

## Impact Of Hypothyroidism On Infertility: A Cross Sectional Study In Tertiary Health Care Centre

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### Abstract

**Background:** Adequate levels of circulating thyroid hormones are of primary importance for normal reproductive function. Thyroid dysfunction has a great impact on fertility in women. Prevalence of hypothyroidism is 2–4% in women in the reproductive age group. Hypothyroidism can affect fertility due to anovulatory cycles, luteal phase defects, hyperprolactinemia, and sex hormone imbalance.

**Aims and Objectives:** To study the prevalence of clinical/sub-clinical hypothyroidism in infertile women

**Materials and Methods:** A total of 300 infertile women visiting the infertility clinic for the first time were investigated for thyroid stimulating hormone (TSH) and prolactin (PRL). Infertile women with hypothyroidism alone or with associated hyperprolactinemia were given treatment for hypothyroidism with thyroxine 25–150 µg.

**Results:** Of 300 infertile women, 30% were hypothyroid (TSH > 4.2 µIU/ml). After treatment for hypothyroidism, 70% of infertile women conceived within 6 weeks to 1 year. Infertile women with both hypothyroidism and hyperprolactinemia also responded to treatment and their PRL levels returned to normal.

**Conclusion:** Measurement of TSH and PRL should be done at early stage of infertility check up rather than straight away going for more costly tests or invasive procedures. Simple oral treatment for about 6 months to 1 year could be beneficial for the infertile women to conceive.

**Keywords:** Infertility, Hypothyroidism, Prolactin, TSH,

### INTRODUCTION

Infertility is the inability of a couple to conceive after one year of regular unprotected intercourse. Its prevalence is estimated to be 10-15% in any community<sup>1</sup>. It is therefore a common condition with important medical, economic and psychological implications. WHO estimates the overall prevalence of primary infertility in India to be 3.5–16.8%.<sup>[2]</sup>

Thyroid dysfunction is more common (4–5 times) in females than in males. Both hyperthyroidism and hypothyroidism have profound effects on estrogen and androgen metabolism, menstrual function and fertility.<sup>[3]</sup> They may cause delayed onset of puberty, menstrual abnormalities, anovulatory cycles, miscarriages and infertility.<sup>[4,5]</sup> If thyroid disease is left untreated, it can be a cause for sub-fertility as well as infertility. Thyroid evaluation should be done in any woman who wants to conceive with family history of thyroid problem or irregular menstrual cycle or had more than two abortions or unable to conceive after 1-year of unprotected intercourse. <sup>[6]</sup>

Hypothyroidism can be easily detected by assessing serum thyroid stimulating hormone (TSH) levels. A slight increase in TSH levels with normal T<sub>3</sub> and T<sub>4</sub> indicates subclinical hypothyroidism whereas high TSH levels accompanied by low T<sub>3</sub> and T<sub>4</sub> levels indicate clinical hypothyroidism. Elevated thyrotropin-releasing hormone levels due to hypothyroidism are often associated with increased prolactin (PRL) levels and a delayed LH response to GnRH.[7].

Hence, we planned to study the prevalence of hypothyroidism in infertile women as well as to assess their response to drug treatment for hypothyroidism.

## MATERIALS AND METHODS

### Study Design

The study was carried out in the Department of Biochemistry in collaboration with OBG Dept of Mamatha Academy of Medical Sciences and Hospital, Hyderabad from March 2019 to August March 2020. The subjects were selected from the patients coming to endocrinology outpatient department (OPD) and gynecology OPD. After informed consent, thyroid profile (serum TSH, T<sub>3</sub>, T<sub>4</sub>) of all subjects was done at their first visit. As per National Health and Nutrition Examination Survey III<sup>[8]</sup> 2002, the subjects were divided into three groups.

- Group 1 (euthyroid): Infertile women with normal TSH level (0.39–4.6 mIU/ml).
- Group 2 (subclinical hypothyroidism): Infertile women with raised TSH level ranging from 4.6–20 mIU/ml and normal free T<sub>4</sub> level.
- Group 3 (overt hypothyroidism): Infertile women with TSH level > 20 mIU/ml and low free T<sub>4</sub> level.
- As per WHO guidelines, PRL level > 25  $\mu$ g/l is considered as hyperprolactinemia.[9]

### Methods

Samples were taken for evaluation of serum TSH, T<sub>3</sub>, T<sub>4</sub>. These were measured using chemiluminescence assay. The machine used for analysis was CL 1000i, Mindray. (this is a test unit that contains an assay specific coated bead which serves as the reaction vessel for sample processing).

**Table 1. Demographic profile**

Parameters	Ethyroidism group (No=45)	Sub clinical Hypothyroidism (No=50)	Overt Hypothyroidism (No=05)	P -value
Age	26.3±2.65	27.35±3.76	25.47±5.03	>0.05
BMI	22.39±1.87	24.76±3.78	29.17±2.25	<0.001

**Table 2. Pattern of Infertility**

	Euthyroidism group (No=50)	Sub clinical Hypothyroidism (No=45)	Overt Hypothyroidism (No=05)	P -value
Primary infertility	100	48.5	100	--
Secondary infertility	Nil	50.0	Nil	-
<b>Menstrual cycle</b>				
-				
Regular	100	87.5	77.5	-
Oligomenorrhea	Nil	20	-	-
Menorrhagia	Nil	2.5	-	-
Hypomenorrhea	Nil	2.5	-	-

**Table 3. Levels of Thyroid Hormones**

Thyroid hormones	Euthyroidism group (No=50)	Sub clinical Hypothyroidism (No=45)	Overt Hypothyroidism (No=05)	P -value
Mean TSH (mIU/L)	2.70±0.85	8.60±3.08	35.95±4.67	<0.05
Mean T <sub>4</sub> (nmol/L)	104.44±18.25	107.92±24.51	12.35±5.12	-
Mean prolactin (□g/L)	7.00±2.39	16.15±11.05	16.47±7.97	-
Hyperprolactinemia (%)	Nil	23.0	Nil	-
TPOAb (%)	-	23.5	Nil	-
TgAb (%)	Nil	65.54	-	-

## Results

In the present study, Out of the 105 infertile women enrolled for the study, 5 were excluded due to microprolactinoma and endometriosis. Of the remaining 100 women, 51 (53.7%) were hypothyroid while 45 (45%) were euthyroid. Of 55 hypothyroid women, 50 (50%) had subclinical hypothyroidism and 5 (5%) had overt hypothyroidism. Among 50 subclinical hypothyroid infertile women, 20 (40%) were conceived after treatment with thyroxine. Of 15 women, 2 (13.33%) conceived within 6 months of therapy, 5 (10%) conceived after 6 months to 1 year of therapy and rest 10 (66.6%) conceived after 1–2 years of therapy. The mean time to conception was  $14.56 \pm 4.83$  months.

In the present study, None of the overtly hypothyroid women conceived after treatment with levothyroxine. In Group 1<sub>b</sub>, 50% women conceived after levothyroxine treatment. Of these two women, one had an abortion, and another continued her pregnancy. The mean TSH of pregnant women was  $8.60 \pm 3.08$ , and that of nonpregnant women was  $12.35 \pm 5.12$  mIU/L. The difference between these two was found to be statistically significant ( $P < 0.05$ ).

## Discussion

Female infertility occurs in about 37% of all infertile couples and ovulatory disorders account for more than half of these [8]. Thyroid hormone have profound effects on reproduction and pregnancy. Both subclinical hyperthyroidism and subclinical hypothyroidism are increasingly being recognized as having significant health implications.

Prevalence of subclinical hypothyroidism (50.5%) was more common than overt hypothyroidism (3.2%) in this study, and the results were consistent with Verma *et al.*, [9] Biradar *et al.* [10] and Rijal *et al.* (2011). [11] There was no significant difference in age among different groups according to thyroid status ( $P > 0.05$ ). The difference in the body mass index in infertile women with hypothyroidism was highly significant when compared to infertile women with normal thyroid levels ( $P < 0.001$ ).

In the present study, Most of the study population belonged to primary infertility. Most of the women of all groups had regular cycles [Table 2]. Higher TSH levels were associated with lower conception rate which was similar to that of Raber *et al.* [7] and Gerhard *et al.* [13] The percentage of abortion in hypothyroid infertile women who conceived with the help of levothyroxine was 31.3%, and 80% of those aborted women were positive for thyroid antibodies. Increased number of abortion was noted in this study when compared to Raber *et al.* [7] and Rahman *et al.* [12] The association between thyroid antibodies and abortions could not be made out in this study due to small sample size.

The percentage of conception in euthyroid women who were positive for antithyroid antibodies was 50% (2/4) after levothyroxine treatment. Of these, 50% had miscarriage and rest 50% continued with their pregnancy. The result of the present study was not consistent with Negro *et al.*<sup>[14]</sup> who reported that the pregnancy rate was not affected either by the presence of antithyroid antibodies or treatment with levothyroxine.

The impact of hypothyroidism on ovulation and menstrual function is related to numerous interactions of thyroid hormones with the female reproductive system, thus finally leading to infertility. In hypothyroidism, increased TRH production leads to hyperprolactinaemia and altered GnRH pulsatile secretion. This leads to a delay in LH response and inadequate corpus luteum leading to abnormal follicular development and ovulation. Thyroid hormones receptors are expressed in human oocytes and granulosa cells. At the cellular level, thyroid hormones synergize with the FSH-mediated LH/hCG receptor to exert direct stimulatory effects on granulosa cell function (e.g. progesterone production) [15]. Another pathway by which hypothyroidism may impact on fertility is by altering the peripheral metabolism of estrogen and by decreasing SHBG production. Both pathways may result in an abnormal feedback at the pituitary level 24.

Thyroid dysfunction is a common cause of infertility which can be easily managed by correcting the appropriate levels of thyroid hormones. The decision to initiate thyroid correction therapy in subclinical thyroid dysfunction at early stage is justified in infertile women. Our data also indicate that variations in TSH levels in the narrower range should not be ignored in infertile women who are otherwise asymptomatic for clinical hyperthyroidism.

## CONCLUSION

Our study reveals that subclinical thyroid dysfunction is more prevalent than overt thyroid dysfunction in infertile women. Hyperthyroidism seems to be dominant thyroid dysfunction in infertile women. These disorders may lead to menstrual irregularities and anovulation resulting in infertility. Hence, estimation of serum T3, T4 and TSH levels should be included in the infertility workup. The patient may be treated accordingly with medications and can revert back to the fertile state.

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## Conflict of Interest

None

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Nil

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