



Sub-clinical hypothyroidism in infertile Nigerian women with hyperprolactinaemia

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Summary: Studies on the impact of subclinical hypothyroidism in infertility are scarce and this seeks to determine the proportion of infertile Nigerian women with hyperprolactinaemia that had subclinical hypothyroidism. Serum prolactin and thyroid stimulating hormone were determined using ELECSYS 1010 auto analyzer. Two hundred infertile women were evaluated and 67(33.7%) had hyperprolactinaemia. Subclinical hypothyroidism was observed in 14.9% of women with hyperprolactinaemia, 4.5% and 10.5% of women with primary and secondary infertility, while hyperprolactinaemia was observed in 29.9% and 70.1% in primary and secondary infertility respectively. Mean levels of thyroid stimulating hormone and prolactin were higher in secondary infertility than primary infertility. Subclinical hypothyroidism and hyperprolactinaemia were higher in secondary infertility than primary infertility. The ratio of proportions between hypothyroidism and hyperprolactinaemia was 1:7.

Keywords: Sub clinical hypothyroidism, Hyperprolactinaemia, Primary infertility, Secondary infertility.

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INTRODUCTION

Infertility is a worldwide reproductive health issue and it is the commonest presenting complaint among gynaecological patients in Nigeria (Megafu, 1988; Otubu and Olarewaju, 1989). The causes which vary from one geographical area to another are wide and efficient treatment are also available (Razzak and Wais, 2002; Avasthi *et al.*, 2006). Thyroid dysfunction was reported to reduce the likelihood of conception and may affect pregnancy outcome (Akhter and Hassan, 2009). Subclinical hypothyroidism (SCH) has long been considered as an infertility factor as women with an elevated serum thyroid stimulating hormone (TSH) had lower pregnancy rate than those with normal circulating levels (Bohnet *et al.*, 1981). Grassi *et al.*(2001) observed that the mean duration of infertility was significantly longer in subjects with SCH compared with those who had normal levels of thyroid hormones. However no consensus has been reached regarding indication for treatment of SCH in infertile women (Poppe *et al.*2007). Hypothyroidism is

characterized by low serum level of thyroxine, because of this low level there is an increase secretion of thyrotropin releasing hormone (TRH), TRH then stimulates thyrotrophs and lactotrophs thereby increasing the levels of both thyroid stimulating hormone (TSH) and Prolactin (PRL) in some individuals (Cramer *et al.*,2003).

Hyperprolactinaemia has been reported to be common in patients with infertility in Nigeria (Emokpae, 1999; Emokpae *et al.*, 2005). In our previous report on infertile women, it was observed that a significant proportion of the subjects were observed to have high prolactin levels (Emokpae *et al.*, 2005). This present study was designed to evaluate the proportion of these women with hyperprolactinaemia who have abnormal TSH levels and to find out if there are differences in the incidence of TSH between primary and secondary infertility.

MATERIALS AND METHODS

The study was conducted at Aminu Kano Teaching Hospital, Kano, a referral tertiary hospital from January 2004 to December 2008. The patients gave

informed consent and the protocol was approved by the Ethics Committee of the hospital. This study is a cross sectional prospective study.

The subjects, who were consecutively recruited were investigated for infertility and were referred to the Chemical Pathology department for various hormonal assays during their first visit for infertility evaluation. Those patients with hyperprolactinaemia formed the study group while patients on treatment for thyroid disorders or hyperprolactinaemia were excluded from the study. The subjects were females who complained of inability to conceive despite regular unprotected sexual intercourse. They were grouped into primary and secondary infertility. Sociodemographic data and physical examination findings were obtained with the help of a structured questionnaire.

Laboratory determinations:

Blood specimen was obtained from the subjects in follicular phase of the menstrual cycle and was allowed to clot for 30-60minutes at room temperature. The serum was harvested after centrifugation at 3000rpm for 10minutes. The specimens were kept frozen at -20°C until analyzed. The analysis was done within 2 weeks of blood collection. Serum TSH and PRL were assayed using ELECSYS 1010 auto analyzer supplied by Roche, Germany. The principle of the assay is based on electrochemiluminescence immunoassay technique. All sera which gave higher values above the upper limit of the reference range (72-511mIU/mL) for prolactin were analyzed for TSH.

RESULTS

Two hundred infertile women were initially recruited for the study. Out of the 200 women, 67(33.5%) had hyperprolactinaemia, mean value 865 ± 68.9. The

ages of the subjects ranged from 25 to 43 years with a mean of 30.4years.

Of the 67 with hyperprolactinaemia, 20(29.9%) had primary infertility while 47(70.1%) had secondary infertility.

Table 1 shows clinical findings of women with primary and secondary infertility that had hyperprolactinaemia. Among the clinical findings observed in the patients were irregular menstruations, chronic pelvic pain, galactorrhoea, oligomenorrhoea, hirsutism and hyperthyroid features. The prevalence of irregular menstruation did not differ between primary and secondary infertility. The prevalence of galactorrhoea (25%;5/20), oligomenorrhoea (10%;2/20) and hirsutism (10%;2/20) were comparatively higher in primary than secondary infertility while chronic pelvic pain (21.3%;10/47) and hyperthyroid features (10.6%;5/47) were higher in secondary than primary infertility.

Table 2 shows the proportion of the studied subjects with subclinical thyroid disorders and prolactinaemia. In patients with primary infertility, the proportion with subclinical hypothyroidism was 15% (3/20) while 14.9% (7/47) was observed in secondary infertility. No patient with primary infertility had subclinical hyperthyroidism. However, 10.6% (5/47) of them with secondary infertility were observed to have subclinical hyperthyroidism. Subclinical thyroid disorders were observed in 15% (3/20) of primary and 25.5% (12/47) of secondary infertility.

Table 3 indicates serum TSH and PRL levels in primary and secondary infertility. In primary infertility, the mean TSH level was 2.4±2.5µIU/mL while the mean PRL level was 632±46.4mIU/mL. The mean TSH level in the 3 subjects with subclinical hypothyroidism was 4.9±1.8µIU/mL while PRL level was 618±50.2mIU/mL.

Table 1.
Clinical findings of hyperprolactinaemic women with primary and secondary infertility

Clinical findings	Primary infertility	Secondary infertility
Irregular menstruation	9(45%)	22(46.8%)
Chronic pelvic pain	2(10%)	10(21.3%)
Galactorrhoea	5(25%)	6(12.8%)
Oligomenorrhoea	2(10%)	3(6.4%)
Hirsutism	2(10%)	1(2.1%)
Hyperthyroid features	0(0%)	5(10.6%)
Total	20(100%)	47(100%)

Table 2.
Prevalence of sub-clinical thyroid disorders in women with prolactinaemia

Type of infertility	Scl. Hypothyroidism	Scl. Hyperthyroidism	Total thyroid Disorder	Hyper Prolactinemia
1 ⁰ (n=20)	15% (3/20)	0(0%)	15% (3/20)	29.9% (20/67)
2 ⁰ (n=47)	14.9% (7/47)	10.6% (5/47)	25.5 (12/47)	70.1% (47/67)
Total (n=67)	14.9% (10/67)	7.5% (5/67)	23.4% (15/67)	100% (67/67)

1⁰= primary, 2⁰= secondary, Scl.= subclinical

Table 3.

Serum TSH and prolactin levels in women with primary and secondary infertility (mean±SD)

Type of infertility	TSH level (reference range 0.27-0.7µIU/mL)	Prolactin level (reference Range 72-511mIU/mL)
Primary (n=20)	2.4±2.5	632±46.4
Hypothyroid (1 ⁰ , n=3)	4.9±1.8	618±50.2
Secondary (n=47)	3.9±3.4	824±68.2
Hypothyroid (2 ⁰ , n=7)	5.4±1.2	804±70.1

1⁰ = primary, 2⁰ = secondary

In secondary infertility, the mean TSH level was 3.9±3.4µIU/mL while the level in subclinical hypothyroidism was 5.4±1.2µIU/mL and mean PRL value was 824±68.2mIU/mL.

The mean TSH value was higher in secondary infertility than in primary infertility. This was not however statistically significant ($p>0.05$). The mean PRL level in secondary infertility was higher ($p<0.001$) than in primary infertility. The ratio of proportions between hyperprolactinaemia and hypothyroidism was 7:1; in other words in every seven women with hyperprolactinaemia one had hypothyroidism.

DISCUSSION

This study evaluated the proportion of infertile women with hyperprolactinaemia who had SCH and observed that 14.9% of the subjects had SCH and 7.5% had subclinical hyperthyroidism. Subclinical thyroid disorders were observed in 23.4% of the subjects. The observed SCH is higher than those reported elsewhere even though this study was done on patients with hyperprolactinaemia. Shalev *et al.* (1994) observed 0.67% of SCH among 444 infertile women with ovulatory dysfunction (Grassi *et al.*, 2001), while 4.6% SCH was reported in a group of 129 infertile women and Arojoki *et al.* (2000) found 4% SCH among women presenting for the first time especially in those with an ovulatory infertility. Some authors are of the opinion that SCH should not be treated while others support the normalization of plasma TSH levels. Those that were against treatment based their argument on the report observed in women with normal menstruation. It was reported that routine assays of TSH and PRL in infertile women with normal menstruation was not necessary, because only 2.48% of abnormal serum TSH and 1.77% of hyperprolactinaemia was observed in a large study of infertile women (Olivar *et al.*, 2003). Others considered SCH as an infertility factor by itself since 11 of 20 women with SCH were treated and the treatment normalized the mid-progesterone secretion and some of the women became pregnant (Bohnet *et al.* 1981). In the same vein, a positive correlation was observed between basal TSH, LH and testosterone concentration in the

early follicular phase with the women with elevated TSH had a lowering pregnancy rate compared with control group. From our study, it was observed that 4.5% of patients with primary infertility and 10.5% of patients with secondary infertility who had hyperprolactinaemia also had subclinical hypothyroidism. Subclinical hypothyroidism has also been implicated in infertility in some European countries (Raber *et al.*, 2003; Poppe and Velkeniers, 2003). A large study of thyroid hormones assessment in infertile women in Nigeria may reveal the true burden of this disorder in this group of subjects. We observed a higher proportion of subclinical hypothyroidism in secondary than primary infertility. This was however consistent with that of Akhter and Hassan (2009).

Hyperprolactinaemia due to abnormal thyroid hormone secretions often lead to delay in luteinizing hormone response and inadequate corpus luteum (Longcope *et al.*, 1990). The sensitivity of ovaries to thyroid hormones could be explained by the presence of hormone receptors in human oocytes (Poppe *et al.*, 2007). Thyroid hormones can act in conjunction with FSH-mediated LH/hCG receptors to stimulate granulosa cells leading to the secretion of progesterone and abnormal TSH levels has been reported in women who produced oocytes that could not be fertilized among patients undergoing in vitro fertilization (Cecconi *et al.*, 1999; Cramer *et al.*, 2003). Hypothyroidism can also impact on fertility by changing the peripheral metabolism of estrogen and by reducing steroid hormone binding globulin secretion (Poppe *et al.*, 2007).

The observation of 67(33.4%) hyperprolactinaemia in infertile women is in agreement with other studies elsewhere (Kuku, 1995; Imade *et al.*, 1998; Audu *et al.*, 2003). Hyperprolactinaemia is the commonest biochemical abnormality observed in infertility (Emokpae *et al.*, 2005). The proportion of the women with primary infertility that had hyperprolactinaemia was 10% as against 43% observed by Akhter and Hassan, (2009). The 23.5% of secondary infertility observed in this study is consistent with 21% reported in Maiduguri (Audu *et al.*, 2003; 26% in Lagos (Kuku, 1995) and 21% in Bangladesh (Akhter and Hassan, 2009) but higher than 3.2% observed in Ilorin (Akande *et al.*, 2009).

Hyperprolactinaemia is often associated with menstrual irregularities particularly secondary amenorrhoea. In India and Bangladesh, the opposite is the case, where prevalence of hyperprolactinaemia was reported to be higher in primary than secondary infertility (Avasthi *et al.*, 2006; Akhter and Hassan, 2009).

In conclusion, subclinical hypothyroidism was observed in women with hyperprolactinaemia and the occurrence of subclinical hypothyroidism with ratio of proportion 7:1 underscores the need to assay TSH in selected patients with hyperprolactinaemia.

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