Prevalence of Hypothyroidism in Infertile Women Attending a Tertiary Care Centre in West Bengal, India - A Prospective Observational Study

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ABSTRACT

BACKGROUND

Hypothyroidism is the most common endocrinological problem affecting women who present with ovulatory dysfunction resulting in infertility. Its milder form, subclinical hypothyroidism (SCH) characterised by mildly elevated thyroid stimulating hormone (TSH) levels and normal free thyroxin (FT4) levels, may also contribute to disturbed reproductive function. The prevalence of SCH has been reported to be 0.7 % - 2.3 % in large series of unselected infertile women. Undiagnosed and untreated thyroid diseases can be a cause for infertility as well as sub fertility. Prevalence of hypothyroidism in the reproductive age group ranges from 2 - 4 %. We wanted to study the prevalence of hypothyroidism as one of the causes of infertility in infertile women who attended a tertiary care centre, to study the prevalence of clinical / subclinical hypothyroidism in infertile women and to assess the thyroid status in infertile women.

METHODS

This is a prospective observational study done in the Gynaecology and Obstetrics outpatient department at R.G. Kar Medical College and Hospital, Kolkata, India from 1^{st} January 2017 to 1^{st} July 2018. 314 infertile women in the reproductive age of 20 - 40 years attending the outpatient department were included in this study.

RESULTS

In our study out of the total of 314 cases, 270 patients (86 %) were suffering from primary infertility and 44 patients (14 %) had secondary infertility. Prevalence of hypothyroidism (both clinical and subclinical) was 21.9 % (69 cases) among the infertile patients attending outpatient department of a tertiary care centre. Clinical hypothyroidism was detected in 7.3 % (23 cases) and subclinical hypothyroidism was seen in 46 cases (14.6 %). Among the hypothyroid infertile patients, 75.4 % (52 cases) was of primary infertility.

CONCLUSIONS

Hypothyroidism is an emerging cause of infertility (both primary and secondary). Subclinical hypothyroidism is more prevalent than clinical hypothyroidism in infertile women.

KEYWORDS

Hypothyroidism, Subclinical Hypothyroidism, Infertility, Tertiary Care Centre

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BACKGROUND

Thyroid is a highly vascular organ and is regulated by TSH from the anterior pituitary. Iodine is essential for the synthesis of thyroid hormones.1 Thyroid hormones do not have any discrete target organ. They affect cells of almost all the tissues of the body.² The two thyroid hormones, thyroxine (T4) and tri-iodothyronine (T3) which helps in growth and development of the body, sexual development, increases basal metabolic rate and modulates reproductive functions.³ Hypothyroidism is the most common endocrinological problem affecting women who present with ovulatory dysfunction resulting in infertility. Its milder form, subclinical hypothyroidism (SCH) characterised by mildly elevated thyroid stimulating hormone (TSH) levels and normal free thyroxine (FT4) levels, may also contribute to disturbed reproductive function. The prevalence of SCH has been reported to be 0.7 % - 2.3 % in large series of unselected infertile women.4

Undiagnosed and untreated thyroid diseases can be a cause for infertility as well as subfertility. Both these conditions have important medical, economical and psychological implications in our society.

Infertility have been defined as inability to conceive after one year of regular intercourse without contraception and accounts for one in six newly married couples.⁵ Infertility is a world health issue affecting approximately 8 - 10 % of women worldwide.⁶ It is primary if couple does not turn to be successful in achieving pregnancy, secondary if couple had achieved a pregnancy previously but are currently with conception difficulty. WHO estimates the overall prevalence of primary infertility in India to be 3.5 % - 16.8 %.^{6,7} In certain percentage of infertile couples, it is seen that there is no attributable cause. In these cases, all relevant parameters are normal and as such these groups are separately classified as unexplained infertility.⁸

Prevalence of hypothyroidism in the reproductive age group ranges from 2 - 4 %.⁹ Thyroid dysfunction can affect fertility in various ways resulting in-

- 1. Ovulatory dysfunction: failure to produce competent ovum to be fertilised.
- Luteal phase defect with a short secretory phase of the menstrual cycle resulting in failure of implantation of the fertilised egg and it ends up as bleeding per vagina (very early miscarriage) and 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 and
- Other hormonal imbalances: reduced sex hormone binding globulins (SHBG), oestrogen dominance, progesterone deficiency, all of which interfere with proper reproductive hormonal balance within the body.

TSH, prolactin and growth hormone with FSH, LH acts synergistically in recruitment of new follicles. Even in absence of hyperprolactinaemia, thyroid dysfunction may contribute to infertility. Thyroid hormone is essential for production and balance of estradiol and progesterone and amplitude of LH pulses. Morphological changes observed in follicles in hypothyroidism can be a consequence of higher prolactin production, that may block both secretion and action of gonadotropins. Adequate thyroid supplementation corrects prolactin levels and normalises ovulatory function resulting in pregnancy.

It is seen that prevalence of hypothyroidism in infertile women is much higher in women in reproductive age group. 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 problems or irregular menstrual cycle or had more than two miscarriages or is unable to conceive after 1 year of unprotected intercourse.

Hypothyroidism has been shown to be a cause of infertility and repeated abortions.¹⁰ Subclinical hypothyroidism is more prevalent than overt hypothyroidism. Hypothyroidism can be easily detected by estimating thyroid stimulating hormone [TSH] levels in the blood.

Subclinical hypothyroidism (SCH) is more common and asymptomatic. But it can cause anovulation directly or by causing elevation in prolactin hormone in long standing cases. Hypothyroid infertile women are associated with hyperprolactinemia due to increased production of thyrotropin releasing hormone [TRH] which further increases the level of TSH as well as prolactin. This elevated TRH levels in ovulatory dysfunction due to hypothyroidism causes raised prolactin and is associated with delayed LH response to gonadotropin-releasing hormone (GnRH).¹¹ It has been recommended that in the presence of raised prolactin hormone, the treatment should be first given to correct the hypothyroidism before evaluating other causes of raised prolactin level. Measurement of TSH and prolactin is routinely done as a part of infertility workup. Treatment of overt or subclinical hypothyroidism with appropriate dose of thyroxine would benefit the hypothyroid infertile couples to be blessed with a baby.

Objectives

- 1. To estimate the prevalence of hypothyroidism among the women who are attending outpatient department of tertiary care centre with infertility.
- 2. To assess the prevalence of clinical and subclinical hypothyroidism among the women who are attending outpatient department of tertiary care centre with infertility.

METHODS

This is a prospective observational study done in the Gynaecology and Obstetrics outpatient department at R.G. Kar Medical College and Hospital, Kolkata, India from 1st January 2017 to 1st July 2018. Total 314 infertile women in reproductive age of 20 - 40 years attending the outpatient department were included in this study.

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Inclusion Criteria

- Reproductive age group (20 40 yrs.)
- All infertile women of the above age group (both primary and secondary).

Exclusion Criteria

- Infertile women having tubal defect
- History of hypophysio-hypothalamic disorders
- Liver, renal, cardiac or any chronic systemic diseases
- Any congenital anomaly of urogenital tract / obvious organic genital lesions
- Male factor infertility

Sample Size

Sample size calculation was done by using the following formula-

$$n = \frac{(z\alpha / 2)^2 \times p \times q}{I^2} = \frac{1.96^2 \times 20.9 \times 79.1}{4.5^2}$$
$$= 313.62$$

n = Sample size required

Za / 2 = Constant; a confidence level of 95 % = 1.96

 P = Measure of prevalence or proportion of event in % = 20.9 %

q = Opposite of p = 100 - p = 79.1

I = Precision value (95 % confidence interval) = 4.5

It was estimated that 314 subjects will be required for our study. Systematic random sampling technique was adopted for selection of cases. Sampling interval = expected attendees / 314 = 5040 / 314 = 16. Therefore every 16th case is our study subject. 1st case was selected by simple random technique. 314 women aged 20 - 40 years attending Gynaecology and Obstetrics OPD of R. G. Kar Medical College and Hospitals, Kolkata for the first time were recruited for the study. The study was carried out during the period of 1st January 2017 to 1st July 2018. Out of 314 women recruited for the study, 270 women were belonging to primary infertility category and remaining 44 women were of the secondary infertility group.

The study was approved by the institutional ethics committee (Registered with The Drug Controller General India, Registration No - ERC / 322 / Inst / WB / 2013) and informed consent was obtained from all patients.

Protocol of infertility workup in the women included a detailed clinical history, information about age, marital status, menarche, menstrual history, obstetrical history, coital history, clinical features of hypothyroidism, family history of thyroid diseases, anthropometric measurements of weight, height, body mass index (BMI), medical and surgical history. A detailed gynaecological examination and general survey of the patients was done. Routine investigations such as complete haemogram, random blood sugar, hormonal profiles like - TSH, FT3, FT4, prolactin (PRL), luteinising hormone (LH), follicle stimulating hormone (FSH), estradiol (E2), free testosterone, semen analysis of husband and screening for infectious diseases were done. Hysterosalpingography, pelvic ultrasonography, diagnostic laparoscopy, tuberculosis- polymerase chain reaction (TB-

PCR) of menstrual blood or endometrial tissue was done when indicated.

This study was conducted in collaboration with the Department of Biochemistry and Community Medicine Department, R.G. Kar Medical College and Hospital, Kolkata, India. Blood samples were collected in fasting state. About 3 mL of blood is collected from the antecubital vein. TSH, FT3, FT4 and prolactin were measured by the electrochemiluminescence method (Immulite-1000). Other hormonal (baseline FSH, LH, estradiol, free testosterone) estimation was done on specific day of period if previous reports were not available or not done previously. Normal value of different hormone was as per test kit supplier's instruction and as follows - FT3: 0.2 - 0.5 ng / dL, FT4: 0.8 - 2.0 ng / d, TSH: 0.4 - 4.2 micro IU / mL, prolactin: 3.8 -19.0 ng / microL, LH (early follicular): 1.9 - 12.5 IU / L, FSH (early follicular): 0.2 - 17.2 IU / L, E₂ (early follicular): 2.5 -10.2 pg / mL, free testosterone (early follicular): 0.3 - 2.0 pg / mL respectively. Therefore, hypothyroidism was considered if TSH levels > 4.2 microIU / mL and hyperprolactinemia if prolactin levels > 19.0 ng / microL. Results were tabulated and statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 20.

RESULTS

In our study out of total 314 cases, 270 patients (86 %) were suffering from primary infertility and 44 patients (14 %) had secondary infertility (Figure 1).



| Parameters | Total (N = 314) | Primary Infertility (N = 270) | Secondary Infertility (N = 44) | | |
|-----------------------------------|--------------------|-------------------------------------|--------------------------------------|--|--|
| Mean age (year) | 23.6 | 23.2 | 26.3 | | |
| Duration of infertility (year) | 3.06 | 2.92 | 3.94 | | |
| Religion | | | | | |
| Hindu | 239 (76.1 %) | 225 (83.3 %) | 14 (31.8 %) | | |
| Muslim | 68 (21.7 %) | 40 (14.8 %) | 28 (63.6 %) | | |
| Others | 07 (2.2 %) | 05 (1.9 %) | 02 (4.5 %) | | |
| Literacy rate | 64 % | 67 % | 48.7 % | | |
| Table 1. Demographic Profile | | | | | |

In our study as shown in Table 1, the mean age was 23.2 years and 26.3 years in primary and secondary infertility patients whereas the overall mean age was 23.6 years. Mean duration of infertility in our study was 3.06 years.



Whereas the duration of infertility was 2.9 years and 3.9 years in primary and secondary infertility group respectively. In our study, 64 % patients were literate and literacy rate was 67 % and 48.7 % in primary and secondary infertility group respectively.

Figure 2 shows endocrinological profile of our study patients. Mean value of different hormones are comparable in both primary and secondary infertility group.

| | | Parity Status or Infertility | | Total | |
|--|----------------------------|---------------------------------|--------------------------|------------|--|
| Thyroid Status | | Primary Infertility | Secondary Infertility | | |
| Euthyroid | Count | 218 | 27 | 245 | |
| | % within thyroid status | 89.0 % | 11.0 % | 100.0 % | |
| Hypothyroid | Count | 52 | 17 | 69 | |
| | % within thyroid status | 75.4 % | 24.6 % | 100.0 % | |
| Total | Count | 270 | 44 | 314 | |
| | % within thyroid status | 86.0 % | 14.0 % | 100.0 % | |
| Table 2. Thyroid Status with Regard to | | | | | |
| Parity Status or Type of Infertility | | | | | |

Table 2 shows that among the euthyroid patients, 218 patients (89.0 %) were suffering from primary infertility and 11.0 % (27 patients) had secondary infertility. In our study 75.4 % hypothyroid patients had primary infertility and 24.6 % had secondary infertility.

| Category | Total (N = 314) | Primary Infertility (N = 270) | Secondary Infertility (N = 44) | | |
|---------------------------------------|--------------------|----------------------------------|-----------------------------------|--|--|
| No. of patients | 69 | 52 | 17 | | |
| Percentage | 21.9 % | 19.2 % | 38.6 % | | |
| Table 3. Prevalence of Hypothyroidism | | | | | |

Our study shows (Table 3) that the overall prevalence of hypothyroidism among the infertile patients attending tertiary care centre is 21.9 %. In primary and secondary infertility group it is 19.2 % and 38.6 % respectively.

| Category | Primary Infertility | Secondary Infertility | Total | | |
|---------------------------------|------------------------|--------------------------|------------|--|--|
| Clinical hypothyroid | 15 (65.2 %) | 8 (34.8 %) | 23 (100 %) | | |
| Subclinical hypothyroid | 37 (80.4 %) | 9 (19.6 %) | 46 (100 %) | | |
| Total | 52 | 17 | | | |
| Table 4. Type of Hypothyroidism | | | | | |

Table 4 shows that 37 patients (71.2 %) of hypothyroid patients in primary infertility group were suffering from subclinical hypothyroidism and 15 patients (28.8 %) had clinical or overt hypothyroidism. Similarly in secondary infertility group clinical and subclinical hypothyroid patients were 8 (47 %) and 9 (53 %) respectively. Clinical hypothyroidism was detected in 7.3 % (23 cases) and subclinical hypothyroidism was seen in 46 cases (14.6 %) of infertile patients.

DISCUSSION

Total 314 women were recruited for the study, the results are tabulated after statistical analysis using Statistical Package for the Social Sciences (SPSS) version 20. Out of total 314 women, 270 (86 %) women were of primary infertility and 44 (14 %) women were of secondary infertility in our study (Figure 1).

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In our study, the mean age of patient was more in the secondary infertility group and longer duration of infertility (mean) was observed in this group.

Table 1 shows, 225 primary infertile patients were Hindu (83.3 %) and 40 were Muslim (14.8.0 %). Among the secondary infertile patients, 31.8 % were Hindu in comparison to 63.6 % Muslim. These are categorical variables so on Pearson chi-square test P value was 0.0001 i.e. the relation was statistically significant. We observed 64 % literacy rate among the study population which is equivalent to national literacy rate among women. Another observation in our study is that women suffering from secondary infertility have less literacy rate in comparison to primary infertility group (48.7 % and 67 % respectively.)

Table 2 shows that among the euthyroid patients 218 patients (89.0 %) were suffering from primary infertility whereas 11.0 % (27 patients) had secondary infertility. In our study 75.4 % hypothyroid patients had primary infertility and 24.6 % had secondary infertility. All these are categorical data so we performed Pearson chi-square test and P value was detected as 0.004 that means the relation was statistically significant. Therefore, it can be said that thyroid dysfunction or hypothyroidism is a cause of infertility.

In our study, mean value of different hormones was within the normal range and it was comparable in both primary and secondary infertility groups. So, the confounding factor has been avoided (Figure 2).

Our study (Table 3) shows that overall prevalence of hypothyroidism among the infertile patients attending tertiary care centre was 21.9 % corroborating with the study by Verma et al. which shows 23.9 % infertile women out of 394 cases had hypothyroidism.¹² In primary and secondary infertility group it is 19.2 % and 38.6 % respectively. Our findings are supported by the study by Akhter et al.⁹

Table 4 shows that 15 primary infertile women i.e. 65.2 % and 8 secondary infertile women i.e. 34.8 % were suffering from clinical / overt hypothyroidism, 37 primary infertile women i.e. 80.4 % and 9 secondary infertile women i.e. 19.6 % were suffering from subclinical hypothyroidism. We also observed that 218 (89.0 %) primary infertile and 27 (11.0 %) secondary infertile women were euthyroid. These are categorical variables so P value was calculated by Pearson chi-square test which shows P = 0.004 i.e. the relations are statistically significant. From these results, it can be stated that subclinical hypothyroidism is more common and important factor for primary infertility than clinical hypothyroidism whereas clinical hypothyroidism is more common for secondary infertility in our study. These results corroborate with the study of Indu Verma et al. 2012.12

In our study clinical hypothyroidism was detected in 7.3 % (23 cases) and subclinical hypothyroidism was seen in 46 cases (14.6 %) of infertile patients thereby it indicates that subclinical hypothyroidism is more common among infertile women than clinical hypothyroidism. It is supported by the study by Dilruba Rahman et al.¹³ done on 30 subfertile women which showed that the proportion of women suffering from hypothyroidism was 33.3 % (subclinical hypothyroidism 26.7 % and clinical hypothyroidism 6.7 %). A study by Mohana Priya et al.¹⁴ on 98 infertile women

showed that 53.7 % were suffering from hypothyroidism (50.5 % - subclinical hypothyroidism and 3.2 % - overt hypothyroidism). Similarly, study by Raber's W et al.¹⁵ and Bals-Pratsch M et al.¹⁶ showed a high number of subclinical hypothyroidism in infertile women which was 34 % and 25 % respectively. This difference is probably attributed to the small sample size in these above-mentioned studies.

Hypothyroidism is prevalent in infertile women as well as in general women population. In India, prevalence of hypothyroidism among the women is estimated to be 15.86 % as per the study by Unnikrishnan and Menon¹⁷ but this prevalence rate in general women population is less than the prevalence rate among infertile women in our study (21.9 %). Therefore, thyroid screening should be done in basic infertility work up and we recommend it as a routine investigation for infertile women.

CONCLUSIONS

Hypothyroidism is an emerging cause of infertility both in primary and secondary infertility. Subclinical hypothyroidism is more prevalent than clinical hypothyroidism. Subclinical hypothyroidism is more common and important factor for primary infertility than clinical hypothyroidism whereas clinical hypothyroidism is comparatively more prevalent in secondary infertility. Infertility due to hypothyroidism can be easily diagnosed by simple and cost-effective thyroid profile test. Treatment of hypothyroidism can help to overcome infertility before getting expensive investigations and invasive procedures done.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

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