Original Article

Evaluation of Reproductive Outcome in Infertile Hypothyroid Women on Thyroxine Therapy

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Abstract

Introduction: Thyroid dysfunction is associated with increased risk of infertility. Serum thyroid stimulating hormone (TSH) screening in all women seeking infertility care is recommended and hypothyroid infertile women should be treated with thyroxine until the preconception serum TSH level is <2.5 mU/l.[1] However, insufficient evidence exist to determine if thyroxine therapy improves fertility in subclinical hypothyroid women who are trying to conceive naturally. **Objectives:** The objective is to study the effect of thyroxine therapy on reproductive outcome in infertile women with clinical and subclinical hypothyroidism (SCH). **Materials and Methods:** The study is a descriptive cohort study with 72 subjects. Women between 20 and 40 years of age with primary or secondary infertility with hypothyroidism were studied and thyroid profile including free T3, T4, TSH, and thyroid antibodies were done. Thyroxine was given to clinical, subclinical hypothyroid subjects depending on TSH levels such that serum TSH levels are maintained < 2.5 mU/L. Serial thyroid function test was done every 6 weeks until the optimal levels were reached. Once normal TSH levels were reached subjects were followed up for 6 months. Reproductive outcome was analyzed in two groups. Group A included hypothyroid infertile women who conceived and Group B included those who did not conceive following thyroxine therapy. **Results:** Thirty-eight out of 72 subjects (54%) conceived during thyroxine treatment (Group A) of which 4 cases had miscarriage. Maximum infertile women in Group A (20/38) conceived between 6 and 12 months (52.6%) of thyroxine therapy. Significant decrease was observed in mean TSH levels over a period of 6 months ($P < 0.001$). The infertility period until pregnancy in Group A reduced significantly from 5.2 ± 1.8 years to 0.5 ± 0.8 years after thyroxine treatment ($P = 0.001$). **Conclusion:** Thyroxine therapy enhances fertility in infertile women with clinical and SCH.

Keywords: *Hypothyroidism, infertility, reproductive outcome, subclinical hypothyroidism*

Introduction

Thyroid dysfunction is very common among infertile women. As per the American Thyroid Association Guidelines 2017, thyroid function should be tested in all infertile women seeking treatment which includes free T3, T4, thyroid stimulating hormone (TSH).[1]

According to the WHO, the prevalence of infertility in India is 3.5%–16%.[2] The prevalence of hypothyroidism in the reproductive age group ranges from 2% to 4%. In infertile women, the prevalence of hypothyroidism

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was found to be 6.7% by Rahman *et al*., 14.8% by Binita *et al*., 20% by Sharma *et al*. and 16% by Pushpagiri *et al*.[3-6] Undiagnosed and untreated clinical and subclinical thyroid disease can be a cause for infertility and needs to be treated. Majority of studies show that hypothyroidism has negative influence on the reproductive outcome in infertile women.

The prevalence of subclinical hypothyroidism (SCH) in female infertility is very variable ranging from 4.6% to 25% as described by Krassas *et al*. and Bals-Pratsch *et al*., respectively.[7,8]

SCH likely affects assisted reproductive techniques (ART) outcomes in a dose-related fashion, such that impact worsens as TSH concentrations rise. It is therefore essential to treat subclinical hypothyroid women seeking pregnancy with ART for any TSH elevation >2.5 mIU/L. However, there is paucity of studies in recommending for or against routine thyroxine therapy in subclinical hypothyroid infertile women who are attempting natural conception but not undergoing ART. The benefits of strictly controlled TSH level below 2.5 mIU/l in treated subclinical and clinical hypothyroid women before conception are still unknown. Hence, this study was planned to evaluate the reproductive outcome in infertile hypothyroid women on thyroxine therapy.

Aim and objectives

The study aims to study the effect of thyroxine therapy on reproductive outcome in infertile women with clinical and SCH.

Materials and Methods

This was a descriptive cohort study conducted in the infertility clinic in the department of Obstetrics and Gynaecology of a tertiary care center for 18 months from October 2017 to March 2019. Previously researchers[9,10] had performed studies on the prevalence of hypothyroidism in infertile women and the response of thyroxine treatment. The sample size found in these articles ranged between 65 and 85. Therefore, assuming P = 75% with 10% as margin of error, the minimum required sample at 5% level of significance is 72 patients. Descriptive statistics was analyzed with SPSS version 17.0 software (Statistical Package for the Social Sciences, Nie, Bent & Hull, US). Continuous variables were presented a mean ± standard deviation. Categorical variables were expressed as frequencies and percentages. The Pearson's Chi-square test was used to determine if there was a relationship between two categorical variables. For all statistical tests, a $P < 0.05$ was taken to indicate a significant difference. Women between 20 and 40 years of age with primary or secondary infertility with hypothyroidism and with basal follicle stimulating hormone <10 mIU/ml were included. Infertile women having, bilateral tubal blockage, endometriosis, male factor infertility, active pelvic inflammatory diseases, organic lesions in pelvis, and primary hyperprolactinemia were excluded. The study was approved by the institutional ethical committee. Women enrolled for infertility treatment meeting the inclusion and exclusion criteria was selected after obtaining an informed consent in a language understood by the patient.

According to the American Thyroid Association 2017,[1] hypothyroidism was classified as follows:

Euthyroid-infertile women with normal TSH Level SCH-infertile women with mildly raised TSH level above 2.5 mIU/l–10 mIU/l with normal free T4 level.

Clinical hypothyroidism-Infertile women with raised TSH between 4.8 and 10 m IU/l with low free T3 or T4 levels or TSH > 10 mIU/l irrespective of free T3, T4 levels.

Following the basic infertility workup, thyroxine therapy was given to clinical, subclinical hypothyroid subjects depending on TSH levels such that serum TSH levels were maintained < 2.5 mIU/l. Serial thyroid function tests were done every 6 weeks until the optimal levels are reached. Once normal TSH levels are reached subjects were followed up for 6 months.

Finally, reproductive outcome was analyzed in two groups. Group A included hypothyroid infertile women who conceived following thyroxine therapy. Group B included hypothyroid infertile women who did not conceive following thyroxine therapy. Primary outcome was pregnancy rate (pregnancy confirmed by both positive urine pregnancy test and ultrasound confirmation of a gestational sac and cardiac activity) and miscarriage rate (loss of gestational sac or cardiac activity on ultrasound). Secondary outcome was duration of infertility before and after thyroxine therapy.

Results

Out of 483 infertile hypothyroid women, 90 women were selected after fulfilling the inclusion and exclusion criteria. All subjects were between 20 and 40 years of age with primary or secondary infertility with hypothyroidism. Infertile women having bilateral tubal blockage, endometriosis, male factor infertility, active pelvic inflammatory diseases, organic lesions in pelvis and primary hyperprolactinemia were excluded. Out of 90 selected women, 18 women were lost to follow-up. Rest 72 women completed the study. Among 72 infertile hypothyroid women, 26 cases (36.5%) had clinical hypothyroidism and the remaining 46 subjects (63.9%) had SCH.

The subjects were further divided into two groups:

- Group A – Subjects who conceived after thyroxine therapy (n = 38)
- Group B– Subjects who did not conceive after thyroxine therapy (n = 34).

Of 72 subjects included in the study, 38 subjects conceived after thyroxine treatment and were included under Group A. Thirty-four subjects continued to be infertile after thyroxine treatment and were included under Group B. The incidence of SCH was higher in both groups as compared to clinical hypothyroidism, although it was not significant (P = 1.000).

The maximum study subjects were in the age group of 21–25 years (44.4%) followed by 26–30 years (33.33%), 30–35 years (20.8%), and > 35 years (1.3%). Twenty-two cases had normal body mass index (BMI) (<23 kg/m^2), 27 were overweight (23–24.9 kg/m^2), 18 were preobese (25–29.9 kg/m^2) and 5 were obese (>30 kg/m^2). However, there was no statistically significant difference in the distribution of cases according to BMI (P = 0.216) [Table 1]. The distribution of SCH was significantly high in cases of primary infertility (71.1%) (P = 0.001) as compared to secondary infertility in which clinical hypothyroidism was more common (69.2%). Overall menstrual dysfunction was high 43/72 (59.7%) in infertile hypothyroid women. Oligomenorrhea was significantly higher 35 cases (81.3%) in both clinical and SCH (P = 0.002), when compared to hypo menorrhea (4.6%) and menorrhagia (13.9%).

In both Groups A and B, the mean decrease in TSH values was similar in both the groups. No difference was seen in both groups at baseline, at 6 weeks, at 12 weeks, and at 6 months of thyroxine therapy [Table 2].

In both Groups A and B, the mean decrease in TSH values in cases with SCH were similar in both groups. No differences were seen in both groups at baseline, at 6 weeks, at 12 weeks, and at 6 months after thyroxine therapy [Table 3].

The estimated duration of infertility in Group A was compared before and after the T4 treatment until pregnancy. The infertility period was shorter after the thyroxine treatment (P = 0.001). In 38 subjects who conceived, infertility period reduced significantly from 5.2 ± 1.8 years to 0.5 ± 0.8 years after the thyroxine treatment.

In Group A, among 38 subjects who conceived, 4 subjects (10.5%) had miscarriage. Remaining 34 subjects continued their pregnancies. Of 4 subjects, 3 had clinical hypothyroidism and 1 had SCH. In miscarriage group, baseline TSH was 10.02 m IU/l which was higher when compared to nonmiscarriage group which was 7.28 mIU/l even though it was not statistically significant. In miscarriage group, the TSH levels decreased from 10.02 mIU/L to 1.650 m IU/l after 6 months of thyroxine therapy. In nonmiscarriage group, the baseline TSH decreased from7.28 mIU/l to 2.288 mIU/L after thyroxine therapy. In both subgroups, the decrease in TSH levels after 6 months of thyroxine therapy were comparable to each other and were in optimal levels (<2.5 mIU/l).

In the present study, of 72 cases, 3 were thyroid antibodies positive, one in Group A and 2 in Group B, the remaining 69 were thyroid antibodies negative. Since significant thyroid autoimmunity was not associated with this group of population, the association between thyroid autoimmunity and miscarriage could not be evaluated in this study (P = 0.599).

Discussion

In the present study, women of <25 years of age group had higher cases of hypothyroidism (44.4%) although it was not statistically significant. The mean BMI of

Table 1: Demographic profile of Group A and Group B (n=72)

Demographic profile	Group A (n=38)	Group B (n=34)	P
Age (years)	26.56	27.47	0.306
BMI (kg/m^2)	24.97	24.67	0.708
Duration of marriage (years)	5.20	5.15	0.932
Primary infertility	33	26	
Secondary infertility	5	8	0.253

BMI=Body mass index

Table 2: Effect of thyroxine therapy on thyroid stimulating hormone levels (mIU/L) in Group A and Group B over 6 months

Duration of treatment	Group A (n=38)	Group B (n=34)
Baseline	6.638	6.87
At 6 weeks	4.736	5.94
12 weeks	2.392	2.46
6 months	2.078	2.046
P	0.064	0.613

Table 3: Effect of thyroxine therapy on thyroid stimulating hormone levels in Group A and Group B with subclinical hypothyroidism over 6 months

Duration of treatment	Group A (n=24)	Group B (n=22)
Baseline	6.326	6.22
At 6 weeks	4.56	4.86
12 weeks	2.32	2.20
6 months	2.04	2.15
P	0.064	0.061

Table 4: Distribution of cases showing the number of pregnancies achieved after different duration of thyroxine therapy in Group A

Duration of infertility until pregnancy after thyroxine therapy	<3 months	3-6 months	6-12 months	>12 months
Number of subjects conceived (*n*=38)	3 (7.8)	9 (23.6)	20 (52.6)	6 (15.7)
Number of subjects with clinical hypothyroidism who conceived (*n*=14)	-	2	7	5
Number of subjects with subclinical hypothyroidism who conceived (*n*=24)	3	7	13	1

Table 5: Comparison of infertility duration before and after thyroxine treatment in Group A

Group A (*n*=38)	Duration of infertility (years)	*P*
Before thyroxine treatment	5.20±181	
After thyroxine treatment	0.5±0.8	0.001

subjects was 24.49 kg/m^2 ± 2.44, which was in the overweight range for Asian population BMI suggesting that hypothyroidism decreases the basal metabolic rate leading to increased BMI. In Pushpagiri *et al*. study,[6] 91.4% (75 patients out of 82) among hypothyroid women were obese (BMI > 25). In case control study by Rahman *et al*.[3] in 2008, infertile hypothyroid cases had significant higher BMI (27.9 kg/m^2) (P < 0.001) while fertile controls had BMI of 24.6 kg/m^2.

In the present study, 38 subjects conceived after thyroxine treatment and were included under Group A, of which 24 subjects (52.1%) had SCH. Thirty-four subjects continued to be infertile after thyroxine treatment in which 22 (47.9%) had SCH and were included under Group B. Maximum spontaneous conception (52.6%) was attained within 6–12 months of thyroxine therapy [Table 4].

A study by Mohanapriya *et al*.[11] had maximum conception (68.7%) in 1–2 years of thyroxine therapy. Yoshioka *et al*.[10] found that 58 subjects (84%) conceived in 1 year of thyroxine supplementation both spontaneously and with ART. However, in study by Verma *et al*.,[9] maximum spontaneous conception (62.5%) occurred in 6 weeks to 3 months. It included cases with raised TSH and prolactin level and found that, out of 94 hypothyroid women, 18 had raised prolactin levels, correction of which had improved their conception rate and decreased the period of conception. In the present study, primary hyperprolactinemia was an exclusion criteria and no cases of hyperprolactinemia were studied. In Yoshioka *et al*.'s[10] study, it took 2–4 months of thyroxine therapy for the TSH levels to decrease significantly from 5.46 m IU/l to 1.25 m IU/l. In our study, it took 3–6 months of thyroxine therapy to decrease TSH levels significantly from 6.63 m IU/L to 2.278 m IU/l in Group A, as baseline TSH value was higher in our study as compared to Yoshioka *et al*.'s[10] study. In both studies, the free T3, T4, and TSH levels were significantly below the target levels after thyroxine treatment. However, the difference in clinical pregnancy rate can be attributed to the longer study period and the possible effects of ART in Yoshioka *et al*.'s[10] study. To further evaluate the effects of thyroxine therapy in natural conception in infertile patients, more extensive case–control studies are needed.

In the present study, the duration of infertility until pregnancy after thyroxine therapy in Group A decreased significantly from 5.20 ± 181 years to 0.5 ± 0.8 years (P = 0.001) [Table 5]. A study by Yoshioka *et al*.[10] also showed significant decrease in the duration of infertility after thyroxine therapy in subjects who conceived spontaneously as well with ART (P = 0.001). However, the mean duration of infertility before thyroxine therapy in Yoshioka *et al*.'s[10] study was less, i.e., 2.1 years and 3.1 years (in the present study was 5.20 years) which decreased to 0.8 years and 0.9 years in spontaneous conception and in ART after thyroxine treatment respectively (P < 0.001). The difference in duration of infertility in both studies may be due to the fact of early marriage in the Indian population. Even though in the present study, there is statistically significant decrease in the duration of infertility until pregnancy following thyroxine treatment, the previous thyroid status of the patient (before the diagnosis of infertility), the exact period of prevalence of thyroid dysfunction in these patients is unknown.

In the present study, in Group A, 4 subjects (10%) had miscarriage [Table 6]. Mean age at pregnancy in miscarriage subgroup was 34.25 years and was significantly higher than that of nonmiscarriage subgroup (26.85 years, P < 0.05). This indicates that increase in age may affect the ovum quality and affect implantation. Out of 4 subjects, 3 had clinical hypothyroidism and 1 had SCH. The baseline TSH in miscarriage group was 10.02 m IU/l which was higher when compared to the nonmiscarriage group (7.28 m IU/l). One patient in miscarriage group was thyroid antibody positive. These could have been the reasons associated with miscarriage. In the present study, of 72 cases, 3 were thyroid antibodies positive, the remaining 69 were thyroid antibodies negative [Table 7]. Since significant thyroid autoimmunity was not associated with this group of population, the association between thyroid autoimmunity and miscarriage could not be evaluated in this study.

Table 6: Reproductive outcome in infertile hypothyroid women on thyroxine therapy

Group A (*n*=38)	Frequency (%)	
	Clinical pregnancies (nonmiscarriage)	Miscarriages
Clinical hypothyroidism (*n*=14)	11 (78.5)	3 (21.4)
Subclinical hypothyroidism (*n*=24)	23 (96.1)	1 (3.8)

Table 7: Distribution of cases in Group A and Group B according to thyroid antibodies

Thyroid antibody	Group A (*n*=38), *n* (%)	Group B (*n*=34), *n* (%)	*P*
Positive	1 (3.8)	2 (5.9)	0.599
Negative	37 (96.2)	32 (94.1)	
Total	38 (100)	34 (100)	

Although LT4 treatment has been associated with better reproductive outcomes in infertile women with SCH undergoing ART,[12] there has been no randomized controlled trial examining whether LT4 therapy improves outcomes for infertile women with SCH not undergoing assistive reproductive techniques. A study by Yoshioka *et al*.[10] reported that out of 69 infertile women with SCH on LT4 therapy, 84% became pregnant with treatment although 29% had a miscarriage afterward.[10]

All the studies show higher clinical pregnancy rates (both spontaneous conception and with assisted reproductive techniques) following thyroxine therapy. However, the significance in terms of clinical pregnancy rates in this study could not be achieved due to the lack of adequate control group, shorter duration of study period and different TSH cut offs used to define clinical and SCH.

Randomized controlled trials involving infertile patients with fertile controls need to be conducted to confirm the effectiveness of the thyroxine therapy in infertile women not undergoing ART and help clinicians provide care using appropriate reference ranges.

Conclusion

From the present study, it is reasonable to conclude that thyroxine therapy should be started in subclinical and clinical hypothyroid infertile women to achieve a target TSH level of 2.5 mIU/l before conception. This study included subjects who conceived spontaneously thus eliminating the possible effects of ART on reproductive outcome following thyroxine therapy. However, due to small sample size and shorter duration of the study period, the statistical power of this study is limited. According to the American Thyroid Guidelines 2017, 2.5 mIU/l was taken as the TSH threshold for SCH, even though reference range may vary in different ethnic groups. Well-conducted, large randomized trials are still needed to study the effect of thyroxine in infertile hypothyroid women that can help clinicians provide care using appropriate reference ranges and help in defining the TSH cut offs according to ethnic groups.

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Conflicts of interest

There are no conflicts of interest.

References

1. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, *et al*. Guidelines of the American thyroid association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 2017;27:315-89.
2. World Health Organisation. Infecundity, Infertility and Childlessness in Developing Countries. DHS Comparative Reports No. 9. Calverton, Maryland, USA: ORC Marco and World Health Organisation; 2004.
3. Rahman B, Fatima P, Banu J. Thyroid disorders in female subfertility. JCMCTA 2008;19:46-50.
4. Binita G, Suprava P, Mainak C, Koner BC, Alpana S. Correlation of prolactin and thyroid hormone concentration with menstrual patterns in infertile women. J Reprod Infertil 2009;10:207-12.
5. Sharma R, Sharma TK, Kaushik GG, Sharma S, Vardey SK, Sinha M. Subclinical hypothyroidism and its association with cardiovascular risk factors. Clin Lab 2011;57:719-24.
6. Pushpagiri N, Gracelyn LJ, Nagalingam S. Prevalence of subclinical and overt hypothyroidism in infertile women. Int J Reprod Contracept Obstet Gynecol 2015;4:1733-38.
7. Krassas GE, Pontikides N, Kaltsas T, Papadopoulou P, Paunkovic J, Paunkovic N, *et al*. Disturbances of menstruation in hypothyroidism. Clin Endocrinol (Oxf) 1999;50:655-9.
8. Bals-Pratsch M, de Geyter C, Müller T, Frieling U, Lerchl A, Pirke KM, *et al*. Episodic variations of prolactin, thyroid-stimulating hormone, luteinizing hormone, melatonin and cortisol in infertile women with subclinical hypothyroidism. Hum Reprod 1997;12:896-904.
9. Verma I, Sood R, Juneja S, Kaur S. Prevalence of hypothyroidism in infertile women and evaluation of response of treatment for hypothyroidism on infertility. Int J Appl Basic Med Res 2012;2:17-9.
10. Yoshioka W, Amino N, Ide A, Kang S, Kudo T, Nishihara E, *et al*. Thyroxine treatment may be useful for subclinical hypothyroidism in patients with female infertility. Endocr J 2015;62:87-92.
11. Mohanapriya A, Nishat A, Jamal A. Prevalence of hypothyroidism in infertile women and response of treatment of hypothyroidism in infertility. Indian J Endocrine Metab 2015;19:504-06.
12. Maraka S, Singh Ospina NM, Mastorakos G, O'Keeffe DT. Subclinical hypothyroidism in women planning conception and during pregnancy: Who should be treated and how? J Endocr Soc 2018;2:533-46.