Thyroxine Supplementation May Improve Ovulation and Pregnancy Rates in Infertile Patients with Polycystic Ovary Syndrome and Subclinical Hypothyroidism

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Abstract:

This prospective observational study was conducted on 220 patients with polycystic ovary syndrome (PCOS) and subclinical hypothyroidism (SCH) who were allocated into two groups; group one (n=112) received clomiphene citrate (CC) plus thyroxine while group two received only CC for ovulation induction. Patients receiving CC and thyroxine exhibited higher ovulation rate (p<0.001), higher endometrial thickness (p<0.05), higher number of dominant follicles (p<0.001) and higher pregnancy rate (p<0.001) compared to their counterparts receiving only CC. Thyroxine supplementation improves ovulation and pregnancy rates in infertile patients with PCOS and SCH receiving CC for ovulation induction who are therapy naive.

Key words: clomiphene citrate; polycystic ovary syndrome; subclinical hypothyroidism; induction of ovulation.

Introduction:

Polycystic ovarian syndrome (PCOS) is characterized by menstrual and hormonal irregularities with associated anovulation, infertility, and hyperandrogenism [1]. Hypothyroidism by virtue of raised thyroid stimulating hormone (TSH) causes insulin resistance and stimulation of FSH receptors [2]. The coexistence of hypothyroidism and PCOS has been related to complex pathophysiological changes, not conclusively proven [2-4]. PCOS patients with subclinical hypothyroidism may have a poorer treatment response to ovulation induction with clomiphene citrate (CC) as recently reported [5].

The aim of this study was to assess whether thyroxine supplementation could improve ovulation and pregnancy rates in infertile patients with PCOS and subclinical hypothyroidism receiving clomiphene citrate (CC) for ovulation induction, or not.

Materials and methods:

This was a prospective observational study carried out at the Department of Obstetrics and Gynecology, Faculty of Medicine, Menoufia University, Shibin El-Kom city, Menoufia governorate, Egypt during the period between the beginnings of January 2017 and July 2019. The study protocol has been revised and approved by the medical ethics committee at Menoufia Faculty of Medicine with informed consent form signed by all patients before conducting the study. The sample size was calculated based on the assumption of a difference of 10% between the two groups regarding the clinical pregnancy rate. The study was designed to have 90% power at the 5% significance level via enrollment of 100 patients in each group.

Criteria of inclusion are PCOS patients based on the revised Rotterdam criteria with the coexistence of subclinical hypothyroidism (no symptoms, normal free T4 and elevated TSH levels), normal semen analysis, normal uterine cavity and bilateral tubal patency. All included patients did not receive prior induction of ovulation.

Patients with endocrine disorders affecting ovulation as hyperprolactinemia, and adrenal gland disorders as well as those with structural abnormalities as uterine fibroids, endometriosis, ovarian cyst and pelvic inflammatory disease were excluded from the study.

After enrolment of 240 patients with PCOS, 20 cases dropped out and 220 completed the study (Figure 1: The flow diagram).
Figure (1): Flow diagram of recruitment and retention of participants in the study.

- 240 patients with PCOS and hypothyroidism
  - 4 patients with exclusion criteria
  - 10 patients declined to participate
  - 226 patients were included

Clomiphene & Thyroxine group (n=114)
- 2 patients dropped out (did not complete the 3 months of induction)
- Clomiphene & Thyroxine group (n=112)

Clomiphene group (n=112)
- 4 patients dropped out (did not complete the 3 months of induction)
- Clomiphene group (n=108)
Enrolled patients were equally allocated into one of the two treatment groups via restricted shuffled approach, as follows:

**Group 1** (Clomiphene citrate and thyroxine group): included 112 patients who received CC (Clomid, 50 mg tablets, Sanofi-aventis, Egypt) twice daily from the 3rd day of the cycle for 5 days combined with thyroxine (Eltroxin 50 mcg tablets, GlaxoSmithKline, Egypt) once daily for 1-3 cycles.

**Group 2** (Clomiphene citrate only group): included 108 patients who received CC only (Clomid, 50 mg tablets, Sanofi-aventis, Egypt) twice daily from the 3rd day of the cycle for 5 days for 1-3 cycles.

In both groups, folliculometry was started on day 8 till confirmation of ovulation and administration of human chorionic gonadotrophins (Epifasi 5000 IU, ampoule, EIPICO pharmaceuticals, Egypt).

**Outcome measures**

- Ovulation rate, number of mature follicles and endometrial thickness on the day of hCG administration.
- Clinical pregnancy rate during every cycle of stimulation. Pregnancy was diagnosed by positive pregnancy test in the serum to be confirmed by transvaginal ultrasound for the confirmation of fetal cardiac activity.

**Statistical analysis**

Data was analyzed with an IBM computer using the SPSS 22 statistical software package (SPSS Inc., Chicago, IL). Student's t test and Chi square tests were used when appropriate. P-value ≤ 0.05 was statistically significant and < 0.001 was highly significant.

**Results:**

There was no significant difference between the two groups regarding patients’ characteristics as age, duration of infertility, body mass index and basal hormonal levels (FSH, LH and TSH) as depicted in table (1).

| Age (years) | Clomiphene and Thyroxine (n=112) | Clomiphene only (n=108) | Student’s t-test | P-value |
|------------|----------------------------------|------------------------|-----------------|---------|
| 23.5±2.2   | 23.3±2.5                         | 0.63                   | >0.05           |

| Duration of infertility (months) | Clomiphene and Thyroxine (n=112) | Clomiphene only (n=108) | Student’s t-test | P-value |
|---------------------------------|----------------------------------|------------------------|-----------------|---------|
| 17.3±3.2                        | 17.2±3.3                         | 0.23                   | >0.05           |

| Body mass index (Kg/m²): <25 | Clomiphene and Thyroxine (n=112) | Clomiphene only (n=108) | Student’s t-test | P-value |
|------------------------------|----------------------------------|------------------------|-----------------|---------|
| 24.2±4.7                     | 60                               | 24.8±4.2               | 1.1             | 0.16†   |

| Basal hormones: | Clomiphene and Thyroxine (n=112) | Clomiphene only (n=108) | Student’s t-test | P-value |
|-----------------|----------------------------------|------------------------|-----------------|---------|
| FSH (IU/L)      | 6.3±1.3                          | 6.4±1.2                | 0.59            | >0.05 >0.05 |
| LH               | 4.4±1.1                          | 4.5±0.9                | 0.89            | >0.05 >0.05 |
| TSH (mIU/L)     |                                  |                        | 0.74            | >0.05 >0.05 |

| Duration of infertility (months) | Clomiphene and Thyroxine (n=112) | Clomiphene only (n=108) | Student’s t-test | P-value |
|---------------------------------|----------------------------------|------------------------|-----------------|---------|
| 17.3±3.2                        | 17.2±3.3                         | 0.23                   | >0.05           |

**Table (1) Patients characteristics**

Patients receiving CC and thyroxine exhibited higher ovulation rate (p<0.001), higher endometrial thickness (p<0.05), higher number of dominant follicles (p<0.001) and higher pregnancy rate (p<0.001) compared to their counterparts receiving only CC as revealed in table (2).

| Ovulation rate | Clomiphene and Thyroxine (n=112) | Clomiphene only (n=108) | Chi square t-test | P-value | Odd’s ratio at 95% CI |
|----------------|----------------------------------|------------------------|-----------------|---------|---------------------|
| First cycle    | 70 (62.5%)                       | 38 (35.18%)            | 15.27           | <0.001  | 3.07(1.77-5.32)     |
| Second cycle   | 76 (67.85%)                      | 40 (37.03%)            | 34.19           | <0.001  | 3.59(2.06-6.26)     |
| Third cycle    | 88 (78.57%)                      | 42 (38.8%)             |                 |         | 5.76(3.18-10.44)    |

| Endometrial thickness (mm) | Clomiphene and Thyroxine (n=112) | Clomiphene only (n=108) | Chi square t-test | P-value | Odd’s ratio at 95% CI |
|---------------------------|----------------------------------|------------------------|-----------------|---------|---------------------|
| First cycle               | 8.8±2.6                          | 7.4±2.4                | 4.15†           | <0.001  |                     |
| Second cycle              | 8.7±2.4                          | 7.7±2.3                | 2.6†            | <0.05   |                     |
| Third cycle               | 8.6±2.8                          | 7.6±2.2                | 3.54†           | <0.001  |                     |

| Number of dominant follicles | Clomiphene and Thyroxine (n=112) | Clomiphene only (n=108) | Chi square t-test | P-value | Odd’s ratio at 95% CI |
|-----------------------------|----------------------------------|------------------------|-----------------|---------|---------------------|
| First cycle                 | 1.7±0.7                          | 1.2±0.1                | 7.35†           | <0.001  | 1.60(1.11-2.31)     |
| Second cycle                | 1.8±0.7                          | 1.3±0.2 1.5±0.4        | 7.15†           | <0.001  | 1.54(1.06-2.24)     |
| Third cycle                 | 1.8±0.5                          | 4.9†                   |                 |         |                     |

| Clinical pregnancy rate     | Clomiphene and Thyroxine (n=112) | Clomiphene only (n=108) | Chi square t-test | P-value | Odd’s ratio at 95% CI |
|-----------------------------|----------------------------------|------------------------|-----------------|---------|---------------------|
| First cycle                 | 46 (41.07%)                      | 22 (20.37%)            | 10.09           | <0.001  | 2.72(1.49-4.97)     |
| Second cycle                | 12 18                             | 7 8                    |                 |         |                     |

†Chi square test, FSH=Follicle stimulating hormone, LH=Leutinizing hormone, TSH=Thyroid stimulating hormone.

| Ovulation rate | Clomiphene and Thyroxine (n=112) | Clomiphene only (n=108) | Chi square t-test | P-value | Odd’s ratio at 95% CI |
|----------------|----------------------------------|------------------------|-----------------|---------|---------------------|
| First cycle    | 70 (62.5%)                       | 38 (35.18%)            | 15.27           | <0.001  | 3.07(1.77-5.32)     |
| Second cycle   | 76 (67.85%)                      | 40 (37.03%)            | 34.19           | <0.001  | 3.59(2.06-6.26)     |
| Third cycle    | 88 (78.57%)                      | 42 (38.8%)             |                 |         | 5.76(3.18-10.44)    |

†Student t-test.
The current study confirmed the beneficial use of thyroxine concurrently with CC for ovulation induction in patients with PCOS and subclinical hypothyroidism (SCH) who are therapy naïve when used for one to three cycles. The addition of thyroxine significantly increased ovulation and pregnancy rates.

One hundred and ninety-six women with PCOS were divided into two groups: the SCH group with 92 patients and the euthyroid (EU) group with 104 patients. The prevalence of CC resistance (30.4%) in the SCH group was significantly higher than that in the EU group as recently reported [5].

In another recent observational study, 716 patients, 462 with true PCOS, 31 with PCOS-SCH, and 223 normal cycling women were enrolled for anthropometrical parameters and hormonal profile. Anthropometric parameters and ovary morphology were similar in both PCOS and SCH patients. Regarding hormones, only C-peptide was higher in PCOS group [6].

About 14% of SCH patients may present dyslipidemia, dysglycemia, insulin resistance, infertility, ovulatory dysfunction, obesity, and abnormal menstrual cycle, simulating PCOS [8, 9].

Some advocate before the diagnosis of PCOS, thyroid dysfunction should be standardized and subclinical hypothyroidism should not exclude a diagnosis of PCOS [6, 10] while others refute any influence of SCH on hormonal profile in women with PCOS [11, 12]. Subclinical hypothyroidism (SCH), found between 3–8% of women of reproductive age; whether SCH leads to clinical, endocrine, or metabolic alterations that could be misdiagnosed as the early stages of PCOS remains to be elucidated [12].

To the authors’ knowledge, this is the first study to assess the benefit of thyroxine supplementation in conjunction with CC when inducing ovulation in patients with PCOS and SCH.

Inability to conduct a randomized trial and to follow pregnant patients to record their obstetric outcome constitutes unintended limitations of the current study.

Further larger multicenter trials are warranted to confirm or refute our findings and to explore the benefit of addition of thyroxine in patients with CC resistance.

In conclusion, thyroxine supplementation improves ovulation and pregnancy rates in infertile patients with PCOS and SCH receiving clomiphene citrate for ovulation induction who are therapy naïve.

**Conflict of interest:** none

**References:**

1. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril. 2008;89(3):505-522.
2. 2-Mueller A, Schöfl C, Dittrich R, et al. (2009) Thyroid-stimulating hormone is associated with insulin resistance independently of body mass index and age in women with polycystic ovary syndrome. Hum Reprod. 24(11):2924-2930.
3. Dunäif A. (1997) Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev.18(6):774-800.
4. Calvar CE, Bengolea SV, Deutsch SI, et al. (2015) High frequency of thyroid abnormalities in polycystic ovary syndrome. Medicina (B Aires). 75(4):213-217.
5. Lu YH, Xia ZL, Ma YY, Chen HJ, Yan LP, Xu HF. (2016) Subclinical hypothyroidism is associated with metabolic syndrome and clomiphene citrate resistance in women with polycystic ovary syndrome. Gynecol Endocrinol 32(10):852-855.
6. de-Medeiros SF, Yamamoto MMW, de-Medeiros MAS, Barbosa JS, Norman RJ. (2017) Should Subclinical Hypothyroidism Be an Exclusion Criterion for the Diagnosis of Polycystic Ovary Syndrome? J Reprod Infertil. 18(2):242-250.
7. Krassas GE, Pontikides N, Kalsas T, Papadopoulou P, Paunovic J, Paunovic N, et al. (1999) Disturbances of menstruation in hypothyroidism. Clin Endocrinol (Oxf). 50(5):655-9.
8. Mueller A, Schöfl C, Dittrich R, et al. (2009) Thyroid-stimulating hormone is associated with insulin resistance independently of body mass index and age in women with polycystic ovary syndrome. Hum Reprod. 24(11):2924-2930.
9. Yu Q, Wang JB. Subclinical Hypothyroidism in PCOS: Impact on Presentation, Insulin Resistance, and Cardiovascular Risk. Biomed Res Int. 2016;2016:2067087.
10. Pergialiotis V, Konstantopoulos P, Prodromidou A, et al. (2017) MANAGEMENT OF ENDOCRINE DISEASE: The impact of subclinical hypothyroidism on anthropometric characteristics, lipid, glucose and hormonal profile of PCOS patients: a systematic review and meta-analysis. Eur J Endocrinol. 176(3):R159-R166.
11. Trakakis E, Pergialiotis V, Hatziagelaki E, et al. (2017) Subclinical hypothyroidism does not influence the metabolic and hormonal profile of women with PCOS. Horm Mol Biol Clin Investig. 31(3).
12. Hollowell JG, Staehling NW, Flanders WD, et al. (2002) Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 87(2):489-99.