



Research Article

Volume 17 Issue 5- January 2020
DOI: 10.19080/JGWH.2020.17.555972

J Gynecol Women's Health

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Levothyroxine with Clomiphene Citrate for Ovulation Induction in Patients with Polycystic Ovary Syndrome and Subclinical Hypothyroidism



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Submission: December 14, 2019; Published: January 03, 2020

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Abstract

Introduction: Polycystic ovary syndrome (PCOS), affecting about 5 to 10% of women [1] Hypothyroid disturbances and elevated TSH levels are common findings in PCOS [2].

Objectives: To study the effect of Eltroxin on ovulatory function in patients with PCO and Subclinical Hypothyroidism (SCH).

Methods: This comparative observational study was conducted on 204 patients with PCO and subclinical hypothyroidism who were subdivided into 2 groups. Control group (1):102 patients who received placebo and Clomiphene Citrate (cc) for 3 successive cycles. Study group (2):102 patients who received Eltroxin and (CC) for 3 successive cycles. Patients were followed up for 3 months for ovulation and pregnancy

Result: There was no significant difference between cases and controls regarding age, parity, BMI. There was no significant difference between both groups regarding ovarian function represented in LH, FSH, TSH, progesterone before treatment. There was significant difference between both groups regarding ovarian function represented in LH, FSH, TSH, progesterone after treatment There was significant difference between both groups regarding ovulation and pregnancy rates.

Conclusion: Eltroxin has beneficial effects on ovulation and pregnancy in patients with subclinical hypothyroidism and PCO

Keywords: Eltroxin; Polycystic ovary; Subclinical hypothyroidism

Abbreviations: SCH: Subclinical Hypothyroidism; CC: Clomiphene Citrate; PCOS: Polycystic Ovary Syndrome; MBS: Metabolic Syndrome; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; DHEA-S: Dehydroepiandrosterone; TSH: Thyroid Stimulating Hormone; USPSTF: United States Preventive Services Task Force

Introduction

Polycystic ovary syndrome (PCOS), affecting about 5 to 10% of women, is characterized by hyperandrogenism, menstrual disturbance, obesity, anovulation, infertility, Insulin Resistance, hyperglycemia, weight gain, and metabolic syndrome (MBS) as hypothyroidism [1]. Hypothyroid disturbances and elevated TSH levels are common findings in PCOS. Nanda et, al. [2] 2014 study revealed the prevalence of hypothyroidism in PCOS was 13.26%. Out of that 57.69% had subclinical hypothyroidism and 42.30 % had overt hypothyroidism Therefore, women with diagnosed PCOS should be screened for thyroid dysfunction.

Hypothyroidism causes altered follicle stimulating hormone (FSH)/luteinizing hormone (LH) ratio and raised

dehydroepiandrosterone (DHEA-S) levels. As excess thyroid stimulating hormone (TSH) causes stimulation of FSH receptor [3]. The National Academy of Clinical Biochemistry suggested serum TSH (0.4– 2.5) mIU/L as the normal range, according to United States Preventive Services Task Force (USPSTF) Guidelines defined subclinical hypothyroidism SCH as high serum TSH (2.5-10 mIU/L) with a normal FT4 concentration [4].

Subclinical hypothyroidism is found between 3–8% of women of reproductive age, has few signs or symptoms of thyroid dysfunction and often remains untreated. Most of the times hypothyroidism is subclinical and diagnosed first time during evaluation of PCOS. In contrast to overt hypothyroidism, where

most evidence appears to support an association with an increased risk of infertility [4]. The most common endogenous cause of SCH is chronic autoimmune thyroiditis (Hashimoto's thyroiditis) associated with anti-TPO antibodies, TSH receptor loss of function mutations and presence of heterophile antibodies [5].

Data assessing effect of SCH on fertility are limited due to varied definitions of SCH (different TSH cutoffs) and lack of adequate control groups [4]. In 2015, the American Society for Reproductive Medicine found insufficient evidence to conclude that SCH is associated with infertility [6]. The ATA has issued a weak recommendation that administration of LT4 may prevent progression to overt hypothyroidism once pregnancy is achieved. ASRM recommendations 2015 states that, it is reasonable to screen infertile women for TSH levels, if it is >4mIU/L. Patients should be treated with Levothyroxine to maintain TSH level below 2.5mIU/L (Grade B), If TSH is between 2.5-4mIU/L management options either observation or giving Levothyroxine (Grade C).

CC resistance represents up to 20-40% of infertile women with PCOS. In one study, a total of 145 PCOS patients were received CC stimulating test. One hundred and twelve patients had ovulation, with an ovulation rate of 77.2%, 35 patients (22.8%) CC resistant. Logistic regression revealed a significant association between SCH and CC resistance. The coexistence of PCOS and SCH has contributed to a clearly higher prevalence of CC resistance (30.4%) than that in the Euthyroid (EU) group (14.5%), this result has demonstrated that SCH would impact the response of ovulation induction with CC in PCOS patients [7].

Patients and Methods

This was a prospective observational study that was conducted at infertility unit in Menoufia university hospitals upon patients suffering from infertility, PCOS and subclinical hypothyroidism from June 2018 till May 2019. 220 patients enrolled into this study, 18 cases dropped out of the study due to failure of follow up of the patients, the 204 patients who completed the study were randomized by random randomization into 2 groups Group (I) in this group 102 patients received 50u Eltroxin till TSH was normalized then they received combined Eltroxin and 100mg Clomid for 3 successive cycles Group (II) 102 patients received sugary tablet and 100m Clomid for 3 successive cycles.

Ethical approval of the study protocol was obtained from Menoufia faculty of Medicine (Ethical clearance letter number 319G/2018) in accordance with the revised Helsinki declaration. All participants signed the informed consent form before commencing the study.

Sample Size

The STATCALC feature of Epi Info™ -Version 6 software was used for calculating the sample size guided by:

Power of the test=80%, Confidence level =95%, Accepted margin of error =5% Risk percent ratio =2.5%, Expected frequency

of condition =10%, Total sample accepted according to inclusion criteria =100. Type of the study: cross sectional observational study. Calculation of the sample size was based on the results of the previous observational studies.

Inclusion Criteria

Infertile females with PCOS and SCH. PCOS were diagnosed according to the criteria of the Rotterdam, European Society of Human Reproduction and Embryology-American Society for Reproductive Medicine-sponsored PCOS consensus workshop group (59T759T). Patients with two out of the following three features will be considered as PCOS: oligoovulation and/or anovulation, clinical and/ or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound examination (the presence of 12 or more follicles measuring 2-9mm in diameter). Oligo/anovulation was defined as the presence of oligomenorrhea (menstrual cycles of >35 days) or amenorrhea (lack of menstrual period for 6 months or more) [7]. Sub clinical hypothyroidism was defined as TSH >2.5mIU/L and normal thyroid hormones [4].

Exclusion Criteria

Patients who had known history of diabetes mellitus, hyperprolactinemia, congenital adrenal hyperplasia, hypothyroidism or hyperthyroidism, Cushing's disease, renal, hepatic, or cardiac dysfunction, a history of ovarian or adrenal neoplasm, and those using any medication (e.g. oral contraceptives, insulin-sensitizing drugs, statins, radioactive Iodine, Levothyroxine, corticosteroids and GnRH agonists and antagonists) within 6 months of the enrollment to the study were excluded.

Methods

Complete systemic clinical examination and anthropometric assessment including height, weight, body mass index (BMI), waist and hip circumferences was done for every patient by a single person and with the same instruments in the clinic so that the inter observer errors were limited. 5mL of venous blood were obtained and used for estimation of fasting plasma glucose, lipid profile, and hormonal analysis. Blood sample were taken on day 2 or 3 of the menstrual cycle (21 for progesterone).

Hormonal analysis included serum free triiodothyronine (T3), free tetraiodothyronine (T4), TSH, anti-thyroperoxidase antibody (anti-TPO ab), LH, FSH, prolactin, insulin, free testosterone, progesterone (assessed at day 21 postmenstrual), estradiol, and SHBG-S using Cobas e-411 analyzer (Roche Diagnostics Ltd., Mannheim, Germany) by electrochemiluminescence immunoassay (ECLIA) method as per manufacturer's protocol (intra-assay and interassay CV<5.0%). Lipid profile and plasma glucose were estimated on Cobas c-311 clinical chemistry analyzer (Roche Diagnostics Ltd., Mannheim, Germany) by standard methods as per manufacturer's protocol. Group (I) in this group patients received 50u Eltroxin till TSH was normalized then they received

combined Eltroxin and 100mg Clomid for 3 successive cycles Group (II) patients received sugary tablet and 100m clomid for 3 successive cycles the patients were followed up for detection of ovulation (folliculometry) and clinical pregnancy by transvaginal ultrasound. Hormonal profile was repeated after treatment for both groups.

Statistical Analysis

Data were tabulated and analyzed by SPSS version 20 on IBM compatible computer.

Result

There was no significant difference between cases and controls regarding age, parity, BMI (table 1) There was significant difference between both groups regarding ovarian function represented in LH, FSH, TSH, progesterone before and after treatment (table 2). There was significant difference between both groups regarding ovulation and pregnancy rate as in (table 3). Comparison between both groups before treatment (table 4).

Table 1: Demographic criteria.

	Group (1)	Group (2)	T test	P value
Age	30.44+4.96	28.96+4.95	2.49	0.013
BMI	35.9+40.35	31.03+28.7	0.9	0.32
Free and gallaway score	16.7+8.6	15.6+8.2	0.86	0.37
			Chi square	
Hypertension				
Yes	43(42.6%)	49(48.5%)	0.719	0.48
No	58(57.4%)	52(51.5%)		
Hirsutism				
Yes	62(61%)	65(64%)	0.191	0.77
no	38(39%)	36(36%)		

Table 2: laboratory characteristics of control group.

	Mean		Standard Deviation		T test	P value
	Before	After	Before	After		
FSH-FSH after	5.59	5.599	1.2	1.3	1	0.32
HOMA-IR - HOMA-IR after	4.56	4.51	0.89	0.86	1.26	0.207
Insulin - insulin after	13.6	13.5	2.08	2.01	1	0.32
Estradiol (pg/mL) - estradiol after	65.8	65.5	11.7	12.2	0.381	0.704
TSH -TSH after	3.7	3.4	4.2	2.9	0.568	0.571
Progesterone (ng/mL) -progest after	2.08	3.16	0.31	2.7	4.02	0.0005

Table 3: laboratory characteristics of Study group.

	Mean		Standard Deviation		T test	P value
	Before	After	Before	After		
LH - LH af	11	8.5	2.5	1.3	11.04	0.0005
FSH - FSH af	5.54	5.48	1.28	1.28	2.07	0.04
HOMA-IR - HOMA-IR af	4.523	2.23	0.86	0.71	19.48	0.0005
Insulin - insulin af	13.52	9.99	2.02	2.22	11.34	0.0005
Estradiol (pg/mL) - estradiol af	65.07	65.07	11.56	46.72	12.24	0.0005
TSH - TSH aft	3.7	1.49	4.25	0.44	5.34	0.0005
Progesterone (ng/mL) - prog aft	6.6	20.8	0.3	4.5	10	0.0005

Table 4: Comparison between both groups regarding.

	Group1	Group2	Chi Square	P Value
Ovulation				
Yes	61(60.4%)	21(20.8%)	32.8	0.0005
No	40(39.6%)	80(79.2%)		
Pregnancy				
Yes	21(20.8)	7(6.9%)	8.12	0.004
No	80(79.2%)	94(93.1%)		

Discussion

Hypothyroidism can interfere with gonadotropin secretion by elevating serum prolactin levels [8]. Clinical manifestations include menstrual irregularities and infertility due to anovulation and/or luteal phase defect, an association has been reported between PCOS and hypothyroidism. hypothyroidism may be subclinical and diagnosed first time during evaluation of PCOS [7]. Probable mechanism of subclinical hypothyroidism in PCOS may be obesity and high BMI. proinflammatory condition and IR, may lead to decreased deiodinase-2 activity and relative low T3 and high TSH levels [9-10]. Alternate mechanism is increased leptin levels stimulating hypothalamus to increase TRH secretion [9]. one or both pathways may be the cause [10,11].

Data assessing the effect of SCH on fertility are limited due to varied definitions of SCH (different TSH cutoffs) and limited control groups [4]. In one study, a total of 145 PCOS patients were received CC, with an ovulation rate of 77.2%, and (22.8%) were CC resistant. Logistic regression revealed a significant association between SCH and CC resistance. The coexistence of PCOS and SCH has contributed to a clearly higher prevalence of CC resistance (30.4%) than that in the EU group (14.5%), with the OR of 2.645 (95%CI: 1.122–6.239). This result has demonstrated that SCH would hamper ovulation induction with CC in PCOS patients [7]. There are two possible explanations for this phenomenon. First, SCH is common in patients with Hashimoto' thyroiditis (HT) with high anti TPO which dramatically increases risk of CC resistant. Second, even a short-term of lifestyle modification had reproductive benefits in overweight and obese patients with PCOS who were resistant to CC [7].

A retrospective study of 394 women found a significantly higher incidence of SCH affecting 13.9% of infertile women compared with controls (3.9%) [12]. This current study included 204 patients divided into 2 groups: Group (I) in this group patients received 50u Eltroxin till TSH was normalized then they received combined Eltroxin and 100mg Clomid for 3 successive cycles Group (II) patients received sugary tablet and 100m Clomid for 3 successive cycles.

The patients were followed up for detection of ovulation (folliculometry) and clinical pregnancy by transvaginal ultrasound.

Hormonal profile was repeated after treatment for both groups. There was no significant difference between cases and controls regarding age, parity, BMI while, there was no significant difference between both groups regarding ovarian function represented in LH, FSH, TSH, progesterone before treatment there was significant difference regarding hormonal levels after and before treatment in both groups. There was significant difference between both groups regarding ovulation and pregnancy rate after treatment. These results suggest that Eltroxin has beneficial effects on ovulation and pregnancy in patients with subclinical hypothyroidism and PCO.

In accordance to the results of this study there was previous studies confirm these results as In Jatzko study about The impact of thyroid function on intrauterine insemination outcome, there was no significant changes as regard demographic criteria as age BMI, hypertension, and hirsutism in both groups .there were highly significant changes as regarding LH,FSH,TSH,HOMA IR and insulin before and after administration of thyroxine in the study group however there was insignificant changes in control group . There were highly significant changes as regarding level of progesterone before and after administration of thyroxine in the study group but no significant difference in control group. there were highly significant changes as regarding the rate of ovulation and pregnancy in the study group but insignificant changes in control group [13].

There are few studies assessing whether LT4 therapy improves outcomes for infertile women with SCH not undergoing assistive reproductive techniques [4]. A retrospective study examining LT4 therapy on 69 infertile women reported 84% pregnancy rate with treatment [14]. In the study by Bohnet et al. [15]. treatment with L-thyroxine 50 ì g/day had normalized mid progesterone secretion and two among the eleven SCH treated women became pregnant.

Raber et al. [16] Investigated a group of 283 women with infertility. All patients underwent a TRH stimulation test (SCH was defined as a serum TSH >15mU/L). Women with a diagnosis of SCH were treated with thyroxine and followed prospectively over a 5-year period. Among these women 34% had SCH. women who achieved a basal serum TSH<2.5mU/L or a TRH stimulated TSH<20mU/L became pregnant more frequently. Randomized controlled trials showed that LT4 therapy improved pregnancy in women with SCH undergoing artificial reproductive techniques [11].

A randomized non-placebo controlled trial reported that after treatment with L-thyroxine, 64 infertile women with SCH (TSH >4.5mIU/L) undergoing IVF/intracytoplasmic sperm injection. The 32 women randomized to 50µg of LT4 with a goal to reach and maintain TSH of <2.5mIU/L had a lower miscarriage rate (0% vs 33%, P=0.02) and higher live birth rate (53% vs 25%, P=0.04)

and a significantly higher embryo implantation rate (RR:1.8, 1.00-3.25; P¼ 0.05) compared with the control group [17]. women with SCH (TSH >4.0mIU/L) undergoing in vitro fertilization (IVF)/intracytoplasmic sperm injection were randomized to 50µg of LT4 therapy with a goal to normalize TSH before IVF or placebo (35 women in each group). The LT4 arm had a lower miscarriage rate (9% vs 13% for control, P=0.03) and a higher live birth rate (26% vs 3% for control, P=0.02) [18].

On contrary. A prospective study of 538 women showed that the mean TSH level was statistically higher in infertile women (1.3mIU/L) compared with controls (1.1mIU/L), but this difference did not appear clinically significant. Additionally, the study found no difference in the prevalence of TSH >4.2mIU/L in the infertile group vs the control group [3]. Similarly, a cross-sectional study analyzed the sera of 704 women undergoing infertility treatment and found only 16 with a raised TSH level (2.3%), which is similar to general population rates [19]. Moreover, a prospective cohort study found that among healthy fecund women with a history of pregnancy loss, a TSH level ≥2.5mIU/L was not associated with fecundity, pregnancy loss, or live birth [10].

A large prospective study of 270 patients with SCH undergoing IVF who received LT4 therapy showed. that there may be no benefit in strictly controlling TSH levels (<2.5mIU/L) for those women with SCH receiving LT4 therapy who are undergoing assistive reproductive techniques.as similar miscarriage and live birth rate between those who achieved a target TSH level of 0.2 to 2.5mIU/L compared with a TSH level of 2.5 to 4.2mIU/L [20].

Limitation

Inability to extend the period of follow up to record the clinical outcome of the pregnant patients as well as the low number of patients, constitute unintended limitations of the current study.

Conclusion

Eltroxin has beneficial effects on ovulation and pregnancy in patients with subclinical hypothyroidism and PCO.

Acknowledgment

All authors have contributed significantly, and agree with the content of the manuscript.

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DOI: [10.19080/JGWH.2020.17.555972](https://doi.org/10.19080/JGWH.2020.17.555972)

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