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Hyperprolactinemia as a cause of female primary infertility and its prevalence in Gezira State, Central Sudan

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ABSTRACT

Background: Hyperprolactinemia is a condition of elevated serum prolactin. Prolactin is a 198-amino acid protein (23-kD) produced in the lactotrophs cells of the anterior pituitary gland. Hyperprolactinemia is the most common hypothalamo-pitiutary disorder; it can also occur secondary to use of some drugs, chronic illnesses like hypothyroidism, chronic liver and kidney disease, stress and neurogenic disorders. Idiopathic Hyperprolactinemia refers to elevation of serum prolactin in the absence of the above conditions.

Objective: The aim of this study is to explain scientifically hyperprolactinemia as a cause of female primary infertility and its prevalence in Gezira State, Central Sudan.

Method: Serum prolactin, FSH and LH levels were estimated using commercially specific enzyme immunoassay (EIA) technique in serum from 200 women (150 primary infertile and 50 fertile non-pregnant and non-lactating) attending Wad Medani teaching hospital in Wad Medani city, Central Sudan, from 2011 till 2013.

Results: Hyperprolactinemia was found in 33.3%, irregular menstrual cycle 66%, amenorrhea 6.7%, oligomenorrhoea 59.3%, normal menorrhea (33,3%) and galactorrhoea 3.3% of primary infertile women.

Conclusion: The prevalence of hyperprolactinemia was about one-third of primary infertile women in Gezira State (Central Sudan). The main aetiology of primary infertility was anovulatory cycle due to high level of prolactin.

Keywords: Hyperprolactinemia- female primary infertility- Gezira State

INTRODUCTION

Prolactin is a peptide hormone synthesized by lactotropes of the anterior pituitary gland. Lactotrope function is a primarily regulated by thyrotropin-releasing hormone (TRH) and dopamine, which enhance and inhibit respectively, the synthesis and secretion of prolactin. The most well recognized physiological effect of prolactin is to initiate and support lactation. Bromocriptine, a dopamine agonist is used to inhibit prolactin release in hyperprolactinemia, a major cause of infertility (Bayliss, 2003).

Hyperprolactinemia is characterized by increased production of prolactin, often leading to reproductive dysfunction and galactorrhoea (Biller, 1999). It is the most common endocrine disorder of the hypothalamic-pituitary axis. A prolactinoma is the most common cause of chronic hyperprolactinemia once pregnancy, primary hypothyroidism, and drugs that elevate serum prolactin levels have been excluded Patient can present with hypogonadism, infertility, galactorrhoea, osteopenia and mass effects of the tumor. When hyperprolactinemia is confirmed, a cause

for the disorder needs to be sought. This involves a careful history and examination, followed by laboratory tests and diagnostic imaging of the sella turcica (Mah and Webster, 2002).

Hyperprolactinemia may occur due to physiological, pharmacological, or pathological causes. The most relevant physiological causes of the disorder are pregnancy and breastfeeding. Drug induced hyperprolactinemia may be caused by neuroleptics, tricyclic antidepressants, some antihypertensive drugs, gastrointestinal-acting drugs and oral contraceptives, among others (Molitch, 2005). Prolactinomas, i.e., pituitary adenomas that express and secrete prolactin to variable degrees, are the main pathological cause of hyperprolactinemia (Casanueva *et al*., 2006).

The clinical features of hyperprolactinemia are shortened luteal phase, oligomenorrhoea, amenorrhoea and galactorrhoea. Mild hyperprolactinemia can cause infertility even when there is no abnormality in the menstrual cycle. Women with amenorrhoea due to hyperprolactinemia have lower bone mineral density BMD (Wing-bun, 2008).

Hyperprolactinemia affecting about one-third of infertile women (Rebar, 1997). It has been suggested that hypogonadism seen in hyperprolactinemic women is due to high circulating levels of prolactin interfering with the action of the gonadotrophin at the ovarian level and impaired gonadal steroid secretion, which in turn alters positive feedback effects at the hypothalamic and pituitary levels. This leads to lack of gonadotrophin cyclicity and to infertility (Thorner and Besser 1978). In a study performed in Sudan the hyperprolactinaemic patients were mostly from Central Sudan (Sinar, White Nile and Gezira region + Khartoum); 57% (Satti, 2007).

Serum prolactin, FSH and LH levels has been estimated by using commercially specific enzyme immunoassay (EIA) kits, the procedure for hormonal estimation has been followed as given in the EIA kits (Kalsum and Jalali, 2002).

The diagnostic evaluation first requires exclusion of other causes of hyperprolactinemia, such as pregnancy, primary hypothyroidism and numerous medications. The second step in the diagnostic evaluation is to perform a head scan, preferably a Magnetic Resonance Imaging (MRI) (Biller, 1999).

Dopamine agonists are the treatment of choice for the majority of hyperprolactinemic women wishing to conceive. Cabergoline has been shown to be more effective and better tolerated than bromocriptine. (Mah and Webster, 2002)**.**

MATERIALS AND METHODS

Five ml of peripheral venous blood were collected from infertile women patients of the study population by venipuncture. Blood samples were placed in plain containers and allowed to clot at room temperature before centrifugation for three minutes at 3000 rpm. Serum separated and stored in an Eppendorf tubes at -20°C until analyzed for reproductive function test. Blood specimens also collected from fertile non-pregnant and non-lactating women with no past history of hypothyroidism or depression.

Collected samples were matched with age, tribes, menstrual cycle, menorrhoea and galactorrhoea. Patients were categorized according to the stock of Sudanese tribes into 9 groups, which represent all the ethnic groups of Sudanese.

For the determination of serum Prolactin, FSH and L.H levels, enzyme immunoassay (EIA) technique used. Serum and standards into 200 tubes. Then working suspension of Magnetic

Antibody, Wash Buffer, diluted Enzyme Labelled Antibody, Substrate and Stop Buffer were added to each tubes at room temperature. Each assay includes a calibration (six) and substrate blank. Finally the colored products were read using spectrophotometer (BioSystems).

RESULTS

A total of 200 women, of whom 150 (75%) were infertile taken as case group and 50 (25%) were fertile non-pregnant and non-lactating women taken as control group. The initial finding revealed that 50 (33.3%) out of 150 infertile women were hyperprolactinemic and 100 (66.7%) were normoprol-actinemic. Menstrual cycle was devided into two types; regular and irregular menstrual cycle. The regular were 50 (33.3%) and the irregular were 100 (66.7 %) infertile women (Table 1).

Table 1: Frequency and Percent of the study group, prolactinemia in the infertile group and the regularity of the menstrual cycle in the case group.

Samples		Frequency	Percent
Study group:	Case	150	75.0
	Control	50	25.0
	Total	200	100.0
Prolactin:	Hyperprolactinemia	50	33.3
	Normal	100	66.7
	Total	150	100
Menstrual Cycle:	Regular	50	33.3
	Irregular	100	66.7
	Total	150	100.0

Prolactin, FSH and LH levels of women patients were high significant compared to Control (p = 0.000, 0.001, and 0.000 respectively) (Table 2).

Table 2: Group Statistics of samples by means, Std. Deviations and *p*. value.

Samples		N	Mean	Std. Deviations	*p*. value
Prolactin level **mU/L**	Case	150	428.85	361.818	.000
	Control	50	201.48	91.363	
FSH level **mU/L**	Case	150	18.1800	24.54364	.001
	Control	50	10.6800	4.83373	
LH level **mU/L**	Case	150	18.0200	21.24844	.000
	Control	50	7.5800	3.16930	

The mean-age of the infertile women was 30.91 ± 6.424 (minimum 18 and maximum 44 years). They were classified into two age groups; 16-30 (50.7%) and 31-45 (49.3%). Prolactin, FSH and LH levels of age groups were decreased significant p=0. 845, 0.333, and 0.02) respectively.

All the women patients were distributed in Sudanese tribes from high to low frequencies include; Gaalieen (28%), Rufaieen (18.7%), Kwahla (10%), Shigea (9.3%), Augaylieen (9.3%), Shukrea (6.7%), Bataheen (6.7%), Western (6%), and Danagla (5.3%) (Fig. 1).

Highly significant Prolactin, FSH and LH levels were observed in women with irregular menstrual cycle (*p*=0.000, 0.000, and 0. 000) respectively, (Table 3).

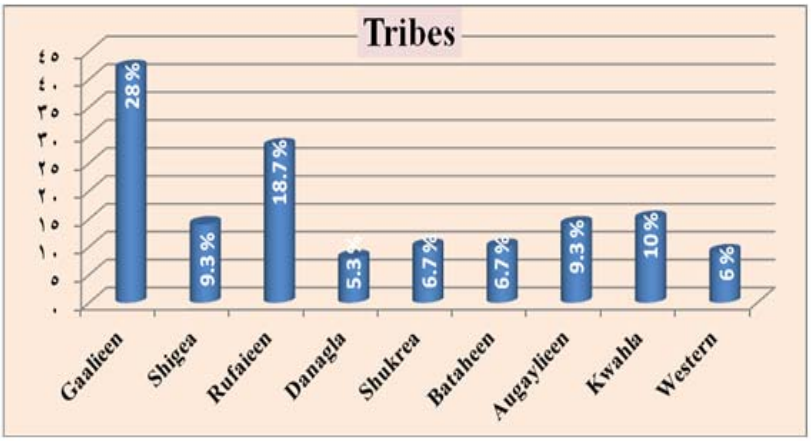

Fig. 1: Frequency and percent of Tribes.

Table 3: Group Statistics of Menstrual Cycle by mean, Std. Deviations and p. value.

Menstrual Cycle		N	Mean	Std. Deviations	*p.* value
Prolactin level **mU/L**	Regular	50	306.34	168.114	0.000
	Irregular	100	490.10	414.332	
FSH level **mU/L**	Regular	50	10.1200	7.72127	0.000
	Irregular	100	22.2100	28.77334	
LH level **mU/L**	Regular	50	7.6400	4.32251	0.000
	Irregular	100	23.2100	24.26216	

Menorrhea classified- according to last menstrual period- into four groups; Oligo menorrhea (59.3%), Amenorrhea (6.7%), Normal menorrhea (33.3%), and Short menorrhea (0.7%) (Fig. 2).

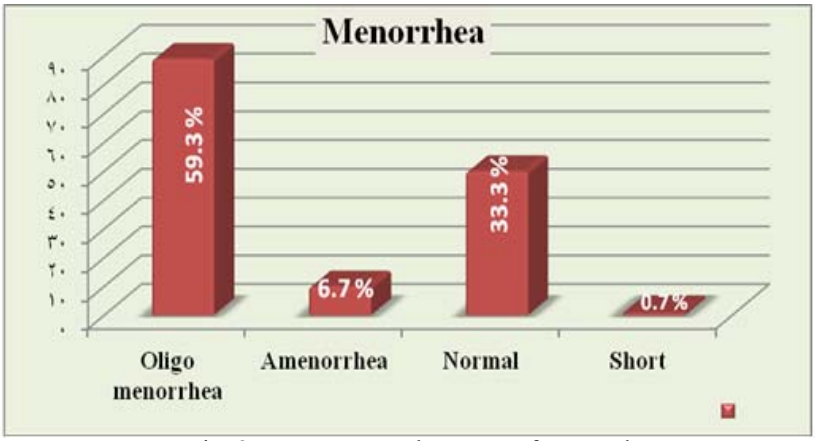

Fig. 2: Frequency and Percent of Menorrhoea.

Galactorrhoea was estimated by self testing (questionnaire). The infertile women with galactorrhoea were 5 (3.3%) and whom without galactorrhoea were 145 (96.7%).

Doubtless resident of husband plays very important role for each couples seeking to have a baby. The frequency of infertile women whom their husbands were abroad were 3 (2.0%) and whom their husbands were residents were 147 (98.0%).

Decreased significant of Prolactin, FSH and LH levels was found in Husband abroad (p=0.492, 0.930 and 0.586) respectively.

DISCUSION

Serum LH, FSH and prolactin levels were estimated by using commercially specific enzyme immunoassay (EIA) kits, the procedure for hormonal estimation was followed as given in the EIA kits (Kalsum and Jalai, 2002). The diagnostic evaluation first requires exclusion of other causes of hyperprolactinemia, such as pregnancy, primary hypothyroidism and numerous medications. The second step in the diagnostic evaluation is to perform a head scan, preferably a Magnetic Resonance Imaging (MRI). This is essential in order to exclude a prolactinoma which would require surgery (Biller, 1999). In this study, a total of 200 women, of whom 150 (75%) were infertile taken as cases and 50 (25%) were fertile non-pregnant and non-lactating women taken as control. The initial finding revealed that 50 (33.3%) out of 150 infertile women were hyperprolactinemic and 100 (66.7%) were normoprolactinemic. This prevalence agree with study performed showed that hyperprolactinemia is a common problem in reproductive dysfunction affecting about one-third of infertile women (Rebar, 1997, Thorner and Besser 1978)**.**

Highly significant increase in serum prolactin, FSH and LH levels (P=0.000, 0.001 and 0.000) were observed in the present study and this agree with hyperprolactinemia lead to the high circulating levels of prolactin interfering with the action of the gonadotrophins at the ovarian level and impairing normal gonadal steroid secretion, which in turn alters positive feedback effects at the hypothalamic and pituitary levels. This leads to lack of gonadotrophin cyclicity and to infertility (Yamaguchi *et al*., 1991). In study performed in Gezira State (Central Sudan) declare that the main aetiology of female primary infertility was anovulation due to high level of prolactin (Osman, 2010). Female patients were in the age 16 to 45 years at the time of study. It is well known that age plays an important role in female infertility, however, in this study, the correlation between age and prolactin level was decreased significant (P=0.011) and strong correlation (r=1.094). This may be due to all females have been already diagnosed infertile. In spite of female patients were from different tribes from different parts of Sudan, 28% of them were from Jaalieen tribe, and this did not indicate that there was high rate of infertility. This ratio may be due to the wide prevalence of tribes belong to the Northern Sudan, in addition to percentage of distribution throughout Gezira state. The irregular cycle was 100 (66.7%) out of 150 (100%). Prolactin, FSH and LH levels were highly significant *p.* value = 0.000, 0.000 and 0.000 respectively and this indicate that the irregular cycle was one of the clinical features of hyperprolactinemia. Menorrhoea was classified- according to last menstrual period- into four groups; Oligo menorrhea (59.3%), Amenorrhea (6.7%), Normal menorrhea (33.3%), and Short menorrhea (0.7%). The *p.* value of Galactorrhoea for Prolactin and FSH levels were decreased significant (p =0. 313, 0. 086) respectively, but for LH were high significant (p=0.000).

CONCLUSION

In conclusion, the present study revealed that in different groups of hyperprolactinemic women, an increase in serum Prolctin level and variation in other hormonal levels were observed.

The main aetiology of primary infertility was anovulatory cycle due to Hyperprolactinemia which represent a common problem in reproductive dysfunction affecting about one-third of infertile women in Gezira State (Central Sudan). Hyperprolactinemia lead to the high circulating levels of prolactin and hypogonadism which lead to lack of

gonadotrophin cyclicity and to infertility. The clinical features can range from irregular cycle, to oligomenorrhoea, to amenorrhoea and galactorrhoea. Even mild hyperprolactinemia can cause infertility even when there was no abnormality in the menstrual cycle.

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ARABIC SUMMARY

إرتفاع مستوى هرمون البرولاكتين كسبب للعقم الأولي عند النساء وإنتشاره في ولاية الجزيرة - وسط السودان

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يمكن وصف فرط بروﻻكتين الدم بأنه حالة إرتفاع مستوى هرمون البروﻻكتين في مصل الدم عن المدى الطبيعي. البروﻻكتين هو بروتين الحمض الأميني 198 (23-kD) والذي ينتج في خلايا (Lactotrophs) للفص الأمامي من الغدة النخامية. فرط بروﻻكتين الدم يمثل الإضطراب الأكثر شيوعا للغدة النخامية، ويمكن أن يحدث أيضاً بطريقة ثانوية لإستخدام بعض الأدوية والأمراض المزمنة مثل إنخفاض مستوى هرمونات الغدة الدرقية (T_3) و (T_4) وأمرض الكبد المزمنة وأمرض الكلى المزمنة، والإجهاد والاضطرابات العصبية ويكون فرط بروﻻكتين الدم لأسباب مجهولة عند غياب الحالات المذكورة أعلاه .

الهدف من هذه الدراسة هو توضيح فرط بروﻻكتين الدم علميا كسبب للعقم الأولي عند النساء وانتشاره في ولاية الجزيرة - وسط السودان.

تم قياس هرمونات البروﻻكتين و FSH و LH باستخدام تقنية المقايسة المناعية (EIA) في المصل من 200 إمرأة (150 إمرأة تعاني من العقم الابتدائي و 50 إمرأة خصبة غيرحامل وغيرمرضع) حضرن إلى مستشفى ود مدني التعليمي للنساء والتوليد بمدينة ود مدني - وسط السودان، في الفترة من 2011 وحتى 2013.

تم الحصول على النتائج من حالات Hyperprolactinemia (33.3٪) Irregular menstrual cycle (66٪) و Amenorrhoea (6.7٪)، و (59.3٪) oligomenorrhoea، Normal menorrhoea (33.3٪)، Galactorrhoea (3.3٪) من النساء المصابات بالعقم الابتدائي .

نستخلص من هذه الدراسة أن معدل إنتشار فرط بروﻻكتين الدم يمثل حوالي ثلث من النساء المصابات بالعقم الابتدائي في ولاية الجزيرة - وسط السودان. وأهم الأسباب الرئيسية للعقم الابتدائي عند النساء هو غياب التبويض نسبة لإرتفاع مستوى البروﻻكتين.