

## **A-Case Control Analysis of Thyroid Disorders in Infertile Women at the University of Port Harcourt Teaching Hospital, Nigeria**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Author MO carried out the conceptualization of the research, data collection and initial draft of the manuscript. Author GB carried out the study design, data/statistical analysis, literature review and correspondence. Authors TK and TKN took part in data analysis, proforma design, proof read the final draft and contributed to the intellectual content of the manuscript. All authors read and approved the final manuscript.*

### **Article Information**

#### Editor(s):

(1) Dr. Oslinah Buru Tagutanazvo, Department of Midwifery, University of Swaziland, Swaziland.

#### Reviewers:

(1) Iya Eze Bassey, University of Calabar, Nigeria.

(2) Rana Choudhary, Wockhardt Hospital, India.

(3) Franco Cervellati, University of Ferrara, Italy.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/54691>

**Original Research Article**

**Received 07 December 2019**

**Accepted 14 February 2020**

**Published 21 February 2020**

### **ABSTRACT**

**Background:** Thyroid disorders have been associated with anovulatory infertility. The paucity of institution-based infertility data of women with thyroid disorders necessitated this study.

**Aims and Objectives:** To determine and compare the prevalence and pattern of thyroid disorders in infertile and fertile women at the University of Port Harcourt Teaching Hospital and to assess the predisposing factors to thyroid disorders.

**Methodology:** It was a case control study involving 162 eligible women with anovulatory infertility from the Gynaecology clinic and 162 eligible fertile women from the family planning clinic. A structured proforma was used to obtain relevant information from participants. Thyroid function test was conducted for each participant. The results were analyzed using the SPSS version 23 software package. Chi-square test was used to compare variables between groups and *P* value < .05 was considered significant.

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**Results:** Subclinical hypothyroidism was the only thyroid disorder noted with a prevalence of 3.1% among infertile women and 5.6% in fertile women, with no significant difference between both groups ( $P= .27$ ). Igbo tribe was the commonest ethnic group among the hypothyroid women. Dietary intake of iodine was 'inadequate' in all (100%) of the infertile hypothyroid women and 88.9% of the fertile hypothyroid women ( $P = .439$ ).

**Conclusion:** Subclinical hypothyroidism was the only identified thyroid disorder and its prevalence was comparable in both fertile and infertile women. Age, family history, dietary intake of iodine, ethnicity and socioeconomic status were not significantly associated with thyroid abnormality.

*Keywords: Thyroid disorders; infertility; Port Harcourt.*

## 1. INTRODUCTION

The classic clinical definition of infertility is the absence of conception after twelve months of regular, unprotected intercourse [1]. Infertility is of public health importance in Nigeria and many other developing nations because of its high prevalence and especially due to its serious social implications [2]. Worldwide, infertility is generally quoted as occurring in 8-12% of couples in the developed countries, but notably highly variable in sub-Saharan Africa ranging from 15.4 - 46% [3-7]. Infertility may have far-reaching consequences, often resulting in marital disharmony, domestic violence, social discrimination, psychological disturbances, divorce as well as physical and financial stress on the couple [8].

Infertility is attributable to both female and male factors. The female factors may result from tubal, ovulatory or uterine abnormalities [1]. Ovulatory disturbances are the principal factor in about 20 – 32% of couples presenting to infertility clinics, caused by polycystic ovarian syndrome; hypothalamic/pituitary failure; hyperprolactinemia as well as thyroid disorders like hyperthyroidism and hypothyroidism [1,9]. The thyroid hormones affect function of almost all the organs in the body. It is of common knowledge that patients suffering from hypothyroidism have various abnormalities ranging from menorrhagia, polymenorrhoea, oligomenorrhoea, anovulatory cycles and infertility [10,11].

Worldwide, hypothyroidism in the reproductive age group has been shown to be the cause of infertility and habitual abortion [12]. In Lahore-Pakistan, the prevalence of thyroid disorders in infertile women was 10.7% [13,14]. Nigerian data on prevalence of thyroid disorders in infertile women are few, with a recently published study in Port-Harcourt recording a prevalence of 4.6% [9].

Age is one of the most significant risk factor for thyroid disorders according to several epidemiologic studies, with decreased biological activity of TSH and reduced sensitivity of the thyroid gland to TSH as possible mechanisms [15]. Iodine intake could also affect thyroid function via a direct toxic effect or via immunological alterations [15]. A food frequency questionnaire, food diary or urinary iodine concentration measurement is useful in estimating iodine intake [16]. In recent years, there has been an approximately six-fold increase in frequency of thyroid pathologies amongst pregnant women [17]. There is some controversy about the effect of ethnicity on thyroid disorders as highlighted by different studies [15,18].

Hyperthyroidism results in increased serum levels of sex-hormone binding globulin and estradiol compared to those in euthyroid women [11]. This results in increased negative feedback on gonadotrophin production and thus preventing ovarian follicular development [11]. The main changes explaining infertility in patients with hypothyroidism are altered peripheral estrogen metabolism with decreased clearance of androstenedione and estrone [13] hyperprolactinemia due to increased thyrotrophin releasing hormone hypothalamic secretion causing a reduction in dopamine secretion; disturbances in gonadotrophin releasing hormone secretion that result in abnormal pulsatile release of luteinizing hormone. Subclinical hypothyroidism is more common and causes anovulation directly or by causing elevation in prolactin [13].

Hypothyroidism can be easily detected by assessing thyroid stimulating hormone (TSH) levels in the blood [19]. A slight increase in TSH levels with normal triiodothyronine and thyroxine indicates subclinical hypothyroidism whereas high TSH levels accompanied by low triiodothyronine and thyroxine levels indicate

clinical hypothyroidism [19]. Subclinical hyperthyroidism is defined as a serum TSH concentration below the statistically defined lower limit of the reference range when serum free thyroxine (fT4) and free triiodothyronine (fT3) concentrations are within their reference ranges, while decreased TSH accompanied by raised fT3 and fT4 indicate clinical/over thyroidism [20].

This study was set out to determine and compare the prevalence, socio-demographic characteristics and predisposing factors of hypothyroidism and hyperthyroidism in both infertile and fertile women. Also, this study will form an objective platform for future policies on awareness of predisposing factors to thyroid disorders as well as their prevention in women of reproductive age.

## 2. METHODOLOGY

The study was a case control study carried out at the University of Port Harcourt Teaching Hospital (UPTH) on infertile and fertile women attending the gynecology and family planning clinics respectively from May 2017 to December 2017. Ethical approval for the conduct of the study was obtained from the ethics committee of the hospital (UPTH/ADM/90/S.11/VOL.XI/328). Women diagnosed with either anovulatory infertility (diagnosed with mid-luteal phase progesterone assay < 10 ng/ml) [21] or unexplained infertility, presenting for follow-up and review of investigations, were recruited by simple random sampling after giving written informed consent. For the 'fertile arm', consenting women presenting newly for contraception (postpartum or after miscarriage) at the family planning clinic of the hospital were also recruited by simple random sampling following technique. Exclusion criteria for both groups included other causes of infertility, antithyroid and thyroid replacement therapies, as well as previous thyroidectomy.

The sample size was determined using the Leslie-Kish formula [22], based on a known population prevalence of 10.7% [14] and estimated as 162 women for each group. Structured study proforma was used to obtain relevant information from consenting women. Information obtained included duration of infertility, history of menstrual irregularity, history of heat or cold intolerance, family history of thyroid disease, history of neck swelling/surgeries and use of thyroid medications. Also, dietary intake of iodine was determined by

assessing the consumption of iodized-salt and iodine-rich foods (fish, beans, potato) using a modified food frequency questionnaire [16]. Women who consumed up to 3 of the 4 listed food groups at least thrice weekly were deemed as having 'adequate' dietary iodine intake [16]. The social classes of the participants were determined using the Olusanya et al classification model [23].

Each consented participant underwent a thyroid examination and then five millilitres of blood sample was taken by venepuncture through a peripheral vein in the cubital fossa under aseptic technique and the samples were immediately sent to the chemical pathology laboratory of the hospital for analysis. The samples were analyzed by a medical laboratory scientist and a consultant chemical pathologist. Each sample was centrifuged and the serum collected and stored at -20°C. The Enzyme Linked Immunosorbent Assay (ELISA) method was used to perform thyroid function tests using commercially prepared ELISA kits by Diagnostic Automation, INC. California, USA. The thyroid function test consists of fT3, fT4 and TSH on the serum samples, whilst ensuring appropriate quality assurance in line with the internal departmental quality control protocol. Kits and reagents were supplied with same levels of control to ensure effectiveness, stored at optimum temperature (2-8°C) and used according to manufacturer's specifications.

Expected normal values were: free T3 (1.4 – 4.2 pg/ml); free T4 (0.8 – 2.0 ng/dl); TSH (0.45 – 4.5 mIU/L). Hyperthyroidism was diagnosed if serum TSH was < 0.45 mIU/L and hypothyroidism was diagnosed if serum TSH was > 4.5 mIU/L. [19,20].

Information obtained at the end of this study was processed using the Statistical Package for Social Sciences computer software (SPSS; version 23). Frequency tables were generated and the results tested for statistical significance using the Chi-square test. Statistical test of association was carried out at the level of significance set at *P* value < .05 at 95% confidence interval.

## 3. RESULTS

The study showed an age range of 23-42 years for respondents with anovulatory infertility, while the age range for women who presented for family planning was 25-41 years. The mean age of participants in both groups was 34.6±3.2

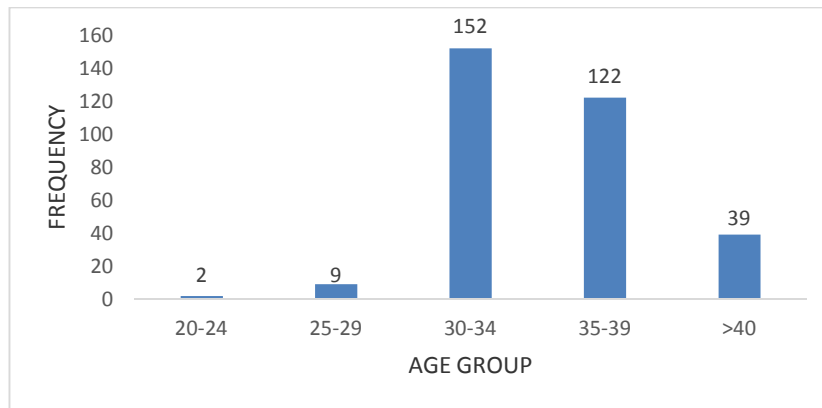
years. Figure 1 summarizes age range details. In Fig. 2, based on the Olusanya et al social classification model [23], 219 of the women in the study were of middle socioeconomic class (67.6%).

The type of hypothyroidism noted in these women was subclinical hypothyroidism. There was no case of hyperthyroidism noted in all women who took part in the study. Table 1 shows that the prevalence of hypothyroidism was 3.1% in women with infertility and 5.6% in women presenting for family planning. The difference in prevalence of hypothyroidism in both groups was not statistically significant ( $X^2 = 1.19, P = .27, OR = 0.54$ ).

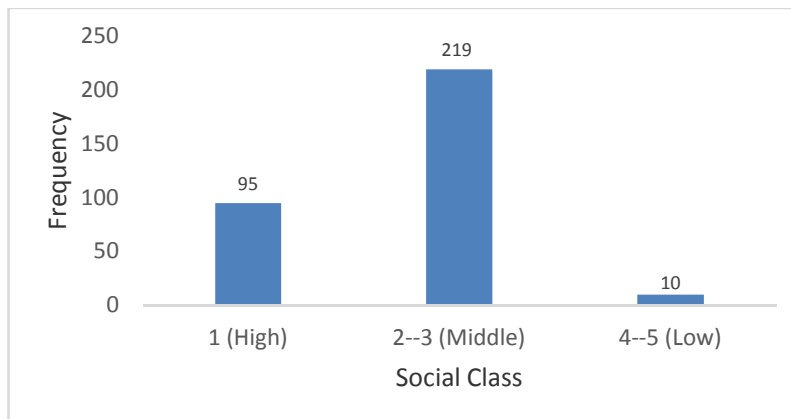
Table 2 compares the mean values of the thyroid function between both groups with no significant difference noted for any of the parameters. Table 3 summarizes the predisposing factors to thyroid disorders. All the hypothyroid women in the infertile arm were within the 30-34 years age

range. This same age range had the highest proportion (66.7%) of the hypothyroid women in the fertile arm. All the 324 women who took part in the study were Africans and of Nigerian descent. It was noticed that the prevalence of hypothyroidism among infertile and fertile women was highest in the Igbo tribe with 3 (60%) and 5 (55.6%) women respectively. This difference between the two groups was not statistically significant, with a  $P$  value of .861. The study revealed that none of the women with hypothyroidism in both groups had a family history of thyroid disease.

Figure 3 a and b show dietary intake of iodine as assessed for all the women sampled using a modified food frequency questionnaire. This was further sub-classified as 'adequate' or 'inadequate' in Table 2, with all 5 (100%) of infertile women with hypothyroidism having 'inadequate' dietary intake of iodine. Also, 8 (88.9%) of hypothyroid fertile women had inadequate dietary intake of iodine (Table 2).



**Fig. 1. Age-group distribution of women studied**



**Fig. 2. Socio-economic classes of women studied**

**Table 1. Prevalence of thyroid disorder in infertile and fertile women**

		Infertile		Fertile		Total		
		N	%	N	%	N	%	
Hypothyroidism	Yes	5	3.1%	9	5.6%	14	4.3%	$X^2=1.19$
	No	157	96.9%	153	94.4%	310	95.7%	$P\text{-value}=0.27$ $OR=0.54$ $95\%CI (0.14 \text{ to } 1.85)$
Total		162	100.0%	162	100.0%	324	100.0%	

\* $X^2$  – Chi-Square value, C.I -Confidence Interval, OR- Odds Ratio

**Table 2. Means of thyroid function test parameters in infertile and fertile women**

Parameter	Group of women		P-value
	Infertile (Mean± S.D)	Fertile (Mean± S.D)	
T3	2.2 ± 0.5	2.4 ± 0.5	0.147
T4	1.5 ± 1.1	1.3 ± 0.7	0.107
TSH	2.3 ± 1.6	2.4 ± 1.7	0.601

**Table 3. Contributing factors associated with thyroid disorders**

		Fertility of women with hypothyroidism				P-value	(95% C.I of OR)	
		Infertile		Fertile				Total
		N	%	N	%			
Age	<20	0	0.0%	0	0.0%	0	0.0%	$X^2=2.12$ <b>.346</b>
	20-24	0	0.0%	0	0.0%	0	0.0%	
	25-29	0	0.0%	1	11.1%	1	7.1%	
	30-34	5	100.0%	6	66.7%	11	78.6%	
	35-39	0	0.0%	2	22.2%	2	14.3%	
	>40	0	0.0%	0	0.0%	0	0.0%	
Ethnicity	Ikwerre	0	0.0%	1	11.1%	1	7.1%	$X^2=0.752$ <b>.861</b>
	Igbo	3	60.0%	5	55.6%	8	57.1%	
	Ijaw	1	20.0%	2	22.2%	3	21.4%	
	Others	1	20.0%	1	11.1%	2	14.3%	
Social class	1	0	0.0%	5	55.6%	5	35.7%	$X^2=2.24$ <b>.134*</b> 0.07**(0.003 - 1.74)
	2 or 3	5	100.0%	4	44.4%	9	64.3%	
Family history of T.D	Yes	0	0.0%	0	0.0%	0	0.0%	
	No	5	100.0%	9	100.0%	14	100.0%	
Iodine Intake	Adequate	0	0.0%	1	11.1%	1	7.1%	<b>.439</b>
	Inadequate	5	100.0%	8	88.9%	13	92.9%	
<b>Total</b>		<b>5</b>	<b>100.0%</b>	<b>9</b>	<b>100.0%</b>	<b>14</b>	<b>100.0%</b>	

\* Yates correction,  $X^2$  – Chi-Square value, C.I -Confidence Interval, OR- Odds Ratio

\*\*Adjusted OR (zero cell)

#### 4. DISCUSSION

The prevalence of thyroid disorders in infertile women in the study was found to be 3.1%, while for fertile women seeking contraception it was 5.6%. These were accounted for only by hypothyroidism, as there was no case of hyperthyroidism identified. Also, all the hypothyroid women in the study were found to have subclinical hypothyroidism rather than

clinical/overt hypothyroidism. This may suggest that there may be other factors accounting for anovulation in these women such as hyperprolactinaemia as shown by Bassey et al. [24]. Although the difference in prevalence between the two groups was not statistically significant, they were similar to findings by Poppe et al. [25], Agrawal et al. [26], as well as a study in the U.S.A [20]. The recorded prevalence of 3.1% in the infertile women in this study was

lower than the findings of Emokpae et al. [27] and Arojoki et al. [28], possibly because they included women with all forms of infertility in those studies. Studies on infertile women in Lahore-Pakistan [20] and India [11] recorded higher prevalence of thyroid disorders which may be due to their larger study populations and their geographical predisposition to iodine-insufficiency [29].

All the 324 women who took part in the study were Africans and of Nigerian descent. It was noticed that the prevalence of hypothyroidism among infertile and fertile women was highest in Igbo women. This finding was not statistically significant and was at variance with the findings of El-Bashir et al. [30] where there was a preponderance of Hausa/Fulani ethnic group, probably because it was conducted in Northern Nigeria but ours in the South-south part of Nigeria. Although studies have demonstrated race to be a predisposing factor to subclinical hypothyroidism especially being commoner in whites than blacks and Hispanics, opinion differs about the effect of race on subclinical hyperthyroidism [15,18] local data within Nigeria on the effect of ethnicity on thyroid disorders are sparse.

The mean age of participants in the study which was  $34.6 \pm 3.2$  years is similar to findings in Benin, Port Harcourt and Brussels [9,25,27]. Age is a known predisposing factor to thyroid disease even in women with infertility [15,30]. Thyroid disorder (hypothyroidism) in the infertile and fertile arms of this study was commonest in the 30-34 years age group probably because majority of the women were within this age group and though this was not statistically significant, it was similar to the findings of Agrawal et al. [25] and Emokpae et al. [27].

Iodine intake is a known major predisposing factor to the development of thyroid disorders, especially hypothyroidism [15,31]. Adequate iodine nutrition has been recognized and implemented in many parts of the world in the past century as a way of prevention of iodine deficiency disorders. This is a classic form of primordial prevention for avoidance of iodine deficiency, a known risk factor for hypothyroidism and other manifestations of iodine deficiency [32]. In order to ascertain the role played by this predisposing factor, this study tried to assess the main sources of dietary iodine in the infertile and fertile women in terms

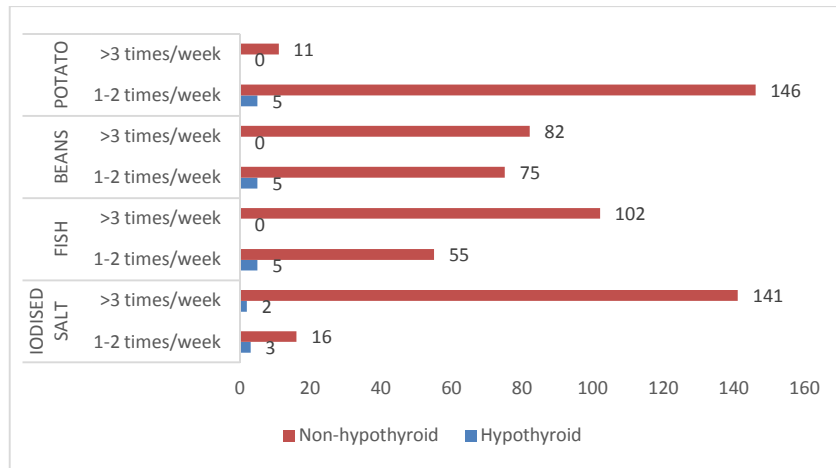
of iodized salt and common iodine-rich foods such as fish and beans using a modified food frequency questionnaire [18,33]. The study revealed that all (100%) of the hypothyroid infertile women and majority (88.9%) of hypothyroid fertile women had 'inadequate' dietary intake of iodine. This was similar to the findings of a large American study [18] and the findings of Teng et al. in China [18,31].

The study revealed that the prevalence of women with subclinical hypothyroidism who were unemployed was higher (60%) in infertile women compared to fertile women (44.4%). In addition, all (100%) hypothyroid infertile women and 44.4% of hypothyroid fertile women were of middle socioeconomic class. Although these were not statistically significant, a similar trend was noted between socioeconomic status and thyroid disorders in a study by Azizi et al. [32].

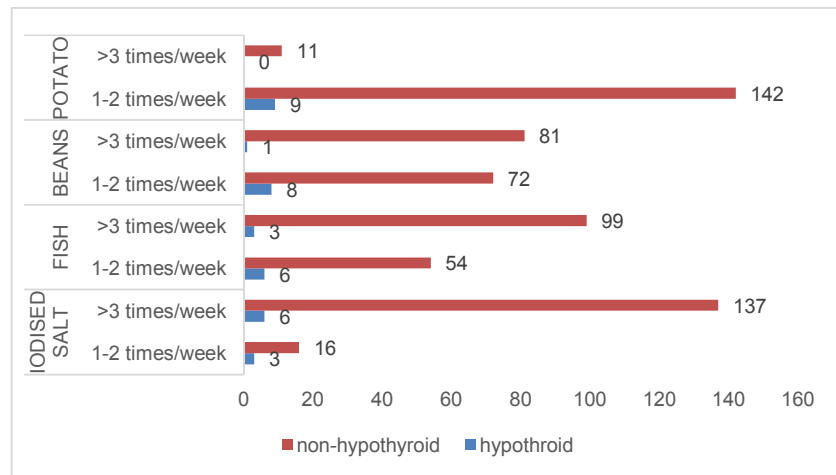
In infertile women who desire pregnancy with a family history of thyroid disease, it has been advocated they should have thyroid function assessment as part of their infertility work-up [9,34]. Maraka et al. suggested that treatment of subclinical hyperthyroidism with levothyronine may be beneficial in patients attempting assisted conception buttressing the reason for thyroid function test [34]. The study revealed that none of the women with hypothyroidism in both groups had a family history of thyroid disease, thus giving a negative correlation between family history and thyroid disease. This was similar to the findings of a study in Chennai – India [2].

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 and hyperthyroidism is mainly associated with menstrual disorders [11,35]. Hyperthyroidism (subclinical or overt) was not identified in either of the two groups of women in this study. This was similar to the findings of Agrawal et al. [26] but differed from the findings of a Port Harcourt study in which hyperthyroidism was noted among infertile women probably because the women recruited had infertility of varying aetiologies other than anovulation [9]. As such, this study did not reveal any correlation between hyperthyroidism and anovulatory infertility.

The limitations of this study include not assessing the effect of autoimmunity and hyperprolactinaemia on infertility.



**Fig. 3a. Frequency of consumption of iodine-rich foods in 'infertile' arm**



**Fig. 3b. Frequency of consumption of iodine-rich foods in 'fertile' arm**

**5. CONCLUSION**

Subclinical hypothyroidism was the only identified thyroid disorder in both groups of women. When compared, the difference in prevalence of thyroid disorders in both study groups was not statistically significant. Thyroid function testing may be of benefit in the management of women with anovulatory or unexplained infertility in order to exclude subclinical hypothyroidism. Sequel to this, appropriate counseling and treatment should be offered where necessary.

**CONSENT**

As per international standard guideline, patient's written consent has been collected and preserved by the author(s).

**ETHICAL APPROVAL**

Ethical approval for the conduct of the study was obtained from the ethics committee of the hospital (UPTH/ADM/90/S.11/VOL.XI/328).

**COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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