



HYPERPROLACTINAEMIA – NEED FOR AN EARLY ENDOCRINOLOGY REVIEW IN INFERTILITY ASSESSMENTS

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Abstract:

Hyperprolactinaemia, a frequent cause of female infertility, presents with galactorrhoea or interference with menstrual cycles leading to primary or secondary amenorrhoea. It could, also, be asymptomatic. The objective of this report is to draw attention to this treatable cause of infertility which when asymptomatic may cause unnecessary delay in definitive infertility treatment. Two cases of hyperprolactinaemia were managed in Abia State University Teaching Hospital (ABSUTH), Aba, with favorable outcome after variable delays before treatment. One of the women had no symptoms of hyperprolactinaemia while the second presented with the nonspecific symptoms due to mass effect of prolactinoma. In conclusion, if male factor for infertility and structural/anatomic disorders in female are excluded, hypothalamic-pituitary-ovarian axis should be assessed early in all infertility cases. Early endocrinology review is, therefore, important in the evaluation of female infertility.

Key words: hyperprolactinaemia, female infertility, endocrinology review.

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Background:

Hyperprolactinaemia causes hypogonadotropic hypogonadism in both men and female by inhibition of the release of the hypothalamic gonadotrophin releasing hormone [1.] (GHRH). It is the most common endocrine disorder of the hypothalamic - pituitary axis. Not all patients with hyperprolactinaemia are symptomatic or are concerned by their symptoms and may remain undiagnosed [2.]. In their study in Nigeria, Idris AI et al noted that a quarter of their participants that have hyperprolactinaemia did not have symptoms and signs suggestive of hyperprolactinaemia [3.]. Contrary to the report in North-west Nigeria that hormonal factors are infrequent cause of female infertility in sub-saharan Africa compared to tubal disease which

is mostly secondary to sexually transmitted disease [4.], a study in North Eastern region of Nigeria showed an increase in the trend of hyperprolactinaemia among infertile females where prevalence of 31.7% has been reported [5.]

It has been noted that there is a higher incidence of hyperprolactinaemia among infertile women [6.] such that when determination of serum prolactin is done at an early stage of infertility Workup it is cost effective with better outcome. Kredentser JV et al in another report noted that hyperprolactinaemia is a common finding in an infertile population [7.]. Prolactinoma account for 35 - 40% of functioning pituitary tumors and are the most frequent cause of chronic hyperprolactinaemia [8.]. When a pituitary tumor

is present, a patient often presents with endocrine dysfunction in addition to pressure symptoms (mass effects) such as headache, visual field defects or cranial nerve deficits. Prolactinomas, which can be micro- or macro-prolactinoma (less than 10mm or more than 10mm respectively), can be successfully treated with dopamine agonist drugs as first line treatment with significant tumor shrinkage, normalization of prolactin secretion and gonadal function[9.]. Currently, the most commonly used dopamine agonists for treatment of hyperprolactinaemia are bromocriptine, cabergoline, pergolide and quinagolide

Two cases of women managed in a tertiary institution in Nigeria are described here to draw attention to the need to involve the endocrinologist and measure the prolactin level of infertile women early in their diagnostic Workup since a significant number of infertile women have been found to have hyperprolactinaemia with or without symptoms. It, also, highlights the cost effectiveness of such measure as it prevents delays in commencing definitive management. Approval was obtained from the Health Research Ethics Committee of ABSUTH and consent was obtained from the patients to use their clinical details.

Case Description:

Case 1

A 25 year old lady presented at the medical outpatient clinic (MOPC) barely 4 months after her marriage on account of a febrile illness. While interacting with the medical officer, she expressed worry and concern that she has not conceived after 4 months of living and having unprotected sexual intercourse with her husband. As expected, she was just reassured. About seven weeks later, she was seen again in the MOPC where she insisted on being investigated for subfertility/infertility. A medical officer in the clinic obliged her and checked her hormone profile; result of which is shown below:

Test	Result	Normal range
Luteinizing hormone, LH	6.16mIU/ml	1 - 19
Follicle stimulating hormone, FSH	4.13mIU/ml	2 - 12
Prolactin	47.31ng/ml	1 - 23
Progesterone	5.58ng/ml	2 - 28
Estradiol, E2	112.54pg/ml	48 - 172

She was, subsequently, referred to the endocrine clinic for review and treatment. She gave no history of headache or visual disturbances, milk secretion from her nipples or menstrual disturbances. She gave no history of use of metoclopramide, domperidone, neuroleptic drugs (psychiatric medications), antidepressants or substance abuse. Her thyroid function and renal function tests were normal. Her general and systemic examinations were essentially normal. She was placed on tablet bromocriptine 2.5mg twice daily and by the second month of commencing treatment, she became pregnant and had a baby girl.

Case 2

Mrs JZ, a 47 year old teacher who had been married for 15 years, was referred to the MOPC on account of a nonspecific headache which has lasted for more than 4 years and which in the last couple of months has been associated with visual disturbances. The headache has been of insidious onset, generalized, mild - moderate, not associated with neck stiffness, fits or vomiting. She gave a history of use of herbal remedies in the past for primary infertility and, because she presented to the endocrine unit on their MOPC day, part of her workup investigations was determination of her hormonal profile. Her general and systemic examinations were essentially normal. Hormonal profile of Mrs JZ is shown below:

Test	Result	Normal Range
Luteinizing hormone, LH	7.65mIU/ml	1 - 19
Follicle stimulating hormone, FSH	3.80mIU/ml	2 - 12
Prolactin	69.72ng/ml	1 - 23
Progesterone	9.86ng/ml	2 - 28
Estradiol, E2	50.85pg/ml	48 - 172

A Magnetic Resonance Imaging (MRI) scan of her brain done later showed a pituitary adenoma measuring about 1.3cm and a diagnosis of macro-prolactinoma was considered in view of her raised prolactin level. She was placed on tablet bromocriptine 2.5mg twice daily and she achieved pregnancy between the 4th and 5th month of her treatment. Her other symptoms (headache and visual disturbances) showed remarkable improvement.

Discussion:

Hyperprolactinaemia causes hypogonadism in both sexes, and, in females, it presents with galactorrhea, decreased fertility, menstrual

disturbances, recurrent abortions, hirsutism, osteopenia and or combinations of these [10.][11.][12.][13.]. The index patient in this report (case 1) did not have symptoms of hyperprolactinaemia except subfertility, therefore, could have belonged to the 25% hyperprolactinaemic infertile women noted in the Zaria³ report who were symptomless.

The pituitary gland tonically releases prolactin. There is a Pituitary Inhibitory Factor (PIF), believed to be dopamine, which is produced by the hypothalamus and released into the portal venous system to reach the pituitary gland where it acts on the D2 receptors to prevent unrestrained release of prolactin by the adenohypophysis (anterior pituitary gland)[14.]. The causes of raised prolactin levels (hyperprolactinaemia) include physiological causes (nipple stimulation, stress, coitus, pregnancy), pathological causes (prolactinomas, craniopharyngiomas, any pituitary or hypothalamic tumors that compress the pituitary stalk preventing dopamine from reaching the pituitary gland), idiopathic hypersecretion of prolactin, primary hypothyroidism, pharmacological causes (phenothiazines, butyrophenones, cimetidine and methyldopa), polycystic ovary syndrome, renal and liver failure[15.]. The aetiology of the hyperprolactinaemia in the first index case is not known as the patient was lost to follow up as soon as she achieved conception while in the second case, the cause was macroprolactinoma

Hyperprolactinaemia in females suppress the release of GNRH by the hypothalamus leading to decreased follicle stimulating hormone (FSH) and luteinizing hormone (LH), and thus secondary hypogonadism and infertility. In a study conducted in southwestern Nigeria [16.] the causes of female infertility included fallopian tubal diseases (39.5%), uterine factor including myoma (30%), ovarian/ovulation factor (13%), pelvic infection disease (5.5%), cervical factor (3%), endometriosis (2.5%) and increasing age of women due to decreasing number and quality of ova. Hyperprolactinaemia was not recognized in that southwestern Nigerian study as a cause of female infertility. This southwestern Nigerian study contrasts with the findings of the Zaria³ study where 25% of the infertile women that participated had hyperprolactinaemia. As hyperprolactinaemia is being recognized as a significant cause of female infertility, it is cost effective to exclude it early in the workup of female infertility. The early involvement of the endocrinologist in the index first case made all the difference in the outcome and cost

effectiveness of the management. The index case (case 1) did not wait for one year of regular unprotected sexual intercourse as recommended by most infertility treatment protocol before she was found to have hyperprolactinaemia

Prolactinomas are benign neoplasms of the pituitary gland, the most common of the hormone-secreting pituitary tumors, accounting for about 40% of all pituitary tumors. Suprasellar extension of pituitary adenoma often compresses the optic chiasm and classically presents with bitemporal hemianopia. Visual field defects are present in 35% of patients with macroprolactinoma[17.]. The second case in this report had macroprolactinoma that presented with the symptoms of pressure/mass effects (headache and visual disturbances). If her prolactin level had been determined years before presentation, she would have been found to have hyperprolactinaemia and saved the huge cost and burden of living with primary infertility.

Finally, it is important to highlight that the readily available dopamine agonist (bromocriptine) is efficacious, safe and affordable. It is, therefore, used in resource-constrained centres as the first line treatment choice in hyperprolactinaemia.

Conclusion:

Hyperprolactinaemia, except from the physiological causes, is a cause of female infertility. Involving the endocrinologist early in the investigation and management of couple infertility could make a lot of differences in their outcome. This case report does not support most practitioners who would start investigating if the woman does not conceive after a period of one year as individual circumstances differ. The report, therefore, recommend that couples should generally be seen and investigated whenever they think they have a problem, advanced woman age (more than 37 years), previous surgery or irregular menstrual cycles with timely involvement of the endocrinologists.

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