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Subclinical Hypothyroidism and Infertility at the Federal Teaching Hospital, Ido-Ekiti, Ekiti State, Nigeria

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Abstract
Background: *Infertility is a problem of global proportions. Reproductive failure has very far social implications on affected couples especially in Africa and other developing nations. Overt hypothyroidism is an accepted cause of female infertility but its milder form, subclinical hypothyroidism, has not been widely accepted as a contributing factor to disturbed reproductive function.*
Objective: *This case controlled study aims to determine the contribution of subclinical hypothyroidism to infertility at the Federal Teaching Hospital Ido-Ekiti.*
Method: *Thirty-three eligible women with infertility who presented for evaluation at the gynaecological clinic of Federal Teaching Hospital, Ido-Ekiti were matched in terms of age with a fertile control that was managed at the same period in the study centre. Fasting venous blood samples were obtained and analyzed for serum thyroid stimulating hormone and free thyroxine levels. Ethical clearance was obtained from the institution review board, data analysis was carried out using SPSS version 21 and statistical significance between variables was determined using independent t-test, Chi-square and Fisher's exact test as appropriate.*
Results: *All the women in the case and control groups were within the reproductive age group. The mean age of the infertile subjects was 35.3 ± 4.4 years while that of their fertile counterparts was 36 ± 4.6 years. The more frequent type of infertility was secondary (72.7%), mean duration of infertility was 3.2 ± 2.6 years. Less than one-third of the women in the two groups were obese, and the majority had normal menstrual pattern. The mean TSH and free T4 levels in the infertile subjects were 1.49 ± 0.9mIU/L and 1.16 ± 0.3ng/dl respectively; comparable values were obtained in the control group. The serum TSH and free T4 levels were not statistically different between the two groups (P=0.797). In women with infertility,*

the prevalence of subclinical hypothyroidism was 6.1% while a prevalence of 3% was observed in the control group (P=1.000). The two cases of subclinical hypothyroidism observed among the infertile group occurred in women with secondary infertility.

Conclusion: *It is concluded that subclinical hypothyroidism may not be a contributory factor to infertility as there is no statistical significant difference in the prevalence of subclinical hypothyroidism among infertile and fertile women at Federal Teaching Hospital, Ido-Ekiti.*

Keywords: *hypothyroidism, infertility, subclinical, overt.*

Introduction

Infertility is a complex disorder with significant medical, psychosocial, and economic impact, [1,2,] the diagnosis of infertility can be an assault on self-image, sexuality and relationship[3], the prevalence of infertility varies worldwide being highest in the so-called infertility belt of Africa[4,5]. Community based data suggest that up to 30% of couples in some parts of Nigeria may have proven difficulties in achieving a desired conception after two years of marriage without the use of contraceptives[6,7,8].

Thyroid hormones are essential for normal growth, sexual development and reproductive function[9]. Thyroid dysfunction are associated with a variety of changes in the reproductive functions; including delayed onset of puberty, menstrual disorders, anovulatory cycles, infertility and reproductive wastage when pregnancy is achieved[9]. Hypothyroidism is a common but subtle endocrinological problem that could affect women who present with ovulatory dysfunction resulting in infertility[10]. Its milder form, subclinical hypothyroidism, characterized by mildly elevated thyroid stimulating hormone (TSH) levels and normal free thyroxine (fT_4) levels; has also been implicated as a contributing factor to disturbed reproductive function[10]. Overt hypothyroidism describes an increase in serum TSH levels (generally >10mIU/L) and decrease in serum T_4 concentrations while mild or subclinical hypothyroidism is characterized by normal serum free thyroxine concentration with elevated serum TSH concentrations ranging between 4.5mIU/L and 10mIU/L[11]. The prevalence of clinical hypothyroidism in women of reproductive age varies between 2% and 4% and in this age group, autoimmune thyroid disease (e.g Hashimoto's thyroiditis) is the most common cause of hypothyroidism[12]. Other causes of hypothyroidism include congenital hypothyroidism, iodine deficiency, inflammation of the thyroid, overtreatment of hyperthyroidism, drugs (e.g amiodarone, interferon alpha, lithium, interleukin-2 etc) and iatrogenic causes like post surgical and post irradiation hypothyroidism [13,14,15].

Data on the relationship between subclinical thyroid dysfunction and infertility remain scarce as these subgroups of infertile patients pass unrecognized[9]. The period of infertility among women with subclinical hypothyroidism is significantly longer when compared with those who had normal levels of thyroid hormones[16]. Similarly, women with elevated serum TSH levels were observed to have lower pregnancy rate than those with normal circulating levels[17]. These findings suggest that early or mild thyroid failure (subclinical hypothyroidism) may have impact on female fertility. Hence, this comparative study was designed to determine the contribution of subclinical hypothyroidism to infertility in our environment

Sample Size Determination

The sample size was calculated based on the prevalence of subclinical hypothyroidism among infertile women found in a previous which was 12%, [18]. The prevalence of subclinical hypothyroidism among women in the reproductive age in the general population was estimated as 3%[19]. The sample size was therefore determined using the formula for comparative study as shown below:

$$n = \{(P_1 q_1) + (P_0 q_0)\} (Z\alpha/2 + Z\beta) / (P_1 - P_0)^2$$

Where:

n = required minimum sample size for each group

$Z\alpha$ = the standard normal deviate usually set at 1.96 which corresponds to the 95% confidence level.

$Z\beta$ = point of normal distribution corresponding to the statistical power of 80%

P_1 = prevalence of subclinical hypothyroidism among infertile women [18] (12%)

P_0 = prevalence of subclinical hypothyroidism among reproductive aged women in the general population (which is 3%)[19]

$q_1 = 1-P_1$

$q_0 = 1-P_0$

$n = \{(0.12 \times 0.88) + (0.03 \times 0.97)\} (1.96/2 + 0.8) / (0.12 - 0.03)^2 = 30$

An attrition rate of 10% was set, thus a minimum of 33 subjects and 33 controls were recruited.

Study Procedure

Women of reproductive age with primary or secondary infertility without a known history of thyroid disorder who presented at the gynecological outpatient clinic of Federal Teaching Hospital, Ido-Ekiti were recruited; the controls were the next consecutive healthy non-pregnant parous women without reproductive problem or thyroid disease. The diagnosis of infertility was based on the patient's history of inability to achieve conception after one year of regular and unprotected sexual intercourse without contraception. The cases and the controls were matched for age. The subjects who fulfilled the inclusion criteria were recruited after detailed history and thorough physical examination were conducted and a consent form had been signed.

A structured questionnaire was used to obtain relevant data from each subject, the body mass index of each subject was determined and the results of the serum TSH and free T4 concentrations were also recorded.

Reference values

The reference values for the thyroid hormone concentrations in this study are as follows:

- Serum free T4 → 0.76 – 2.24ng/dl
- Serum TSH → 0.5 – 4.5mIU/L

Result

This study involved population of women of reproductive age who had been married for at least one year with no obvious history of thyroid disease who presented with primary or secondary infertility and non-pregnant child-bearing parous women without history of infertility or thyroid disease who served as control. A total of 33 infertile women and 33 age-matched healthy non-pregnant parous women were recruited.

Table 1 shows the socio-demographic characteristics of the infertile women and the control group. All the studied subjects were within the reproductive age, the mean ages of the cases and controls were 35.3 ± 4.4 years and 36.0 ± 4.6 years respectively.

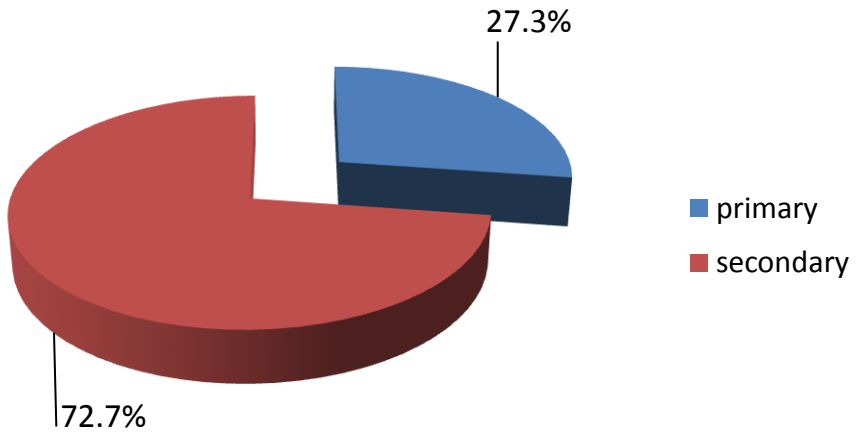
Table 1: Comparison of Socio-Demographic Features of Cases and Control

Variable	Infertile Women (n=33)%	Control (n=33)%	χ^2value	p value
Age(years)				
≤25	0(0.0%)	1(3.0%)	2.518*	0.695
26-30	5(15.2%)	2(6.1%)		
31-35	11(33.3%)	13(39.4%)		
36-40	12(36.3%)	11(33.3%)		
41-45	5(15.2%)	6(18.2%)		
Educational levels				
None	0(0.0%)	0(0.0%)	1.110*	0.796
Primary	3(9.1%	1(3.0%)		
Secondary	4(12.1%)	5(15.2%)		
Tertiary	26(78.8%)	27(81.8%)		
Religion				
Christianity	33(100.0%)	32(97.0%)	1.015*	1.000
Islam	0(0.0%)	1(3.0%)		

Tribe				
Yoruba	32(97.0%)	31(94.0%)	2.820*	1.000
Igbo	0(0.0%)	1(3.0%)		
Hausa	0(0.0%)	1(3.0%)		
Others	1(3.0%)	0(0.0%)		
Family type				
Monogamous	27(81.8%)	31(94.0%)	2.276*	0.258
Polygamous	6(18.2%)	2(6.0%)		
Occupation				
Student	1(3.0%)	0(0.0%)	2.608*	0.654
Unemployed	2(6.1%)	1(3.0%)		
Civil servant	20(60.6%)	25(75.8%)		
Artisan	2(6.1%)	1(3.0%)		
Trader	8(24.2%)	6(18.2%)		
Body Mass Index				
Underweight	0(0.0%)	0(0.0%)	2.218*	0.773
Normal	14(42.4%)	10(30.3%)		
Overweight	11(33.3%)	13(39.4%)		
Obese	8(24.2%)	10(30.3%)		

*Fisher's Exact Test

Figure 1: Types of infertility among study group



Women with primary infertility had a mean age of 34.0 ± 5.9 years, mean serum TSH and fT4 levels of 1.46 ± 0.72mIU/L and 1.07 ± 0.15ng/dl respectively and their infertility duration ranged from 1 to 11 years (mean=3.3 ± 3.5 years). Women with secondary infertility had mean age of 35.8 ± 3.6 years, mean serum TSH and fT4 levels of 1.50 ± 0.96mIU/L and 1.20 ± 0.28ng/dl respectively and their infertility period ranged from 1 to 9 years (mean=3.2 ± 2.5 years). The mean age, TSH, and fT4 of the case and control is as depicted in table 2

Table 2: The Mean Age and Mean Infertility Duration of Cases

VARIABLE	Primary Infertility (n=9) MEAN ± S.D	Secondary Infertility(n=24) MEAN ± S.D	Control	t-test	P value
Mean age (years)	34.0 ± 5.9	35.8 ± 3.6	36.0 ± 4.6	1.078	0.290
Mean infertility duration (years)	3.3 ± 3.1	3.2 ± 2.5	0.00	0.104	0.917
Serum TSH (mIU/L)	1.46 ± 0.72	1.50 ± 0.96	1.54 ± 0.8	0.259	0.797
Serum fT4 (ng/dl)	1.07 ± 0.15	1.20 ± 0.28	1.19 ± 0.3	0.387	0.700

Table 3 shows the menstrual pattern of the cases and controls. Majority of the women in the two groups had normal menstrual cycle (87.9% vs 84.8%, P=0.464).

Table 3: Menstrual Pattern of Cases and Controls

Menstrual Pattern	Infertile Women (n=33)%	Control (n=33)%	χ^2 value	P – value
Normal	29(87.9%)	28(84.8%)		
Oligomenorrhoea	1(3.0%)	3(9.1%)		
Polymenorrhoea	3(9.1%)	1(3.0%)	2.823*	0.464
Amenorrhoea	0(0.0%)	0(0.0%)		
Others	0(0.0%)	1(3.0%)		

*Fisher's Exact Test

The prevalence of subclinical hypothyroidism among the studied group is depicted in table 4.

Table 4: Proportion of Subclinical Hypothyroidism in Infertile and Fertile Women

	Infertile Women (cases) n=33	Fertile Women (controls) n=33	P value
Subclinical Hypothyroidism	2 (6.1%)	1 (3.0%)	1.000
Euthyroidism	31 (93.9%)	32 (97.0%)	

Discussion

Subclinical hypothyroidism is defined as serum TSH concentration above the statistically defined upper limit of the reference range when serum free T_4 (FT_4) concentration is within its reference range[17]. It is considered as the biochemical evidence of thyroid hormone deficiency in patients who have few or no apparent clinical features of hypothyroidism[13]. The reference value for serum TSH concentration in normal individual ranges between 0.45 and 4.5mIU/L,[20,21] asymptomatic subjects with values ranging between 4.5 and 10mIU/L are considered to have subclinical hypothyroidism[22]. More than three quarters of individuals with subclinical hypothyroidism have serum TSH concentrations between 5mIU/L and 10mIU/L[23] and this condition may progress to overt hypothyroidism in approximately 2-5% of cases annually[20].

In this study, the prevalence of subclinical hypothyroidism among women with infertility was 6.1%, this is less than 12% from Mascaren has et al study[18], although the prevalence of 3% observed in the control group is similar to earlier study[19]. The two cases of subclinical hypothyroidism observed among the infertile group occurred in women with secondary infertility and these women had normal menstrual pattern.

The mean age of the infertile women in this study was 35.3 ± 4.4 years. This is comparable to that of their fertile counterparts and similar to the mean age of 35 years found by Sule and colleagues[24]. The commoner type of infertility was secondary, the predominance of secondary infertility in this study agrees with findings from several studies in Sub-Saharan Africa. This is however different from the trend in the developed world where primary infertility is higher. This pattern seen in the developing countries has been attributed to high prevalence of sexually transmitted infections and inadequate treatment of such infections, complications of unsafe abortion and puerperal sepsis[11,25,26]. The mean duration of infertility observed in the studied group is shorter compared to many other studies,[11,27,28]. This may relate to level of literacy, earning power of these women and early treatment seeking behavior among them. It has been noted that Africa-Americans experience longer duration of infertility before presentation than Caucasians and this was said to correlate with the level of education and income[29]. There was no statistical significant difference in mean serum TSH levels of infertile women when compared to controls (P>0.05). Furthermore, it was observed that 6.1% of the studied infertile women were suffering from subclinical hypothyroidism which is less than the incidence of

hypothyroidism found among controls. The prevalence of hypothyroidism observed among the infertile women in this study is similar to 4.6% reported by Grassi *et al*[30] and 4% by Arojoki et al[31], but almost 10 fold higher than 0.67% of subclinical hypothyroidism observed by other workers[23]. This is however inconsistent with findings from several other studies where the prevalence of subclinical hypothyroidism was exceptionally high among the infertile group compared to control. In a study done by Dilruba, *et al*[32], the proportion of infertile women with subclinical hypothyroidism was 26.7% whereas none in the control group had subclinical hypothyroidism. Similarly, the prevalence of subclinical hypothyroidism among infertile women reported by Bals Pratsch, *et al* was 25%[33], Raber *et al* 34%[34], Biradar, *et al* 12%[35] and 11.8% by Rijal, *et al*[36]. The higher prevalence found in these quoted studies might be due to the fact that large population of infertile women especially when women with ovulatory dysfunction were recruited. In addition, some of these studies were conducted in iodine deficient zones where thyroid disorders are prevalent unlike the geographical zone of Ekiti, Nigeria.

The relatively low prevalence of subclinical hypothyroidism found in this study may support the conclusion of some authors that routine assays of TSH in infertile women with normal menstruation was not necessary in routine evaluation of infertile women, because only 2.48% of abnormal serum TSH was observed in a large study of infertile women[37]. In agreement with this statement, the only two infertile women with subclinical hypothyroidism in this study had normal menstrual pattern. The comparable prevalence of subclinical hypothyroidism observed among the case and control groups suggest that subclinical hypothyroidism may not be contributory to infertility among women evaluated in Federal Teaching Hospital, Ido-Ekiti.

Conclusion

This study has found that the prevalence of subclinical hypothyroidism among infertile women was comparable to their fertile counterparts. Although, a bit higher in the case group, it is not significantly different. This suggests that there may not be any association between subclinical hypothyroidism and infertility among women in Ekiti, though a larger population may need to be evaluated to for a more representative conclusion.

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