Implications of new TSH reference range on infertile Bangladeshi women.

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Abstract

Background: For over a decade there has been considerable debate about the correct reference interval for TSH. Practitioners are divided, unfortunately they could not reached at a unanimous decision. More recently, researchers have been looking the implications of the new TSH reference range (0.3 to 3.0 mIU/L). **Objective:** To explore the implications of the newer TSH reference range recommended by AACE and NACB, USA among the infertile women in Bangladesh. **Methods:** This was a cross-sectional descriptive type of study conducted at Gynaecology & Obstetrics Out Patient Department (OPD) of Rajshahi Medical College Hospital (RMCH), Bangladesh. The sample size was 94. Data on clinical presentations, biochemical and ultrasonographic findings were collected by a preformed Data Collection Sheet. Serum hormone assay TSH, T3, T4, and prolactin (PRL) were done in Centre for Nuclear Medicine and Ultrasound (CNMU), Rajshahi, Bangladesh. Data were analyzed in a computer using SPSS for windows. Descriptive analytical techniques involving frequency distribution, computation of percentage etc. were done. **Results:** A total of 94 infertile women, new reference range of TSH identified 10 (10.6%) women having clinical hypothyroidism, 8 (80.0%) of them were identified as same by old reference range. New reference range identified 28 (29.8%) infertile women having subclinical hypothyroidism. But old reference range identified 25 (89.3%) of them as euthyroid. Out of 94 infertile women, Old reference range identified 83(88.3%) women as euthyroid but it was reduce to 56 (59.6%) in new reference range polycystic ovary syndrome (PCOS) was identify as a most common (25; 26.6%) cause of infertility among the present study subjects. But if the new TSH reference range was followed instead of the old then majority of the PCOS accompanied with subclinical hypothyroidism. **Conclusion:** New TSH reference range has a significant implication on Bangladeshi infertile women. Further studies are needed to observe the treatoneut outcomes of subclinical hypothyroid infertile women identified by application of the new THS reference range.

Key owrds: new TSH reference range, hypothyroidism, infertility.

Introduction

Thyroid hormones are essential for normal growth, sexual development and reproductive function. Both hypothyroidism and hyperthyroidism are associated with a variety of changes in reproductive functions including delayed onset of puberty, menstrual disorders, anovulatory cycles and reproductive wastage when pregnancy is achieved.[1-3] Thus thyroid dysfunctions may have a great impact on fertility in females.[4] Thyroid dysfunction particularly hypothyroidism is a well documented, but often overlooked, factor in female infertility.[5]

Thyroid dysfunction, both hyperthyroidism and hypothyroidism can be easily detected by assessing TSH levels in the blood. Low TSH level (< 0.5 mIU/L) accompanied by high T_3 (>3.54 nmol/L) and T_4(>173 nmol/L) levels indicate hyperthyroidism. Hypothyroidism may be either subclinical or overt. A slight increase in TSH levels with normal T_3 and T_4 indicates subclinical hypothyroidism whereas high TSH level accompanied by low T_3 (<1.1 nmol/L) and T_4(<54 nmol/L) levels indicate clinical hypothyroidism.[6] Conventionally TSH reference range used to be from 0.5 to 5 mIU/L.[7] But In late 2002, the National Academy of Clinical Biochemistry (NACB), USA issued new guidelines for the diagnosis and monitoring of thyroid disease.[8] In the guidelines, the NACB reported that the current TSH reference range (0.5 to 5 mIU/L) was too wide and actually included people with thyroid disease. When more sensitive screening was done, which excluded people with thyroid disease, 95 percent of the population tested actually had a TSH level between 0.4 and 2.5 mIU/L. As a result, the NACB recommended reducing the reference range to that. Meaning, anything below or above that could be a sign of thyroid disease. The NACB guidelines led to a recommendation in January 2003 by the American Association of Clinical Endocrinologists (AACE), calling for doctors to "consider treatment for patients who test outside the boundaries of a narrower margin based on a target TSH level of 0.3 to 3.0 mIU/L". The statement also said: "AACE believes the new range will result in proper diagnosis for millions of Americans who suffer from a mild thyroid disorder, but have gone untreated until now".[9]

For over a decade there has been considerable debate about the correct reference interval for TSH. Practitioners are divided, unfortunately they could not reached at a unanimous decision. More recently, researchers have looked at an important question: If the normal TSH range is narrowed, as has been recommended by AACE and NACB, what are the implications?[10] Dr. Vahab Fatourechi and fellow researchers estimated that if the range was narrowed according to the AACE recommendations, the total number of people with thyroid disease in America would expand from approximately 5 percent of the population to an estimated 20% of the population, with most of the added patient population falling in the hypothyroid category. This represents a dramatic increase in the number of thyroid patients nationwide, from an estimated 15

To get the answer of such type of question is also very important in case of infertility in Bangladesh because infertility rate is approximately 15% in Bangladesh, which is the highest among all South Asian countries.[3,4] In this study researchers intended to compare the implications of the newer TSH reference range recommended by AACE and ATA [2], USA among the infertile women in Bangladesh.

Methods

This was a cross-sectional descriptive type of study conducted at Gynaecology & Obstetrics Out Patient Department (OPD) of Rajshahi Medical College Hospital (RMCH), Bangladesh. All the infertile women attending at the OPD of RMCH for seeking fertility treatment constituted the study population. A total of 94 infertile women attended at the OPD were included in this study. The women who were with liver, renal or cardiac diseases, those already on treatment for thyroid disorders or hyperprolactinemia, or whose male partner identified as infertile were excluded from the study. Before selecting the women, informed written consent was taken from each of them.

Data were collected by a preformed Data Collection Sheet [2013]. The DCS was designed to record clinical, biochemical and ultrasonographic findings. The information were recorded from the patients' treatment slips, investigation reports, interview with the patients and consultation with the concerned doctors. If necessary, Serum hormone assay: TSH, T3 and T4, ultrasound were done in Centre for Nuclear Medicine and Ultrasound (CNMU), Rajshahi, Bangladesh.

Data were entered in the computer and processed using SPSS for windows. Descriptive statistical techniques involving frequency distribution, computation of percentage etc. were applied.

Results

On the basis of old reference range, 8 [8.5 %] of the study subjects were suffered from clinical hypothyroidism, only 2[2.2%] of the women were suffered from subclinical hypothyroidism and the rest 83[88.3%] of the women were euthyroid. On the other hand, On the basis of new reference range, 12 [12.8%] of the infertile women had clinical hypothyroidism, 28 [29.8%] of the women had subclinical hypothyroidism and 54 [57.4%] were euthyroid. None of the study subjects were suffered from hyperthyroidism as per both old and new reference range (Figure 1).

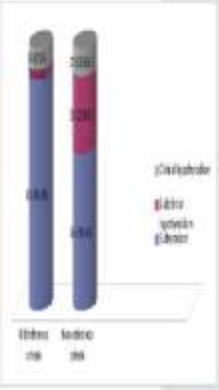

Figure 1 Comparison of thyroid status between old and new reference ranges

A total of 94 infertile women, new reference range of TSH identified 28 [29.8%] women having clinical hypothyroidism, 8 [8.5%] of them were identified as same by old reference range, New reference range identified 28 [29.8%] infertile women having subclinical hypothyroidism, But old reference range identified 2[2.2%] of them as euthyroid. Out of 94 infertile, Old reference range identified 83[88.3%] women as euthyroid but it was reduce to 54 [57.4%] in new reference range (Table-1).

Table-1 Cross-Table of status of hypothyroidism by old and new criteria

Old reference Criteria	New reference Criteria			Total N (%)
	Clinical Hypothyroidism N (%)	Subclinical Hypothyroidism N (%)	Euthyroid N (%)	
Clinical Hypothyroidism N (%)	8 (8.5)	0 (0.0)	0 (0.0)	8 (8.5)
Subclinical Hypothyroidism N (%)	0 (0.0)	2 (2.1)	0 (0.0)	2 (2.1)
Euthyroid N (%)	12 (12.8)	26 (27.7)	54 (57.4)	83 (88.3)
Total N (%)	20 (21.3)	28 (29.8)	54 (57.4)	94 (100.0)

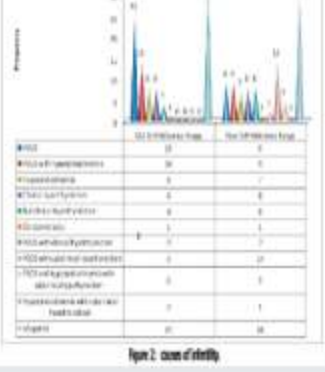

Figure 2: causes of infertility

If conventional TSH reference range was followed, PCOS was identify as a cause of infertility among the highest number (25; 26.6%) of the present study subjects. The second highest (14; 14.9%) cause of infertility was PCOS with hyperprolactinemia. In csae of 4 (4.3%) infertile women, subclinical hypothyroidism was indentified as a cause of their infertility. A major number (34; 36.2%) of the women had unexplained infertility. Instead of that, if the new TSH reference range was followed then PCOS was also identified as the highest cause but majority of them accompanied with subclinical hypothyroidism. In case of 30 infertile women , a cause could not be identified (Figure 2)

Discussion

Until November 2002, doctors had relied on a normal TSH level ranging from 0.5 to 5.0 mIU/L to diagnose and treat patients with a thyroid disorder who tested outside the boundaries of that range. Now AACE encourages doctors to consider treatment for patients who test outside the boundaries of a narrower margin based on a target TSH level of 0.3 to 3.0 mIU/L. AACE believes the new range will result in proper diagnosis for millions of Americans who suffer from a mild thyroid disorder, but have gone untreated until now.[7] But such proposals have been met with substantial critique.14,15 There is a great debate about the upper limit of the new reference range but there is no debates about the lower limit of the new TSH reference range because the lower limits of both the reference ranges, old and new are very closed. The strongest argument in favor of lowering the upper limit of normal for the serum TSH level is the higher level of antithyroid antibodies detected in persons with a serum TSH level between 3.0 and 5.0 mIU/L and the higher rate of progression to clinical thyroid disease.[16] After exclusion of persons with goiter, antithyroid antibodies, and a family history of thyroid disease, the mean serum TSH is 1.5 mIU/L. The serum TSH distribution curve is not Gaussian; there is a tail end at the upper limits of normal. If the distribution is extrapolated to be Gaussian, then the upper limit for the 97.5th percentile will be 2.5 mIU/L.[16] The argument against lowering the upper limit of normal for TSH values is that 22 to 28 million more Americans would be diagnosed with hypothyroidism without any clinical or therapeutic benefit from this diagnosis.[15] The present study data also showed that decreasing the upper limit of the TSH reference range to 3.0 mIU/L resulted in more than a 3-fold increase in diagnosis of hypothyroidism among the infertile women in a tertiary medical hospital, Rajshahi Medical College. The present study suggested that new reference range was more effective to detect the mild /subclinical hypothyroidism. In this study, new reference range identified 89.5% more subclinical hypothyroid patients who were previously marked as euthyroid by old reference range.

Infertility can be caused by many different things For 15- 50% of couples, a cause cannot be identified.[17-19] In the present study 36.2% of infertile women have unexplained infertility, if conventiona TSH reference range was followed. Instead of that, if the new TSH reference range was followed then it is reduced to 31.9%.

Polycystic ovary syndrome (PCOS) is the most common hormonal disorders among women of reproductive age, and is a leading cause of infertility.[2] It was also the most common cause of infertility identified in this study. PCOS is a fairly common condition with hypothyroidism, especially subclinica hypothyroidism. Newer research has shown that women with PCOS are four times more likely to also have Hashimoto's Disease (autoimmune thyroiditis).[2] In this study, according to the new TSH reference range, more than 48% of the women with PCOS having also subclinical/mild hypothyroidism.

PCOS and hypothyroidism have many symptoms in common, such as "anovulation" i.e. menstration without releasing an oocyte (egg cell). Other symptoms the two conditions share are: insulin resistance, blood sugar problems leading to diabetes, high cholesterol levels, heavy periods, weight gain (obesity), hair loss and ovarian cysts. Some suggest this is the cause of PCOS.[21] Many suspect hypothyroidism is related to PCOS, ovarian enlargement and cyst formation. A recent study investigated this hypothesis among the women having PCOS and hypothyroidism with increased ovarian volume and bilateral multicystic ovaries. When thyroid hormone replacement therapy was initiated, in addition to stabilizing thyroid hormone levels, ovarian cysts regressed and ovarian volume was reduced.[2] Recent studies suggested that the patients who were erroneously diagnosed with PCOS when they really had hypothyroidism.[21,22]

Hyperprolactinaemia has been reported to be an important cause of infertility.[23] The present study also identified hyperprolactinemia as an important cause of infertility. Subclinical hypothyroidism can cause anovulation directly or by causing elevation in prolactin (PRL). Many infertile women with clinical or subclinical hypothyroidism had associated hyperprolactinemia due to increased production of thyrotropin releasing hormone (TRH) in ovulatory dysfunction.[23,24] In this study, according to the new TSH reference range, 27.27% of the women with hyperprolactinemia having also hypothyroidism. 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.[25-26] This study suggested that the new TSH reference range facilitates to accept the

hypotheses discussed above regarding the PCOS and hyperprolactinaemia among the infertile women and open a new window for the treatment of infertility.

"The adverse health outcome for individuals with TSH levels between 3.0 and 5.0 is progression to overt hypothyroidism. Levothyroxine treatment would clearly prevent that outcome, but at what price?" However, it must be asked, why is preventing progression to overt hypothyroidism not a desired health objective, given that overt hypothyroidism most definitely can contribute to obesity, heart disease, infertility, depression and host of other health problems? Prevention of disease is a major focus of much of today's medicine, with exercise, diet and medications to prevent heart disease, obesity, stroke, and many other conditions. Some of these preventative approaches, particularly drug therapies, come with some risk factors, but the risks are presented along with benefits, so patients can make an informed choice. Even if there is a small risk to treatment of subclinical hypothyroidism (and the existence of such a risk is a theory, not a proven fact) then why is this same approach not used for thyroid patients, who could be given the opportunity to prevent overt hypothyroidism, realizing that the prevention also comes with some risk?[14]

There is huge debate about narrowing the normal range of TSH. Practitioners are divided about this issue. Opponents of the new range argue against treatment for subclinical thyroid problems because they are concerned about risks of subclinical hyperthyroidism due to overtreatment.[15] Allies of the new reference range argue, however, that there is an equivalent risk of under treatment, and that all of these risks can be minimized by educating doctors about the desirable TSH target and teaching them how to use various dosages to reach those targets in patients.[16]
However, over diagnosis and treatment of hypothyroidism is more justifiable than under treatment specially in case of infertility. Infertile women might take risk of over treatment for conception.

The findings of this study suggested that If the conventional TSH range are narrowed, as has been recommended by AACE and NACB, there are some implications in both practice and further research in infertility in Bangladesh. There are minimum effect to detect hyperthyroidism but increased 3 fold hypothyroidism particularly mild/subclinical. Idiopathic causes of infertility are reduced. During the treatment of infertility, practitioners should first consider the hypothyroidism then PCOS and hyperprolactinemia. Further studies are recommended to observe the treatment benefits of subclinical hypothyroid infertile women considering the risks with a very close supervision.

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