Sub-clinical hypothyroidism and hyperprolactinemia in infertile women: Bangladesh perspective after universal salt iodination

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Citation

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Abstract

Background: Hypothyroidism is an accepted cause of infertility and habitual abortion. We therefore evaluated the status of thyroid function and related hormones in infertile women in Bangladesh. Methods: Serum thyroid stimulating hormone and prolactin was measured in 113 infertile women during their first visit for infertility evaluation. Results: Prevalence of sub-clinical hypothyroidism was 6.5% and 15%, and prevalence of hyperprolactinemia was 43% and 21% in primary and secondary infertility respectively. Mean TSH level was higher in secondary infertility (3.6 +/- 3.7mIU/L) than primary infertility (2.3 +/- 2.7mIU/L), though the difference was not statistically significant (P < 0.11). Mean prolactin level in primary infertility (495 +/-340nmol/L) was higher than secondary infertility (340 +/- 310nmol/L), showing a significant statistical difference (p<.05). Conclusion: Prevalence of hyperprolactinemia was higher in primary infertility and prevalence of sub-clinical hypothyroidism was higher in secondary infertility, showing no correlation between TSH and prolactin levels in these two groups.

DECLARATION

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INTRODUCTION

Infertility is defined as the inability to conceive after one year of regular intercourse without contraception. The prevalence of infertility is estimated at between 12 and 14% and has remained stable in recent years. It thus represents a common condition, with important medical, economic and psychological implications. Sub fertility affects one in seven couples in the United Kingdom and is associated with considerable patient stress and anxiety. According to standard protocol, infertility evaluation usually identifies different causes, including male infertility (30%), female infertility (35%), the combination of both (20%), and finally unexplained or “idiopathic” infertility (15%). Thyroid dysfunction is a condition known to reduce the likelihood of pregnancy and to adversely affect pregnancy outcome. Data on the relationship between thyroid disorders and infertility remain scarce and the association with a particular cause of infertility has not been thoroughly analyzed.[1],[2]

Prolactin is a polypeptide hormone secreted by the anterior pituitary gland, whose main role is the stimulation of lactation in the postpartum period. The increase in prolactin secretion can be physiological (pregnancy and lactation) or pathological (hypothalamic and pituitary diseases, iatrogenic, etc.). Hyperprolactinemia induces suppression of the hypothalamic-pituitary-gonadal axis and resistance of the ovary to gonadotropin action, which results in amenorrhea and lack of ovulation. Infertility associated with hyperprolactinemia is reversible with treatment, irrespective of the type of treatment (radical or medical). Lowering of prolactin levels to normal or near normal is often necessary to allow ovulation.[3]

Traditionally, measurements of prolactin and thyroid stimulating hormone have been considered important components of the evaluation of women presenting with infertility.[4] Hypothyroidism in females, maternal hypothyroidism and sub-clinical hypothyroidism, have all came under a lot of discussion recently. The association of iodine deficiency disorder (IDD) with hypothyroidism is a well-established phenomenon. The prevalence of sub-clinical thyroid disorders in infertility patients and indications for treatment have been discussed, but no

consensus has been obtained.

Mymensingh is a district town about 120 km north of Dhaka, and an endemic zone for iodine deficiency in Bangladesh. As it is an iodine-deficient zone with an iodine supplementation program after a law was passed by parliament in 1989 requiring universal iodination of salt by 1996, our group was interested to look at the current status of thyroid function and related hormones in primary and secondary infertility patients. The aim of the study was to observe any difference in thyroid function between primary and secondary infertility and to correlate the serum prolactin levels in these two groups.

MATERIALS AND METHODS

This was a prospective, cross-sectional study in an iodine-deficient zone in the northern part of Bangladesh. The study was conducted prospectively in the Center for Nuclear Medicine and Ultrasound(CNMU), Mymensingh, from January 2003 to August 2004. 113 consecutive female patients with infertility, who were referred to our center for various hormone assays, including thyroid stimulating hormone (TSH) and/or prolactin (PRL) during their first visit for infertility evaluation, were included in this study. Patients on treatment for thyroid disorders or hyperprolactinemia were excluded from the study. Patients were divided into two groups as primary or secondary infertility. Infertility was defined as inability to conceive for more than a year despite regular unprotected intercourse. Primary infertility was defined as those cases in whom conception had never occurred and secondary infertility was defined as those cases in whom there was an inability to conceive after a previous successful conception. All patients were told about the research study and informed consent was received. Related history and physical examination data were recorded in a pre-designed data collection sheet.

Serum TSH was measured with immuno-radiometric assay (IRMA) and serum PRL was measured with radio-immuno assay (RIA) methods. Kits were supplied by the China Institute of Atomic Energy, Beijing and Beijing Atom Hightech Co. Ltd. All assays were done by a skilled technician from our center. Borderline values underwent a second set of assays by another skilled technician on an entirely separate batch of IRMA or RIA. Results of TSH and prolactin were collected and recorded. According to the kit supplier`s instructions, normal values of TSH (0.3-5 mIU/L) and prolactin (<460 nmol/L) were used to confirm abnormal cases and compare between the two groups. Data analysis was done using a computer-based program, `The Statistical Discovery Software`, JMP IN, version 5.1.2. A p value <0.05 was taken as significant.

RESULTS

A total of 113 women with primary (n=86) and secondary (n=27) infertility were included in this study. All the cases were within the reproductive age limit of 15 to 45 years, with the majority in the age range of 21-30 years (78%). Menstrual cycle was irregular in 70% of cases and oligomenorrhoea was present in 59% of cases. Although the prevalence of other clinical findings did not differ significantly between the two groups, the prevalence of irregular menstruation, acne and polycystic ovaries were comparatively higher in primary infertility and the prevalence of goiter and obesity were comparatively higher in secondary infertility.(Table-1), (Fig-1).

Figure 1

Table 1: Clinical findings of women with primary and secondary infertility, showing no significant difference between the two groups.

Clinical findings	Primary	Secondary
Irregular menstruation	**74.50%**	59.26%
Oligomenorrhea	58.14%	62.96%
Acne	**13.95%**	7.41%
Hirsutism	24.42%	25.93%
Obesity	30.23%	**33.33%**
Goiter	26.74%	**33.33%**
PCO	**22.92%**	10.53%

Comparison of clinical findings and hormonal abnormality, showing a higher prevalence of hyperprolactinemia along with irregular menstruation, acne and PCO in primary infertility, and a higher prevalence of sub-clinical hypothyroidism along with obesity and goiter in secondary infertility.

Serum TSH was measured in 61 primary and 20 secondary infertility cases. Prevalence of sub-clinical hypothyroidism was 6.5% in primary and 15% in secondary infertility. Prevalence of sub-clinical thyroid disorders (both hypo- and hyper-) was 11.5% in primary and 15% in secondary infertility, showing an overall prevalence of 12.3%. PRL was measured in 65 primary and 23 secondary infertility cases. Prevalence of hyper-prolactinemia was 43% in primary and 22% in secondary infertility, showing an overall

prevalence 37.5% (Table-2).

Figure 2

Table 2: Prevalence of sub-clinical thyroid disorders and hyperprolactinemia. Prevalence of sub-clinical hypothyroidism is higher in secondary infertility and that of hyperprolactinemia is higher in primary infertility.

	Sub-clinical hypothyroidism	Sub-clinical hyperthyroidism	Total sub-clinical thyroid disorders	Hyperprolactinemia
Primary	**6.56%**	4.92%	11.50%	**43%**
Secondary	**15%**	0%	**15%**	22%
Total	8.64%	3.70%	**12.34%**	**37.50%**

(Normal level: TSH = 0.3 -5.0 mIU/L, Prolactin <460 nmol/L)

In primary infertility, the TSH level was high in 2 and low in 1 out of 24 cases with hyper-prolactinemia. PRL was normal in 1 sub-clinical hypo- and 2 sub-clinical hyperthyroid cases. A report on PRL was unavailable in 1 sub-clinical hypothyroid case with primary infertility (Fig. 2). In secondary infertility, TSH was normal in all hyperprolactinemia cases and prolactin was normal in all cases with sub-clinical hypothyroidism (Fig. 3). The mean TSH value was higher in secondary infertility (3.6 +/- 3.7 mIU/L) than in primary infertility (2.3 +/- 2.7 mIU/L), although the difference was not statistically significant ($P < 0.11$). The mean PRL level in primary infertility (495 +/-340 nmol/L) was higher than in secondary infertility (340 +/- 310 nmol/L), showing a significant statistical difference ($P<0.05$), (Table-3).

TSH and prolactin levels in primary infertility. There is no correlation between TSH and prolactin levels. (Normal level: TSH = 0.3 -5.0 mIU/L, Prolactin <460 nmol/L)

TSH and prolactin levels in secondary infertility. There is no correlation between TSH and prolactin levels. (Normal level: TSH = 0.3 -5.0 mIU/L, Prolactin <460 nmol/L)

Figure 3

Table 3: Serum TSH and Prolactin level in women with primary and secondary infertility. Prolactin level is higher in primary infertility and TSH level is higher in secondary infertility.

	TSH level	Prolactin level
Primary infertility	2.3 +/- 2.7	**495 +/- 340**
Secondary infertility	**3.6 +/- 3.7**	340 +/- 310
P- value	0.11	**0.05**

(Values are mean +/- S.T.D)

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. Hypothyroidism, as well as hyperthyroidism, can negatively affect reproductive potential. Primary hypothyroidism is associated with increased production of thyrotropin-releasing hormone (TRH), which is known to stimulate pituitary TSH and PRL release. Hyperthyroidism is associated with increased production of sex hormone-binding globulin and androgens. Hyperprolactinemia adversely affects fertility potential by impairing GnRH pulsatility and thereby ovarian function.[5],[6] Most obstetricians and gynecologists check serum levels of TSH and PRL in every female patient undergoing an infertility evaluation regardless of their menstrual rhythm. In a prospective study in the USA, serum TSH and PRL were checked at the time of the couple's initial consultation for infertility. There were 2.48% of patients (21 of 846 patients) with abnormal levels of TSH, and 1.77% (15 of 844 patients) with elevated levels of PRL. From this result, it was concluded that the practice of routinely ordering serum levels of TSH and PRL in infertility patients with normal periods is questionable.[7] In our study, the prevalence of sub-clinical thyroid disorders was 12.3% and the prevalence of hyperprolactinemia was 37.5%, which is higher than the study in the USA.[7] However, the prevalence of galactorrhoea and/ or hyperprolactinemia was higher in Iraq (60%)[8] and similar to our findings in Hyderabad, India (41%).[9] As hyperprolactinemia may result from stress, the variable prevalence may be due to the different stress levels of infertility patients in different areas.

Mild hypothyroidism may contribute to disturbing reproductive function. In a study in Vienna, abortions appeared to be associated with higher TSH, but not with elevated thyroid antibodies.[10] In our study, we did not evaluate thyroid antibodies either, and only TSH was measured to classify cases with sub-clinical thyroid disorders. In a study in Belgium, mean serum TSH levels were significantly higher in women of infertile couples compared to an age-matched control population of parous women: 1.6 +/- 2.6 versus 1.2 +/- 0.7 mIU/L. The study group consisted of couples with 45% female infertility, 38% male infertility and 17% idiopathic infertility.[5] We also found a high level of mean serum TSH both in primary and secondary infertility, and it was comparatively higher in

secondary infertility (3.6 +/-3.7 mIU/L) than in primary infertility group (2.3 +/-2.7 mIU/L), although the difference was not statistically significant ($P < 0.11$). As Bangladesh is an iodine-deficient zone, it recently started an iodine supplementation program and this may be the reason for the overall high prevalence of sub-clinical thyroid disorders and higher mean serum TSH levels in our study group. On the other hand, the prolactin level in primary infertility was significantly higher than in secondary infertility ($P<0.05$). It is well known that hyperprolactinemia is an important cause of infertility and that bromocriptine therapy is effective to treat it.[11] Increased prolactin levels were also observed in women with endometriosis[12] and recurrent spontaneous abortion.[13] We found a higher prevalence of hyperprolactinemia in primary infertility (43%) than in secondary infertility (22%) and a higher prevalence of sub-clinical hypothyroidism in secondary infertility (15%) than in primary infertility (6.5%). As hyperprolactinemia may cause, or result from, infertility, the higher prevalence in primary infertility found in our study may be explained by this phenomenon. As we found only 2 cases of sub-clinical hypo- and 1 case of sub-clinical hyperthyroidism out of 24 hyper-prolactinemia cases with primary infertility, it is not considered to be a sequel to thyroid disorders. On the other hand, the higher prevalence of sub-clinical hypothyroidism in secondary infertility patients may be considered the sequel of previous autoimmune thyroid diseases (AITD) which caused the thyroid function to worsen after the first conception. In a previous study,[14] the prevalence of anti-microsomal antibody (Anti-MCAb) positive cases was 59% in females in the same study area after starting an iodine supplementation program and it was the highest in the age group of 30-35 yrs. Irrespective of sex, patients showing features of Hashimoto's thyroiditis or generalized features of AITD on high resolution ultrasound with hypothyroidism were 89.28% Anti-MCAb-positive cases, followed by goitrous hypothyroid (88.28%) and atrophic hypothyroidism (71.15%). The prevalence was lower in patients with sub-clinical hypothyroidism without features of autoimmune thyroiditis (40%). This suggests that most of the hypothyroid cases were a result of an underlying autoimmune process. Although we could not further investigate to clarify the etiology of such differences, the disease pattern and factors associated with primary and secondary infertility might be different and we should consider such differences during infertility evaluation. Clinical findings from this study also reflect some differences between the two groups, but the difference was not statistically significant. A comparatively higher prevalence of irregular menstruation, acne and polycystic ovaries may reflect the higher prevalence of hyperprolactinemia /high PRL level in primary infertility and a comparatively higher prevalence of goiter and obesity may reflect the higher prevalence of sub-clinical hypothyroidism / high TSH level in secondary infertility. As far as we know, no study has previously analyzed the difference in serum TSH and PRL levels between these two groups, so we could not compare our findings. In a study by Cramer et al., TSH and prolactin were positively correlated in women undergoing In Vitro Fertilization(IVF).[4] In this study, no correlation was observed between TSH and PRL levels in primary or secondary infertility. Further studies with a large sample size and long follow-up are necessary to validate the variation in TSH and prolactin levels in these two groups and to clarify the etiology of the higher prevalence of hyperprolactinemia in primary infertility and higher prevalence of sub-clinical hypothyroidism in secondary infertility for better management of infertility cases.

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