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Effect Of Clinical/Sub-Clinical Hypothyroidism On Fertility In Infertility Case And The Response Of Treatment For Hypothyroidism On Fertility In Cases Of Infertility

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Abstract:
Context:*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.*
Objectives: *To study the effect of clinical/sub-clinical hypothyroidism on fertility in infertility case and the response of treatment for hypothyroidism on fertility in cases of infertility.*
Methods: *A total of 200 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 (12.5-150µg).*
Results: *Of 200 infertile women 24% were hypothyroid (TSH >4.2 µIU/ml.).After treatment for hypothyroidism 77.08% 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 checkup rather than straight away going for more costly tests or invasive procedures. Simple, oral hypothyroidism treatment for three months to one year can be of great benefit to conceive in otherwise asymptomatic infertile women.*
Keywords: *Hypothyroidism, infertility, subclinical, treatment*

I. Introduction

The thyroid gland is located near the front of the throat, just below the voice box & just above the collar bones. Every cell in the body depends upon thyroid hormones for regulation of the body's metabolism, blood calcium levels, energy production, fat metabolism, oxygen utilization, balance of other hormones & weight maintenance.

Hormones involved with thyroid function include Thyroid Releasing Hormone (TRH) released from the hypothalamus in the brain, which stimulates the pituitary gland at the base of the brain to release Thyroid Stimulating Hormone (TSH) which in turn stimulates the thyroid gland to produce Thyroxine (T4) & Triiodothyronine (T3). Much of T4 is converted to T3 (the active form) in the liver. Thyroid hormones are synthesized from iodine and the amino acid Tyrosine (from protein), and the conversion to the active from is reliant on the trace mineral Selenium.

Healthy Thyroid function can be affected by:

- Exposure to environment toxins – electromagnetic radiation, chemicals, pesticides, heavy metals e.g. mercury & fluoride
- Genetic susceptibility
- High levels of stress
- Nutrient deficiencies
- Autoimmune disorders
- Infections
- Other hormone imbalances e.g. oestrogen dominance, high prolactin levels

Hypothroidism (Low) affect fertility by
Anovulatory cycles– Not releasing an egg/ ovulating. This makes pregnancy impossible.
Luteal Phase Problems – With a short second half of the menstrual cycle a fertilized egg can't implant securely and ends up leaving the body at the same time that menstruation would occur (very early miscarriage) & is often mistaken as a regular period.

High Prolactin Levels– due to elevated levels of Thyroid Releasing Hormone (TRH) and low levels of Thyroxine (T4) resulting in irregular ovulation or no ovulation.

Other Hormonal Imbalances– reduced sex hormone binding globulin (SHBG), oestrogen dominance, progesterone deficiency, all of which interfere with proper reproductive hormone balance.

Undiagnosed and untreated thyroid disease can be a cause for infertility as well as sub-fertility. Both these conditions have important medical, economical, and psychology implications in our society. Thyroid dysfunction can affect fertility in various ways resulting in anovulatory cycles, luteal phase defect, high prolactin (PRL) levels, and sex hormone imbalances. Therefore, normal thyroid function is necessary for fertility, pregnancy, and to sustain a healthy pregnancy, even in the earliest days after conception. Thyroid evaluation should be done in any women who wants to get pregnant with family history of thyroid problem or irregular menstrual cycle or had more than two miscarriages or is unable to conceive after 1 year of unprotected intercourse. The comprehensive thyroid evaluation should include T3, T4, Thyroid stimulating hormone (TSH), and thyroid autoimmune testing such as thyroid peroxidase (TPO) antibodies, thyroglobin/ antithyroglobin antibodies, and thyroid stimulating immunoglobulin (TSI). Thyroid autoimmune testing may or may not be included in the basic fertility workup because the presence of thyroid antibodies doubles the risk of recurrent miscarriages in women with otherwise normal thyroid function.[1-3]

Prevalence of hypothyroidism in the reproductive age group is 2 – 4 % and has been shown to be cause of infertility and habitual abortion.[4,5] Hypothyroidism can be easily detected by assessing TSH levels in the blood. A slight increase in TSH levels with normal T3 and T4 indicates subclinical hypothyroidism whereas high TSH levels accompanied by low T3 and T4 levels indicate clinical hypothyroidism [6]. Subclinical hypothyroidism is more common. It can cause anovulation directly or by causing elevation in PRL. It is extremely important to diagnose and treat the subclinical hypothyroidism for pregnancy and to maintain it unless there are other independent risk factors. Many infertile women with hypothyroidism had associated hyperprolactinemia due to increased production of thyrotropin releasing hormone (TRH) in ovulatory dysfunction. [7,8] It has been recommended that in the presence of raised PRL, the treatment should be first given to correct the hypothyroidism before evaluating other causes of raised PRL. Measurement of TSH and PRL is routinely done as a part of infertility workup.

II. Methods

The Study was conducted on 200 women (age group 20 – 40 years) on their first visit to infertility clinic of Gynaecology and Obstetrics Department of a tertiary care hospital. Infertile women having tubular blockage, pelvic inflammatory disease, endometriosis on diagnostic laparoscopy or hysteroscopy and with genital TB (PCR- positive); with liver, renal or cardiac diseases; those already on treatment for thyroid disorders or hyperprolactinemia; or cases where abnormality was found in husband's semen analysis also were excluded from the study.

Routine investigations such as random blood sugar (RBS), renal functions tests (RFT), hemogram, urine routine, and ultrasound (as and when required) were done. TSH and PRL were measured by the electrochemiluminesence method. Normal TSH and PRL levels were 0.27 – 4.2 µIU/ml and 1.9-25ng/ml, respectively, as per kit supplier's instruction. Therefore, hypothyroidism was considered at TSH levels of >4.2 µIU/ml and hyperprolactinemia at PRL levels of >25 ng/ml.

Thyroxine 12.5 – 150 µg (Thyrox, Thyronorm, Eltroxin) was given to hypothyroid infertile females depending upon TSH levels. Statistical analysis of results of results was carried out TSH levels. Statistical analysis of results was carried out using percentages.

III. Results

Table 1 - Demographic distribution of cases

Mean age	29.5±0.62 yrs.	
Religion	Hindu	82%
	Muslim	18%
Geographic distribution	Rural	22%
	Urban	78%
Literacy	Literate	82.5%
	Illiterate	17.5%

Table 1 depicts that mean age of study group was 29.5±0.62 yrs. & majority of patients belongs to Hindu community (82%) and 18% were Muslims.

Table 2 - Serum thyroid stimulating hormone level in 200 infertile females

Hormone	**Status**	**Number of patients**		**Level of hormone**
		n=200	**%**	
TSH µIU/ml.	Normal	152	76%	2.16±0.94
	Hypothyroid	48	24%	8.34±4.10
	(1)Subclinical Hypothyroid	30	62.5%	TSH 4-6 µIU/ml.
	(2) Clinical Hypothyroid	18	37.5%	TSH>6 µIU/ml.

Table 2 depicts that total 48 (24%) female found hypothyroid .In 48 women it was found that 30(62.5%) of hypothyroid infertile women were with subclinical & remaining 18 (37.5%) were with Clinical hypothyroidsm.

Table 3 - Serum prolactin level in 200 infertile females

Hormone	Status	No. of patients	Level of hormone
Serum prolactin ng/ml	Normal	163(81.5%)	12.85±5.97
	Hyperprolactinemia	37(18.5%)	53.26±28.00

Table 3 depicts level of prolactin in infertile females 18.5% females found Hyperprolactinemic

In 48 hypothyroid infertile females, the mean TSH levels were 8.34±4.10 µIU/ml, and in 37 infertile women with hyperprolactinemia the mean PRL levels were 53.26±47.17 ng/ml. Depending upon the TSH levels, hypothyroid infertile women were further subdivided into subclinical (TSH 4-6 µIU/ml) and clinical (TSH > 6 µIU/ml) hypothyroidism. It was found that 30 (62.5%) of hypothyroid infertile women were with subclinical and remaining 18 (37.5%) were with clinical hypothyroidism.

In this study, 39 (19.5%) infertile women had raised TSH levels only, 28 (14%) infertile females had raised prolactin level only, and 9 (4.5%) infertile females have raised levels of both TSH and PRL, which may be due to hypothalamic and/or pituitary diseases.

Table 4 - Effect of treatment of hypothyroidism on fertility

Hypothyroid Patients n=48				Conceived after treatment of hypothyroidism					
Subclinical		Clinical		After 6 wks. to 3months		After 3 months to 1year		Total	
n	%	n	%	n	%	n	%	n	%
30	62.5	18	37.5	23	62.16	14	37.83	37	77.08

Table 4 depicts effects of treatment of hypothyroidism on fertility. Total 37 (77.08%) patients conceived within 1 year of treatment.

Of the 48 infertile women diagnosed with hypothyroidism (alone or with hyperprolactinemia), 37 (77.08%) infertile women conceived after treatment with drugs for hypothyroidism (dose depending upon severity of hypothyroidism, i.e. TSH levels). Of these 37 women, 23 (62.16%) women conceived after 6 weeks to 3 months of therapy and 14 (37.83%) women conceived after 3 months to 1 year of therapy. We further found that hypothyroid infertile women with associated hyperprolactinemia also responded to treatment for hypothyroidism and they conceived. These results correlate with Indu Verma et. al. 2012 [9].

IV. Discussion

Thyroid hormones have profound effects on reproduction and pregnancy. Thyroid dysfunction is implicated in a broad spectrum of reproductive disorders, ranging from abnormal sexual development to menstrual irregularities and infertility. [10,11] Hypothyroidism is associated with increased production of TRH, which stimulates pituitary to secrete TSH and PRL. Hyperprolactinemia adversely affects fertility potential by impairing GnRH pulsatility and thereby ovarian function. [2,12,13] so it is advised to check TSH and PRL levels in every infertile female, regardless of their menstrual rhythm.

In USA, TSH and PRL levels were checked at the time of the couple's initial consultation for infertility. [8] In our study, the prevalence of hypothyroidism was 24% (sub-clinical 62.5% and clinical 37.5%) and hyperprolactinemia was 18.5% which correlates with Indu Verma et. al 2012 [9].The prevalence of hyperprolactinemia was higher in Iraq (60%) and even in Hyderabad, India, it is higher (41%) as compared to the present study in North India. Hyperprolactinemia may result from stress, and the variable prevalence may be due to the different stress levels in different areas. [2,8]

Thyroid dysfunction is a common cause of infertility which can be easily managed by correcting the appropriate levels of thyroid hormones [12,14] It has been recommended that in presence of raised TSH along with raised PRL levels, the treatment should be first to correct the hypothyroidism before evaluating further causes of hyperprolactinemia. Hormone therapy with thyroxine is the choice of treatment in established hypothyroidism. It normalizes the menstrual cycle, PRL levels and improves the fertility rate. Therefore, with simple oral treatment for hypothyroidism, 77.08% infertile women with hypothyroidism conceived after 6 weeks to 1 year of therapy. We tried to maintain normal TSH levels; compliance and adequacy of hypothyroid drug dose were checked by TSH measurement after 6 to 8 weeks interval.

V. Conclusion

We concluded that the normal TSH levels are the pre-requisite requirements for fertilization. The decision to initiate thyroid replacement therapy in subclinical hypothyroidism at early stage is justified in infertile women. Our data also indicate that variations in TSH levels in the narrower range or borderline cases,

i.e. 4-5, 5-6, and >6.0 µIU/ml, should not be ignored in infertile women which are otherwise asymptomatic for clinical hypothyroidism. This group of infertile women, if only carefully diagnosed and treated for hypothyroidism, can benefit a lot rather than going for unnecessary battery of hormone assays and costly invasive procedures. For better management of infertility cause.

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