THYROID DYSFUNCTION IN WOMEN OF REPRODUCTIVE AGE: LABORATORY PROTOCOL FOR INFERTILITY EVALUATION

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ABSTRACT

Background: **Infertility in developing counties worldwide is associated with many social, financial, and medical challenges. With a prevalence rate of between 10 - 14 % and biochemical etiology of about 80% of the cases among Nigerian women, laboratory diagnosis has gradually assumed an important role in improved diagnosis.**

Objective: **The aim was to evaluate the prevalence of thyroid dysfunction in infertility and need to evaluate.**

Method: **This was a descriptive cross-sectional case study of one hundred and twenty-five (125) women selected by stratified random sampling method into two groups of primary and secondary infertility. A total of 125 healthy fertile women served as the control group.**

Serum freeT_3 (fT_3), feeT_4 (fT_4), and TSH were analyzed using commercial ELISA kits. Data were analyzed using SPSS version 20.0 and the p-value of $\leq$0.05 was considered statistically significant.

Result: **Twenty participants (16%) were observed to have associated thyroid dysfunction with infertility. The commonest thyroid dysfunction was overt hypothyroidism (9.6%) and subclinical hypothyroidism (4.0%) respectively and this was found to be commoner in secondary infertility (21.8%).**

Conclusion: **Thyroid function evaluation (especially serum TSH) should be included as a routine assessment in infertility protocol, especially in secondary infertility cases.**

Keywords: Thyroid dysfunction, Reproductive age, Laboratory evaluation, Infertility.

INTRODUCTION

Infertility affects 10-15% of couples at reproductive age[1] and it is of the common conditions associated with a lot of psychosocial, medical, and financial challenges with attendant consequences such as stigma, deprivation, neglect, violence, marital problems, and mental health issues.[2,3]

The most common causes of a couple's inability to conceive are associated with partner factors in males (30%), females (30%), and both (20%), and maybe unknown in other cases.[4] The causes of infertility in the female are however related to both the physical and biochemical challenges relating to the function of gonads and these biochemical challenges are caused by hormonal absence, insensitivity, and inaction in the pituitary-gonad axis with resultant failure of ovulation accounting for as many as half (16%) of the causes in female infertility.[5]

The ovaries are in continuous interaction with the sex hormones and the interplay may account for infertility in several ways. Hypergonadotropic hypogonadism is the most common biochemical pattern in both primary and secondary infertility, while hypogonadotropic hypogonadism is more associated with secondary infertility but hyperprolactinemia is less common in both types of infertility.[6]

However, the other pituitary hormones such as the thyroid and prolactin hormones can interact with the ovaries in women of reproductive age resulting in a direct effect on ovarian function, autoimmunity mechanism as well as alterations of the sex hormone binding protein levels.[7] Although menstrual irregularities are common in hyperthyroidism, subclinical hypothyroidism is associated with anovulation, amenorrhea, and adverse pregnancy outcome in some cases.[8,9]

Laboratory biochemical assessment of both pituitary and sex hormones potentially contribute to the diagnosis of infertility in over 50-75% of couples being investigated.[6] Treatment of hypothyroidism in women is an important part of any effort to correct infertility and it is therefore imperative to put into consideration the serum TSH assessment when requesting an infertility test. It is recommended that only when this ruled out that other interventions to treat infertility is needed.[10]

MATERIALS AND METHODS

The study was a descriptive cross-sectional case study of two hundred and fifty (250) participants attending the Gynecology clinic for treatment of infertility who were recruited after informed consent was obtained in line with the Helsinki Declaration111.

The participants comprised 125 recruited by stratified random sampling method after a computer-generated random number into primary and secondary infertility. The control group of 125 participants was made up of women in the community who had delivered between three months to one year before the time of the study.

All pregnant women, infertile women on hormonal therapy, women presenting with infertility due to male factors, those with congenital anomalities of the female urogenital tract, those with a history of thyroid disease/ surgery, and those treated with thyroid medication or irradiation were excluded from the study. Ethical approval was obtained from the Health Research Ethics committee of ABUTH Zaria.

A blood sample of 5 milliliters was collected from each participant using plain vacutainer bottles from the antecubital fossa under aseptic conditions. The samples were allowed to clot and retract at room temperature for four hours before being centrifuged at 5000 rpm for five minutes and the separated sera were harvested and stored at -20 °C until analysis. All instruments used were validated.

Serum freeT_3 (fT_3), feeT_4 (fT_4), and TSH were analyzed using commercial ELISA kits, and the data were analyzed using SPSS version 20.0, and a p-value of $\leq$0.05 was considered statistically significant.

The reference intervals in the laboratory of assay included: 0.39-6.16 mIU/L for TSH, for FT3 was 2.15- 6.45 pmol/L for, and 10.30-25.78 pmol/L for FT4.

The diagnosis of euthyroid was made as serum TSH, FT3, and FT4 concentrations within the reference interval while overt hypothyroidism was made as serum TSH concentration above the reference interval and FT3, and FT4 concentrations below the reference interval.

Subclinical hypothyroidism and Subclinical hyperthyroidism were defined as serum TSH concentration above the reference interval and FT3, FT4 concentrations within the reference interval and serum TSH concentration below the reference interval and the FT3, FT4 concentrations within the reference interval respectively.

Overt hyperthyroidism was defined as serum TSH concentration below the reference interval and FT3, and FT4 concentrations above the reference interval, and overt hypothyroidism was defined as serum TSH concentration above the reference interval and FT3, and FT4 concentrations below the reference interval.

RESULTS

The mean age of the participants was 31.6 ± 6.4 and 30.4 ± 5.8 years for the infertile and control participants respectively (p = <0.1). The age interval and age group with the highest number of participants were presented in table 1. A total of 47 participants (37.6 %) had primary infertility, while 78 (62.4 %) had secondary infertility.

The mean serum concentrations of fT_3 and fT_4 were significantly lower (p=<0.00) and the serum TSH was

Table 1: Age distribution of the study participants

Age (yr)	Participants n (%)	Mean age (±2SD)	Controls n (%)	Mean age (±2SD)	p-values
18-24	23 (18.4)	21.31±1.62	21 (16.8)	19.7±1.74	0.27
25-34	65 (52.0)	27.23±2.43	74(59.2)	29.90±3.17	0.20
35-44	36 (28.8)	36.70±3.35	30(24.0)	37.32±2.95	0.35
>44	1 (0.8)	-	0 (0)	0±0.0	0.00
Total	125 (100)	31.6±6.4	25 (100)	30.4±5.8	0.10

p = < 0.05,

significantly higher (p=<0-04) among the infertile participants (table 2) compared to the controls.

Twenty participants (16%) were diagnosed to have thyroid dysfunction of either hypo or hyperthyroidism. Overt hypothyroidism accounted for 9.6 % and subclinical hypothyroidism was reported in 4.0 %. Both classes of hypothyroidism were commoners in the secondary infertility group. The majority of the participants were euthyroid in both types of infertility and one participant (2.1%) had overt hyperthyroidism. (Table 3).

Table 2: Serum thyroid hormone concentrations in the study participants

Serum Hormones	Participants (n=125) Mean ± 2SD	Controls(n=125) Mean ± 2SD	p-values
TSH(mIU/L)	4.79±2.9	1.57±1.1	0.00
FT3(pmol/L)	2.95±1.3	3.43±1.2	0.00
FT4(pmol/L)	14.80±14.1	17.50±5.5	0.04

Table 3: Pattern of thyroid dysfunction among the infertile participants

Thyroid dysfunctions	Primary infertility n (%)	Secondary infertility n (%)
Euthyroid	44 (93.7)	61 (78.2)
Overt hypothyroidism	1(2.1)	11 (14.1)
Subclinical hypothyroidism	1(2.1)	4 (5.1)
Overt hyperthyroidism	1(2.1)	2 (2.6)
Subclinical hyperthyroidism	0 (0.0)	0 (0.0)
Total	47 (100)	78(100)

DISCUSSION

Thyroid disease is one of the most common endocrine disorders seen in women in the reproductive age group as observed by the mean age in this study and as reported in other findings.[11,12]

However, it was observed that the majority of the cases of infertility were in the middle of the reproductive age as opposed to other studies which reported that many (44%) of girls are married before their 18th birthday due to the high incidence of early child marriage in the same geopolitical-social area of North East and West of Nigeria.[13] Evidence showed that there is a clear and strong link between Child Early Forced Marriage (CEFM) prevalence and endemic poverty, poor education outcomes, school dropout rates, a high rate of out-of-school children, and poor access to basic social, economic and healthcare services remains the big driver of child marriage.[13] The contrast observed in this study may be due to late presentation for infertility evaluation which is usually due to stigmatization and alternative intervention from traditional and religious institutions. The reason is however different in the USA and may be attributed to the fact that higher education is acquired during the reproductive ages leading to the postponement of starting a family.

This study showed that the prevalence of hypothyroidism (mean serum concentrations of fT_3 and fT_4 significantly lower (p=<0.00) while the serum TSH was significantly higher (p=<0-04) in infertility.

This finding was similar to previous reports that hypothyroidism was the commonest thyroid dysfunction seen among infertile women.[14,15,16.] This finding can be explained based on clinical and experimental studies outcomes which had demonstrated a relationship between the hypothalamic-pituitary axis and ovarian function[16] due to specific thyroid hormone receptors present in the ovary contributing to the regulation of the reproductive function.[17]

Even though euthyroid in infertility was found in the majority of participants as reported in a similar finding,[18] this finding does not downplay the importance of the high prevalence of hypothyroidism observed in this study because of another pituitary hormone as evidenced by the high incidence of hyperprolactinemia which has a positive correlation with hypothyroidism in infertility.[19]

Overt hypothyroidism is a major pattern of thyroid dysfunctions in secondary infertility in our finding

which is similar to other findings.[7,13,19] It has previously been reported that Sheehan's syndrome (SS) which is a postpartum hypopituitarism caused by necrosis of the pituitary gland because of the result of severe hypotension or shock caused by massive hemorrhage during or after delivery. This results in varying degrees of anterior pituitary hormone deficiency leading to secondary infertility, especially in developing countries. The mean age at diagnosis of SS in Nigeria of 35.1 years falls between the middle reproductive age in this study while the average interval between the obstetric injury and diagnosis of 6.9 years and mean parity of four are within the definition of secondary infertility.[20] The resultant serum hypothyroidism as reported also in our finding stimulates the release of Thyroxine releasing hormone (TRH) from the hypothalamus which is associated with increased synthesis of thyroid stimulating hormone (TSH) and prolactin. The implication of the hyperprolactin leads to impairment of growth-releasing hormone (GnRH) pulsatility.[21]

The high prevalence of sub-clinical hypothyroidism (SCH) in this study was similar to earlier studies.[22,23] However, this finding differed from a study conducted in Kano[21] where a higher prevalence was reported. Though the areas of study were geographically similar, the contrast may be due to the evaluation of thyroid function only in the subset of the infertile women with hyperprolactinaemia which in most cases may have resulted from long-standing hypothyroidism.

Also, thyroid dysfunction was commoner among those with secondary infertility as observed in this study and the overt subtype was the commonest in our study. Some other studies have reported subclinical hypothyroidism as the commoner pattern[21,23] but all agreed with the high prevalence of hypothyroidism in infertility. Thyroid dysfunctions thus remain a common cause of female infertility, especially in the secondary type and its inclusion in the investigation profile and subsequent treatment of infertility has been associated with improved clinical outcomes.[10] Therefore, treating hypothyroidism should be an important part of any effort to correct infertility.

CONCLUSION

Hypothyroidism is a common cause of infertility with a higher prevalence in the secondary infertility subset. Therefore, the inclusion of its laboratory assessment and treatment should be considered an important management plan.

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