

Evaluation of thyroid function in infertile female patients in port harcourt, Nigeria

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ABSTRACT

Context: An optimally functional reproductive system and fecundity is fundamental for the sustenance of life. Undiagnosed and untreated thyroid disease may cause infertility.

Aim: To evaluate and compare thyroid function tests of infertile women with those of fertile women.

Settings and Design: There were 216 infertile women and 200 fertile women in this study.

Materials and Methods: Serum thyrotropin (TSH), free thyroxine (FT4), free triiodothyronine (FT3), antibodies to thyroid peroxidase (TPOAb), follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, progesterone, and estrogen were analysed using ELISA techniques.

Statistical Analysis Used: Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc. Chicago, Illinois, U.S.A.).

Results: Overall prevalence of thyroid disorders in infertile women was 4.6%. They had higher prevalence of thyroid autoimmunity (TAI) (2.8%) compared to controls (1.0%). They also had overt hypothyroidism (0.9%) and overt hyperthyroidism (0.9%) whereas controls had only subclinical hypothyroidism (1.0%). Infertile patients had significantly higher FSH, LH, prolactin, and estrogen, but lower progesterone values than controls. There was no significant difference in the mean FT3, FT4, TSH, and TPOAb between patients and controls. However, after further stratification, women with TSH >2.5 mIU/L were observed to have higher mean TSH and prolactin, and lower FT4 and FT3 levels than women with TSH ≤2.5 mIU/L.

Conclusions: Significant findings were observed only in infertile, and also fertile, women with TSH >2.5 mIU/L, who had lower levels of FT4 and FT3 and higher levels of TSH and prolactin compared to women with TSH ≤2.5 mIU/L, respectively.

Key words: Infertile female; Nigeria; Port Harcourt; thyroid function; thyroid hormones.

Introduction

Infertility is the absolute inability to conceive after one year of regular intercourse without conception.^[1] The overall prevalence of infertility is estimated to range from 10% to 15%.^[1,2] Female causes of infertility account for 35% of couples' inability to conceive and comprise endometriosis, tubal occlusion, and ovulatory dysfunction. Other causes of infertility in couples are male factor infertility in 30%, a combination of male and female factors in 20%, and idiopathic


infertility in 15%.^[1,3] Thyroid dysfunction can affect fertility in various ways resulting in anovulatory cycles, luteal phase defect, high prolactin (PRL) levels, and sex hormone imbalances.^[4] Therefore, normal thyroid function is necessary for optimal fertility in order to achieve and sustain a healthy pregnancy.^[4] Thyroid disease has been described as the

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most common endocrine condition affecting women of reproductive age.^[5]

Increasing evidence derived from experimental and clinical studies suggest that the hypothalamic–pituitary–thyroid axis and hypothalamic–pituitary–ovarian axis are physiologically related.^[1,5] Pituitary hormones such as TSH, prolactin, and growth hormone act synergistically with follicle stimulating hormone (FSH) and luteinizing hormone (LH) to enhance the entry of nongrowing follicles into the growth phase.^[6] Thyroid hormones play key roles in virtually every phase of reproduction from folliculogenesis till the early weeks after conception.^[2,6] Thyroid hormone receptors and their mRNA have been detected in human granulosa cells and oocytes, which may have a role in enabling direct effects of thyroid hormones on ovarian function.^[5,7] Thyroid hormone receptors are also present on the placenta, suggesting a role in placental development.^[2,5] Available evidence suggests that TSH may be involved in the process of embryo implantation.^[8]

Undiagnosed and untreated thyroid disease can be a cause for subfertility as well as infertility.^[4,7,9-11] Therefore, assessment of thyroid dysfunction has been considered as an important component in the infertility work-up of women.^[1,7] Thyroid evaluation has been advocated for infertile women desiring to conceive, particularly those with personal or family history of thyroid disorder, autoimmune disease, ovulatory dysfunction, or miscarriages.^[1,4,9] A comprehensive thyroid evaluation should include serum triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), and thyroid autoimmune testing such as thyroid peroxidase antibodies (TPOAb), thyroglobin antibodies (TgAb), and thyroid stimulating immunoglobulin (TSI).^[4]

In our fertility clinic it is not routine practice to check for thyroid function among asymptomatic women presenting with infertility. Due to the lack of population-based data of infertile women with thyroid dysfunction in Rivers State, this research was conducted to evaluate the thyroid status of infertile women. It is hoped that our findings will further clarify the role thyroid hormones play in female infertility.

Patients and Methods

Ethics

Procedures followed were in accordance with the ethical standards of the Ethics Committee of the University of Port Harcourt Teaching Hospital, who gave approval for this study. Informed written consent was obtained from each participant.

Study site and design

This was a cross-sectional study carried out in the Gynaecology clinic in the Department of Obstetrics and Gynaecology of the University of Port Harcourt Teaching Hospital, Choba in Rivers State, Nigeria from January 2016 to July 2016. The hospital is one of the major tertiary health institutions in Southern Nigeria, providing health care services for Rivers state and nearby states like Bayelsa, Imo, Delta, Abia and Akwa-Ibom.

There are five units in the department of Obstetrics and Gynaecology. Gynaecology clinic runs every day by the respective units and on the average 4–6 new cases of infertility are seen daily. Women that were diagnosed with primary or secondary infertility in the gynecology clinic were sequentially recruited after obtaining informed written consent and they served as patients. For the control group, women that attended the family planning clinic of the same hospital were recruited. The family planning clinic is open to clients from Monday to Friday and is manned by consultant gynaecologists, family planning nurse practitioners, and other support staff.

Sample size was determined based on an average prevalence rate of infertility in Nigerian women of 15.7% and was estimated at 200.^[12] After obtaining informed written consent from each participant, an interviewer-administered questionnaire was used to collect data, which included personal biodata, dietary history, history of menstrual cycle disorders, family and personal history of thyroid disease, co-morbidities, and use of medication.

Physical examination

Anthropometric measurements including height, weight, body mass index (BMI), as well as physical examination to elicit any abnormalities in the cardiovascular and endocrine systems, were carried out. Women with known thyroid disorders or associated medical conditions, liver, renal or cardiac diseases, and those on antithyroid drugs, levothyroxine, or any medication that could affect thyroid function were excluded from the study.

Sample collection and laboratory analysis

Venous blood specimen was obtained from the cubital fossa or dorsum of the hand, sent to the laboratory, left to stand for one hour to allow for proper clotting, centrifuged at 3500 rpm, and then separated. The serum was then stored at -20°C and assayed within two weeks. Serum TPOAb (Calbiotech, Spring Valley, California) and TSH were analyzed using immunometric ELISA technique while free T3 (FT3) and free T4 (FT4) were analyzed by competitive ELISA

technique. FSH, LH, prolactin, progesterone, and estrogen were also analyzed using ELISA techniques.

The assay-specific reference ranges were 0.5–5.0 mIU/L for TSH, 0.8–2.0 ng/dL for FT4, 1.4–4.2 pg/mL for FT3 and <45 IU/mL for TPOAb. Overt hypothyroidism (OH) was defined as TSH level greater than 5.0 mIU/L with a FT4 and/or FT3 concentration below the reference range and subclinical hypothyroidism (SCH) was defined as TSH >5.0 mIU/L with a normal FT4 and/or FT3 concentration. Overt hyperthyroidism was defined as TSH level less than 0.5 mIU/L with a FT4 and/or FT3 concentration above the reference range and subclinical hyperthyroidism was defined as TSH <0.5 mIU/L with a normal FT4 and/or FT3 concentration. Women with TPOAb \geq 45 IU/mL were considered to be positive for TPO antibodies.^[13]

Statistical analysis

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc. Chicago, Illinois, U.S.A.). Frequencies and percentages were obtained for categorical variables. Differences in proportions were analyzed using the Chi-square test. Kolmogorov–Smirnov test revealed a skewed distribution for TPOAb, TSH, FT4, and FT3. The means of normally distributed continuous variables were compared using unpaired Students *t*-test and the means of skewed continuous variables were compared using Mann–Whitney U-test and expressed as mean \pm standard deviation (SD). *P* values \leq 0.05 were considered significant in all analyses.

Results

There were 216 patients and 200 controls. Demographic and anthropometric characteristics of patients are compared with that of controls in Table 1. Infertile patients had higher systolic blood pressure and larger waist circumference than controls but had similar mean age, BMI, and diastolic blood pressure.

Six (2.8%) patients had positive TPOAb compared to 2 (1.0%) controls (*P* = 0.155). Two (0.9%) patients had overt hypothyroidism compared to 2 (1.0%) controls who had only subclinical hypothyroidism (*P* = 0.513). Two (0.9%) patients had overt hyperthyroidism. No control subject had subclinical or overt hyperthyroidism (*P* = 0.247). There were no significant differences in these proportions between the two groups.

Details of the biochemical parameters of patients compared with those of controls are summarized in Table 2. There was no significant difference in the mean free T3, free T4, TSH

and TPOAb between patients and controls. Infertile patients had significantly higher FSH, LH, prolactin and estrogen, but lower progesterone values than controls. The study population was further stratified by TSH into women with TSH \leq 2.5 mIU/L and those with TSH >2.5 mIU/L as shown in Tables 3 and 4. Thirty-two percent of controls and 37.0% of patients, respectively, had TSH >2.5 mIU/L. Apart from TPOAb, levels of thyroid function tests were significantly different between the two groups. The mean serum prolactin

Table 1: Comparison of physical characteristics of patients and controls

Characteristic	Patients (n=216)	Controls (n=200)	<i>P</i>
	Mean (SD)	Mean (SD)	
Age (years)	34.8 (5.6)	35.1 (6.4)	0.577
Waist circumference (cm)	86.6 (15.8)	76.4 (18.1)	0.005*
Body mass index (Kg/m ²)	27.6 (5.0)	27.1 (5.3)	0.274
Systolic blood pressure (mmHg)	120.9 (19.7)	116.8 (11.6)	0.013*
Diastolic blood pressure (mmHg)	76.1 (11.2)	74.8 (9.5)	0.213

*Statistically significant (*P* \leq 0.05); SD, standard deviation

Table 2: Biochemical parameters of patients and controls

Parameter	Patients (n=216)	Controls (n=200)	<i>P</i>
	Mean (SD)	Mean (SD)	
Free triiodothyronine (pg/mL)	2.57 (0.60)	2.48 (0.47)	0.140
Free thyroxine (ng/mL)	1.34 (0.39)	1.28 (0.25)	0.263
Thyroid stimulating hormone (mIU/L)	2.19 (1.23)	2.06 (1.08)	0.198
Thyroid peroxidase antibody (IU/mL)	16.77 (15.56)	15.78 (10.45)	0.904
Follicle stimulating hormone (mIU/mL)	12.47 (13.38)	7.33 (3.66)	<0.001*
Luteinizing hormone (mIU/mL)	9.07 (8.34)	5.92 (3.98)	<0.001*
Prolactin (ng/mL)	25.28 (34.18)	17.55 (23.88)	0.004*
Progesterone (ng/mL)	8.68 (8.40)	11.22 (6.46)	0.003*
Estrogen (pg/mL)	72.98 (50.37)	57.43 (27.20)	<0.001*

* Statistically significant (*P* \leq 0.05); SD, standard deviation

Table 3: Hormonal tests of patients stratified by TSH

Test	TSH \leq 2.5 (n=136)	TSH >2.5 (n=80)	<i>P</i>
	Mean (SD)	Mean (SD)	
Free triiodothyronine (pg/mL)	2.79 (0.57)	2.19 (0.43)	<0.001*
Free thyroxine (ng/mL)	1.42 (0.35)	1.21 (0.41)	<0.001*
Thyroid stimulating hormone (mIU/L)	1.53 (0.56)	3.33 (1.23)	<0.001*
Thyroid peroxidase antibody (IU/mL)	15.68 (12.47)	18.62 (19.69)	0.986
Follicle stimulating hormone (mIU/mL)	13.72 (16.39)	10.31 (4.46)	0.192
Luteinizing hormone (mIU/mL)	9.31 (9.66)	8.81 (5.42)	0.730
Prolactin (ng/mL)	20.54 (25.35)	35.10 (49.70)	0.040*
Progesterone (ng/mL)	8.56 (7.90)	8.86 (9.18)	0.794
Estrogen (pg/mL)	72.24 (39.37)	73.95 (63.96)	0.876

*Statistically significant (*P* \leq 0.05); SD, standard deviation

Table 4: Hormonal tests of controls stratified by TSH

Test	TSH \leq 2.5	TSH $>$ 2.5	P
	(n=136)	(n=64)	
	Mean (SD)	Mean (SD)	
Free triiodothyronine (pg/mL)	2.63 (0.43)	2.16 (0.39)	<0.001*
Free thyroxine (ng/mL)	1.36 (0.23)	1.11 (0.18)	<0.001*
Thyroid stimulating hormone (mIU/L)	1.44 (0.55)	3.37 (0.66)	<0.001*
Thyroid peroxidase antibody (IU/mL)	16.33 (11.90)	14.48 (5.61)	0.950
Follicle stimulating hormone (mIU/mL)	7.58 (3.82)	6.72 (3.22)	0.253
Luteinizing hormone (mIU/mL)	5.62 (3.90)	6.63 (4.14)	0.256
Prolactin (ng/mL)	14.50 (6.77)	24.87 (42.38)	0.045*
Progesterone (ng/mL)	11.15 (6.30)	11.41 (6.93)	0.858
Estrogen (pg/mL)	57.75 (26.59)	56.56 (30.46)	0.862

*Statistically significant ($P \leq 0.05$); SD, standard deviation

of infertile women [Table 3], and of fertile women [Table 4], with TSH $>$ 2.5 mIU/L was higher than that of women with TSH \leq 2.5 mIU/L, respectively. Levels of other fertility hormones were similar between the two groups.

Mean duration of infertility was 4.4 ± 3.8 years. One hundred and thirty-four (62.6%) patients had primary infertility and 80 (37.4%) had secondary infertility. Causes of infertility ranged from ovulation dysfunction (21.5%), uterine fibroids (17.8%), tubal blockage (8.4%), endometriosis (4%), male factor (4%), and idiopathic (48.6%). Eight (3.7%), 40 (18.5%), and 38 (17.6%) patients had a positive history of hirsutism, galactorrhea, and abdominal mass respectively. Eighty (37%) patients had a previous history of miscarriages. Seven (3.2%) patients had a previous history of assisted conception.

Average length of the menstrual cycles of patients was 29.0 ± 2.3 days. One hundred and eight (50%) patients had menstrual cycle disorders ranging from hypomenorrhea (23.3%), menorrhagia (15%), oligomenorrhea (6.7%), irregular menstruation (3.3%), and polymenorrhea (1.7%).

Discussion

The overall prevalence of thyroid disorders in infertile women was 4.6%, consisting of TAI (2.8%), overt hypothyroidism (0.9%), and overt hyperthyroidism (0.9%). This is similar to the study by Poppe *et al.* but different from another Nigerian study by Emokpae *et al.* where an overall prevalence of 23.4%, consisting of subclinical hypothyroidism (14.9%) and subclinical hyperthyroidism (7.5%) was reported.^[14,15]

Abnormalities in thyroid function can have an adverse effect on reproductive health.^[5,16] It is not surprising, therefore, that 50% of the patients we studied had menstrual irregularities while 37% had previous miscarriages.

There was a higher prevalence of TAI in patients compared to controls, though this difference was not statistically significant. They also had overt hypothyroidism and overt hyperthyroidism whereas controls had only subclinical hypothyroidism. In general, prevalence of TAI is higher among infertile women than among fertile women, especially among those whose infertility is caused by endometriosis or ovarian dysfunction, varying between 5.4% and 33%.^[1] TAI is the most frequent underlying factor leading to, or associated with, thyroid disorders particularly in developed countries where isolated TAI also occurs in the absence of thyroid dysfunction in euthyroid women.^[10] The presence of TAI in euthyroid women does not seem to affect implantation of the embryo but has been associated with endometriosis, premature ovarian failure, infertility and a three-to-five-fold increased risk of single and recurrent miscarriages mainly in the first trimester.^[1,5,8] Thyroid autoantibodies are present in almost all patients with Hashimoto's thyroiditis and three-quarters of those with Graves' disease.^[5] Serum TSH levels have been observed to be higher in women with TAI than in those without TAI.^[2] In women undergoing assisted conception, TAI has been linked with lower fertilization rates, poorer embryo quality, and lower pregnancy rates.^[5] The benefits of levothyroxine therapy pre-conceptually in euthyroid women with autoimmune thyroid disease (AITD) is inconclusive but it may be considered if the TSH level is over 2.5 mIU/L.^[5,9]

Prevalence of hypothyroidism in women with infertility, particularly subclinical hypothyroidism (SCH), which is more common, has been reported to vary from 0.7% to 43%. This wide range of prevalence has been attributed to the differences in sensitivity of serum TSH measurement.^[1,3,8,11] In our study, 0.9% of patients had overt hypothyroidism but none had subclinical hypothyroidism. Ovulatory dysfunction is dominant in women with hypothyroidism. This can be due to direct effects of hypothyroidism by altering the normal pulsatile release of FSH and LH, and by decreasing levels of sex hormone-binding globulin (SHBG), thereby increasing plasma-free testosterone and free estradiol fractions. It may also be due to the indirect effects of hypothyroidism, by increasing serum prolactin secretion secondary to the stimulatory effect of thyrotropin-releasing hormone (TRH).^[1,2,5-7,11] Prolactin has been shown to correlate positively with TSH and to increase in proportion to increases in TSH levels.^[6,15,16] Our study, which is in consonance with these findings, revealed that high TSH was associated with high prolactin levels both in fertile and infertile women.

Women with high serum TSH levels above 2.5 mIU/L have been observed to have greater menstrual disturbances (oligomenorrhea, amenorrhea, and menorrhagia) and

anovulatory cycles, lower oocyte fertilization and pregnancy rates, higher risk of *in-vitro* fertilization failure and higher recurrent miscarriage rates.^[1,2,5,8,9] Improvements in reproductive outcomes have been demonstrated in women with serum TSH <2.5 mIU/L.^[5] Evidence suggests that treating thyroid disorders and keeping TSH levels below 2.5 mIU/L may improve conception rates in infertile women and reduce early pregnancy loss.^[5,9]

The revised clinical practice guidelines of the Endocrine Society recommends the measurement of serum TSH to screen for thyroid dysfunction in women over the age of 30 years with infertility or a prior history of miscarriage.^[17] The American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA) have recommended that treatment with L-thyroxine should be considered in women with subclinical hypothyroidism, especially those with high TSH levels, when they are planning a pregnancy as other studies have shown improved pregnancy outcomes in those treated.^[5,9,18-20] Moreover, an earlier study carried out in this hospital revealed that maternal subclinical hypothyroidism was associated with neonatal low birth weight, low Apgar scores, preterm birth and high neonatal TSH.^[21] It would, therefore, be wise to screen our women with infertility by measuring serum TSH even if asymptomatic.

Incidence of hyperthyroidism in European women presenting with infertility is approximately 2.3% compared to 1.5% of women in the general population.^[5,22] Hyperthyroidism is characterized by high serum levels of SHBG, accompanied by increased plasma levels of testosterone, androstenedione, and estrogen.^[5,11] Plasma levels of LH, basal FSH, and estrogen levels may be higher in hyperthyroid women compared with normal women during all phases of the menstrual cycle.^[11] Research has shown that most women with hyperthyroidism remain ovulatory, indicating that anovulation may not be the primary mechanism for reduced fertility in these women.^[2,11,22] Hyperthyroidism is mainly associated with menstrual disorders, primarily hypomenorrhea and polymenorrhea. Hyperthyroid women have been reported to have a prevalence of menstrual abnormalities of 2.5 times higher than that of women in the normal population. Treatment of hyperthyroidism frequently corrects these cycle changes and is advisable, particularly before an ART procedure.^[5,11,22]

Conclusion

Overall prevalence of thyroid disorders in infertile women was 4.6%, consisting of TAI (2.8%), overt hypothyroidism (0.9%), and overt hyperthyroidism (0.9%). Thyroid disease can have adverse effects on reproduction, but with appropriate screening and prompt treatment of thyroid disorders in

infertile women, menstrual abnormalities may be corrected, conception rates may be improved, *in-vitro* fertilization success rates increased, and early pregnancy loss reduced. We advocate screening for thyroid function as part of the work-up of women with infertility or miscarriage.

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Conflicts of interest

There are no conflicts of interest.

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