study is to investigate the outcome of intrauterine insemination in patients with subclinical hypothyroidism treated with levothyroxine, for strictly keeping TSH  $\leq 2.5$ .

### Methods

**Study design and setting** This prospective case control study was undertaken in the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies/ Al-Nahrain University during the period from April 2015 to June 2017. One thousand and two hundred sixty four 1264 subfertile women were enrolled in this study, assessment of thyroid function done for all of them before receiving medication for controlled ovarian stimulation. One hundred forty nine 149 patients were diagnosed as SCH. Those 149 women were divided into group A (treated with levothyroxine), and group B (no treatment). Ninety healthy women with normal thyroid function tests were randomly selected as control group C. All the pregnant women followed up till the end of the pregnancy. Comparison between the three groups in IUI cycles Characteristics, pregnancy rate, miscarriage rate, and live birth rate were done.

### Results

No significant difference found in age, duration of subfertility, and history of previous pregnancy between the three groups. Regarding BMI group A showed significantly lower value than group B ( $p=0.0030$ ), but no significant difference with group C. Concerning causes of infertility, anovulation was significantly lower in group A than group B ( $p=0.0056$ ). While mild male factor ( $p=0.0098$ ), and combined factors ( $p=0.0098$ ) were significantly higher in group A than group B. Unexplained infertility was not significant between group A, and group B. All the causes of infertility not significantly differ between group A and Group C.

Group A show significantly higher number of follicles ( $p=0.00012$ ), with larger diameter of follicles ( $p=0.002364$ ), and thicker endometrium ( $p=0.000011$ ) than group B, while no significant difference in other parameters. No significant difference in IUI cycles characteristics between group A and group C. In regard to IUI outcome, clinical pregnancy was significantly higher in group A than group B ( $p=0.03223$ ) but no significant difference between group A and group C. No significant difference in multiple pregnancy, and miscarriage rate, between the three groups. Live birth rate was significantly higher in group A than group B ( $p=0.0219$ ), while the difference was not significant between group A and group C even it was higher in group C

**Conclusions:** Non treated subclinical hypothyroidism (SCH) has negative impact on intrauterine insemination outcome. Thyroxin supplementation and keeping TSH  $\leq 2.5$  can improve intrauterine insemination success, and live birth rate.

**Keywords:** Subclinical hypothyroidism, Thyroxin, intrauterine insemination

## BACKGROUND

Subclinical hypothyroidism is a calm thyroid disorder affecting 4%-8% of reproductive age women [1]. It may contribute to increased risk of infertility and adverse early and late pregnancy problems [2]. Subclinical hypothyroidism (SCH) defined as asymptomatic raise in serum thyroid stimulating hormone (TSH) level associated with normal free thyroxine (FT4) level [3]. Previous studies on effect of SCH on infertility treatment consequence, and pregnancy end result still controversial [4,5]. Fifty percent increment in thyroid hormone production occur during pregnancy as a reaction to physiological rise in serum estrogen level [6]. Assisted reproduction technologies (ART) have international widespread, about 1.6 million ART cycles are being performed annually worldwide, resulted in about 400,000 newborn each year [7].

Intrauterine insemination is one of ART procedures which had universal use, as it less invasive, financially less expensive, in technique less sophisticated and more patient friendly than IVF/ICSI [8]. Controlled ovarian hyper-stimulation is essential in most intrauterine insemination

treatment cycles especially in anovulatory women, and even in ovulatory female partners to improve success rate [9]. Supra physiological levels estradiol usually produced in response to controlled ovarian stimulation [10]. Estrogen stimulate thyroid-binding globulin production, so higher serum concentrations of thyroid-binding globulin, leaving less concentration of free thyroid hormones, as a response thyroid-stimulating hormone (TSH) production increase to maintain adequate thyroid hormone secretion [11]. Many researchers found that controlled ovarian hyper-stimulation led to significant raise in TSH, often even above pregnancy appropriate level. [12, 13] In the other side several data showed that SCH has an adverse effect on success of intrauterine insemination and pregnancy outcome [14]. The upper normal range of TSH is 4.5 mIU/L in non-pregnant women, but TSH should be kept to  $\leq 2.5$  mIU/L in women with overt hypothyroidism treated with levothyroxine before pregnancy, and during the first trimester according to the American Society for Reproductive Medicine recommendation. [1] Whether thyroxin supplementation, and keeping serum TSH equal or less than 2.5 mIU/l can overcome the adverse consequence

of subclinical hypothyroidism still questionable[15].The aim of this study is to investigate the outcome of intrauterine insemination in patients with subclinical hypothyroidism treated with levothyroxine, for strictly keeping TSH $\leq$ 2.5.

## METHODS

**Study design and setting** This prospective case control study was undertaken in the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies/ Al-Nahrain University during the period from April 2015 to June 2017. The study was approved by the Local Medical Ethical Committee of the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies.

**Patients** One thousand and two hundred sixty four 1264 subfertile women were enrolled in this study, assessment of thyroid function done for all of them before receiving medication for controlled ovarian stimulation. One hundred forty nine 149 patients were diagnosed as SCH [3]. Those 149 women were divided into group A (treated with levothyroxine), and group B (no treatment). Ninety healthy women with normal thyroid function tests were randomly selected as control group C. Inclusion criteria were unexplained infertility, anovulation, and mild male factor infertility, when at least two semen analyses revealed sperms count  $\geq$ 10 million per ml and sperms motility grade (a&b)  $\geq$ 50%[16,17].Testing for tubal patency were done either by hysterosalpingography or Laparoscopy +hydrotubation. Exclusion criteria were women with overt endocrine disorder, double-sided tubal pathology, endometriosis(other than minimal),uterine abnormality, diminished ovarian reserve, and women aged  $>$ 40 years.

**Hormonal assays:-** Before initiation of controlled ovarian stimulation /Intrauterine insemination all females partners included in this study had fasting blood samples analyzed for basal levels of Follicle stimulating hormone(FSH), Luteinizing hormone(LH), Thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4) on Day 2or 3 of a spontaneous or induced menstrual cycle. Serum hCG titer measured 14 day post IUI to confirm pregnancy. All hormones were measured using fluorescence assay system (mini VIDAS, bioMerieux, France). Depending on TSH, FT4, FT3 levels patients were classified as: euthyroid (TSH, FT4, FT3 within normal range), subclinical hypothyroid (elevated TSH, with FT4, FT3 within normal range) [15].

### Ovarian stimulation and follicles monitoring:-

Before initiation of controlled ovarian stimulation, group A were received daily levothyroxine, the starting dose was 25-50 $\mu$ g, further modification of the dose was depending on response to treatment, the target was keeping their serum TSH concentrations  $\leq$ 2.5  $\mu$ IU/mL for at least 1 months before IUI, and maintain on the same level throughout the first trimester if IUI succeed, and pregnancy confirmed. Controlled ovarian stimulation for all the groups started between the second and fifth day of natural or induced period, using clomiphene citrate (Sanofi-

Aventis,UK) starting dose 50mg/day up to 100mg/day. Recombinant FSH (75I U/ampoule, Gonal F; Merck Serono.Ltd, United Kingdom), or human menopausal gonadotropin (75 FSH IU 75 LH IU/ampoule; Mengon; Ferring, Germany) were added to the ladies who failed in producing at least one dominant follicles $\geq$ 18mm on clomiphene citrate alone. The dose of gonadotropins was adjusted according to patients' age, BMI, antral follicles count and early follicular phase FSH and LH. Transvaginal ultrasound scan was done five days after initiation of treatment to evaluate the count and size of follicles and endometrial thickness, and consequent scans were performed on individual bases depending on patients' responses to medications. When at least one follicle reach 18 mm ovulation was triggered by 250  $\mu$ g of recombinant human chorionic gonadotropin rhCG (Ovitrelle;Merck Serono, UK) injected subcutaneously, but if  $\geq$ 4 dominant follicles, the cycle canceled. Intra uterine insemination was done using fresh semen obtained from the husband 24- 36 hr later to rhCG injection .

### Sperm preparation and intrauterine insemination

Period of husband abstinence from sexual activity before insemination was 72-120 hr, semen collection was by masturbation three hours before insemination for laboratory preparation, all the samples were prepared by swim-up technique. About 0.25-0.5 ml of prepared semen was inseminated slowly over 15 to 30 second using soft catheter (Rocket Medical, Watford, UK) into the uterine cavity.

### Luteal phase support, and fallow up

Luteal phase was supported by 400 mg vaginal progesterone pessaries (Cyclogest;Actavis, UK) given once daily started 1 day after IUI, till the day of serum beta hCG measurement, which was done at least 14 days after insemination. Vaginal progesterone pessaries continued during the 1<sup>st</sup> trimester of pregnancy in positive cases while, in negative cases stopped immediately. Clinical pregnancy was confirmed by the presence of one or more gestational sacs with cardiac activity on transvaginal ultrasound examination, three weeks later. All the pregnant women followed up till the end of the pregnancy .Comparison between the three groups in IUI cycles Characteristics, pregnancy rate, miscarriage rate, and live birth rate were done.

**Statistical analysis** All statistical analyses were done using statistical package SPSS-24 (Statistical Packages for Social Sciences- version 24). Data were expressed as number and percentage for qualitative variable such as biochemical and clinical pregnancy. Fisher exact test was used to compare the proportions. Mean  $\pm$  SD for quantitative variables such as biomarkers, and stimulation characteristic. Student's t-test was used for comparison of quantitative variables between the three groups. The P value of  $<$  0.05 was considered as statistically significant.

## RESULTS

A total of 1264 subfertile women undergoing IUI, were participated in this study. Women with subclinical hypothyroidism women were 149 (11.78%), who were

divided into group A (treatment group) 75 women, and group B (no treatment) 74 women. Of the 1115 women (88.2%) with normal thyroid function test, 90 were suitable and participated in the study as a group C (control group). All of them completed all study visits and incorporated in the final analysis. Demographic characteristics of the participants are shown in (table 1), no significant difference found in mean age, duration of subfertility, and history of previous pregnancy between the three groups. Regarding BMI group A showed significantly ( $p= 0.0030$ ) lower value

than group B, but no significant difference with group C. Concerning causes of infertility, anovulation was significantly ( $p= 0.0056$ ) lower in group A than group B. While mild male factor ( $p= 0.0098$ ), and Combined infertility ( $p= 0.0098$ ) were significantly higher in group A than group B. Unexplained infertility was not significant between group A, and group B. All the causes of infertility not significantly differ between group A and Group C.

**Table (1) Demographic Characteristics of patients.**

Parameters	Group A n75	Group B n74	Group C n90	p- value*	p- value**
Female age(years) means $\pm$ SD	28.6 $\pm$ 5.31	29.5 $\pm$ 5.4	28.8 $\pm$ 6.25	0.33601	0.4751
BMI means $\pm$ SD	26.26 $\pm$ 2.6	28.61 $\pm$ 1.19	25.4 $\pm$ 2.5	0.0030	0.1828
Duration of infertility (years) means $\pm$ SD	4.2 $\pm$ 1.61	4.6 $\pm$ 1.9	4.13 $\pm$ 1.88	0.2705	0.4589
Previous pregnancy(n, %)	27(36)	30(40)	56(62)	0.3251	0.8137
<b>Causes of infertility</b>					
Anovulation (n, %)	20(26.7)	36(48.6)	28(31.1)	0.0056	0.5313
Mild Male factor (n, %)	22(29.3)	9(12.2)	26(28.9)	0.0098	0.9500
Unexplained (n, %)	11(14.7)	20(27)	11(12.2)	0.0631	0.6455
Combined factors(n, %)	22(29.3)	9(12.2)	25(27.8)	0.0098	0.8255

p- value\* for comparison between group A, and group B, p- value\*\* for comparison between group A, and group C

**Table (2): Comparison of thyroid function, and characteristics of IUI treatment cycles between the three groups**

Parameters	Group A n75	Group B n74	Group C n90	p- value*	p- value**
TSh(mIU/L) means $\pm$ SD	2.18 $\pm$ 0.25	4.19 $\pm$ 0.82	1.99 $\pm$ 0.41	0.00001	0.0742
Ft3 pg/mL means $\pm$ SD	3.32 $\pm$ 0.58	3.32 $\pm$ 0.43	3.35 $\pm$ 0.63	0.01569	0.1493
Ft4 ng/dL means $\pm$ SD	1.31 $\pm$ 1.49	1.24 $\pm$ 1.01	1.29 $\pm$ 1.12	0.283305	0.4294
Number of follicles means $\pm$ SD	2.86 $\pm$ 0.63	1.76 $\pm$ 0.72	2.8 $\pm$ 0.86	0.00012	0.405839
Mean follicles diameter(mm) means $\pm$ SD	20.8 $\pm$ 1.56	19.2 $\pm$ 1	21.6 $\pm$ 1.12	0.002364	0.059563
Endometrial Thickness means $\pm$ SD	8.26 $\pm$ 1.16	6.46 $\pm$ 0.51	8.26 $\pm$ 1.4	0.000011	0.5
<b>Type of treatment</b>					
Clomiphene citrate(n, %)	49(65.3)	41(55.4)	56(62.2)	0.2432	0.746
Clomiphene citrate + Gonadotropin(n, %)	26(34.7)	33(44.6)	34(37.8)	0.2432	0.746
<b>Post-processing semen parameter</b>					
Count / ml / ml means $\pm$ SD	26.2 $\pm$ 5.9	27.9 $\pm$ 6.49	26 $\pm$ 6.73	0.2360	0.4766
Motility (%) means $\pm$ SD	49 $\pm$ 7.87	48.38 $\pm$ 11.7	6.26 $\pm$ 8.38	0.4350	0.1826

p- value\* for comparison between group A, and group B, p- value\*\* for comparison between group A, and group C

**Table (3): Comparison of IUI treatment cycles outcome between the three groups.**

Parameters	Group A n75	Group B n74	Group C n90	p- value*	p- value**
Clinical pregnancy rate (n, %)	19(25.3)	8(10.8)	24(26.7)	0.03223	0.8607
Multiple pregnancy rate. (n, %)	0	0	1(5.55)	1	1
Miscarriage rate (n, %)	2(10.5)	2(25)	2(8.33)	1	1
Live birth rate (n, %)	17(89.5)	6(75)	22(91.66)	0.0219	0.7176

p- value\* for comparison between group A, and group B, p- value\*\* for comparison between group A, and group C

Mean serum TSH was significantly higher ( $p=0.00001$ ) in group B than group A, but no significant difference between group A and group C, while means of free T3, and free T4 showed non-significant diversity between the three groups as demonstrated in table 2.

The Characteristics of IUI treatment cycles for all the groups listed in table 2, group A show significantly higher number of follicles ( $p=0.00012$ ), with larger diameter of follicles ( $p=0.002364$ ), and thicker endometrium ( $p=0.000011$ ) than group B, while no significant difference in other parameters. No significant difference in IUI cycles characteristics between group A and group C. In regard to IUI outcome, clinical pregnancy was significantly higher in group A than group B ( $p=0.03223$ ) but no significant difference between group A and group C. No significant difference in multiple pregnancy, and miscarriage rate, between the three groups. Live birth rate was significantly higher in group A than group B ( $p=0.0219$ ), while the difference was not significant between group A and group C even it was higher in group C

#### DISCUSSION:

The incidence of sub clinical hypothyroidism, depending on the definition that TSH level higher than the upper limit of normal range (4-5mIU/L) with normal FT4 levels has been reported to be around 4-8% in reproductive age females [18]

The reported prevalence of SCH during pregnancy differs between populations which is about 2.5% in southern countries (19,20), while several Indian studies recording higher prevalence reaching 14% [21,]. In infertile women SCH show higher prevalence reaching 25% with higher incidence in women with ovulatory disorders and unexplained infertility [22,23,24]. Subclinical hypothyroidism may have negative impact on ovulation, and even response to ovulation induction [25]. In this work, 1264 subfertile women underwent IUI, assessment of thyroid function revealed that the incidence of SCH was 11.78 which is concur with previous studies [26]. Several researches reported an association of untreated SCH with poor pregnancy outcomes in women went through ART interventions, such as decreased pregnancy rate and live birth rate [27,28,29], on the other hand there is several studies oppose, and found no relation between subclinical hypothyroidism and early miscarriage, recurrent pregnancy loss, and live birth rate [30,31].

Current data have demonstrated some benefits of L-T4 supplementation in reducing those adverse effects, as SCH women were substituted with L-T4 and their TSH levels were maintained  $\leq 2.5$  mIU/L at least one month before intrauterine insemination. All IUI cycles parameters, and outcome were non considerably vary between treated SCH women and euthyroid women, which is consistent with previous studies, that found that IUI outcome was not significantly diverge in women with effectively treated hypothyroidism [14]. Merka et al proved that SCH during pregnancy is related to numerous unfavorable maternal and neonatal outcomes. There is many data found that treating women with SCH with levothyroxine is associated with higher pregnancy rate, and live birth rate [36]. The cutoff of serum TSH, that associated with poor pregnancy outcome vary between literatures. The higher incidence of miscarriage in pregnant women with TSH levels between 2.5 and 5.0 mIU/liter support keeping TSH upper limit in the first trimester to 2.5 mIU/liter [37]. Few studies examined the effect of SCH on live birth when TSH level higher than 2.5mIU/L but less than the upper limit of normal value at the time of conception in IUI., some study found there were no significant differences in live birth delivery-, pregnancy- or miscarriage rate when comparing subgroups according to TSH level (TSH  $\geq 2.5$  mIU/l vs. TSH  $< 2.5$  mIU/l) [32,33]. Other studies suggest that there is a trend toward increasing risk of miscarriage with increasing TSH level, although this trend did not reach statistical significance [34,35].

In our study, there were no significant difference between euthyroid women and treated SCH in clinical pregnancy rate, but both were significantly higher than non treated women. Miscarriage rate were higher in untreated even there were no significance. Live birth rate in treated SCH comparable to euthyroid women, both significantly higher than non treated subclinical hypothyroidism, this be in agreement with Norman J et al who supposed that adverse pregnancy outcomes can be conquered in women with subclinical hypothyroidism who had been diagnosed and treated with thyroxine. [38].

#### CONCLUSIONS:

Non treated subclinical hypothyroidism SCH has negative impact on intrauterine insemination outcome. Thyroxine supplementation and keeping TSH  $\leq 2.5$  can improve intrauterine insemination success, and live birth rate.

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