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Role of Ectopic Prolactin on Thyroid Hormones Level in a Sample of Iraqi Infertile Women with Uterine Fibroids

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Abstract

Background A large number of traditional investigations and bioassay of hormones have been practiced in the diagnosis and management of infertility for a long time. Measurements of prolactin and thyroid stimulating hormone have been considered important components of the evaluation of women presenting with infertility.

Objectives To study the effect of prolactin hormone produced from uterine fibroid(s) on thyroid hormones levels and role of these hormones.

Methods One hundred three women with uterine fibroid were entered to the Obstetrics and Gynecology Department in Al-Kadhimyia Teaching Hospital in Baghdad-Iraq from the 15th of June 2007 to December 30th 2010. Fasting serum prolactin, total T_3, total T_4, and thyroid stimulating hormone (TSH) were estimated using MiniVIDAS [ELFA (Enzyme Linked Fluorescent Assay)] kits.

Results Forty five out of 103 (43.69%) women were found with primary infertility and the rest 58 (56.31%) with secondary infertility. Serum thyroid hormones mean ± standard deviations were found normal before and after surgery in both primary and secondary infertile women. Level of serum prolactin was found elevated about 9 folds in primary infertile women and 8 folds in those with secondry infertility before surgery more than their levels after. No significant difference was found between thyroid hormones before and after surgery in both infertile groups, unlike their prolactin which was found highly significant with p value <0.001 in both groups.

Conclusion It can be concluded that, first, the increase in prolactin level was due to an ectopic production from uterine fibroid(s), and second, there is no effect or role of this prolactin on their thyroid hormones function. Third, their infertility could be due to the presence of prolactin secreting fibroid(s).

Keywords Infertility, Ectopic prolactin, Thyroid hormones, Uterine fibroids

Introduction

Infertility is defined as the failure of a couple to achieve a pregnancy despite one year regular unprotected sexual intercourse. A large number of traditional investigations and bioassay of hormones have been practiced in the diagnosis and management of infertility for a long time. By extensive studies it has been proved that for normal sexual function, thyroid secretion of T_3, T_4 needs to be approximately normal. The actions of thyroid hormones cannot be pinpointed to a specific function but probably result from a combination of direct metabolic effects on gonads and excitatory and inhibitory effects operating through anterior pituitary hormones that control sexual functions [(1)].

Prolactin is a polypeptide hormone secreted by the anterior pituitary gland, whose main role is the stimulation of lactation in the postpartum period. The increase in prolactin secretion can

be physiological (pregnancy and lactation) or pathological (hypothalamic and pituitary diseases, iatrogenic, uterine fibroids, *etc.*). Hyperprolactinemia is usually associated with menstrual and ovulatory disorders like amenorrhea, oligomenorrhea, an ovulation, ovulatory cycles with short or inadequate luteal phase, and galactorrhea [(2)].

Traditionally, measurements of prolactin and thyroid stimulating hormone have been considered important components of the evaluation of women presenting with infertility [(3)].

Uterine fibroids are one of the most common benign tumors of the female genital tract, occurring in 20-50% of women of reproductive age. The presence of uterine fibroids has been connected to fertility problems and many studies have been performed in order to define the correlation between fibroids and infertility. Unfortunately, still nobody can draw definitive conclusions on this matter [(4)].

Although initially identified as a pituitary gland hormone, several studies have demonstrated that prolactin is also produced by uterine tissues, including the endometrium, myometrium, and uterine leiomyomas. The significance of prolactin production in leiomyomas is not yet well defined [(5)]. In this study, we aimed to investigate the relation between thyroid hormones and prolactin produced from uterine fibroid(s) of infertile women, and their role on their infertility.

Methods

One hundred three women with uterine fibroid entered to the Obstetrics and Gynecology Department in Al-Kadhimyia Teaching Hospital in Baghdad-Iraq from the 15th of June 2007 to December 30th 2010 suffering from symptoms associated with their uterine fibroid(s). They were at their reproductive age. Forty five out of 103 (43.69%) women were found with primary infertility and the rest 58 (56.31%) with secondary infertility. All other possible types of infertility were excluded from the study.

Patients with a history of previous operation or medical illness such as diabetes mellitus, thyroid diseases including chronic autoimmune thyroiditis, hypertension, renal disease, pituitary adenoma or those who were taking any medication which might affect their hormonal level or using contraceptives and smoking cigarette were also excluded from this study. All this information in addition to diagnosis whether they were primary or secondary infertility was under the supervision of a specialized gynecologist. Ultrasound was used to confirm the presence of uterine fibroid(s). They were undergone either for hysterectomy or myomectomy after they finished their final phase of the menstrual cycle. Fibroids were benign leiomyoma depending on their histopathological results. Women with serum prolactin levels >742 µIU/ml (normal prolactin reference range 106-742 µIU/ml) were advised CT scan or MRI to exclude the presence of pituitary adenoma under the supervision of specialized radiologist. They were considered as hyperprolactinemic.

Blood samples were drawn under sterile conditions from patients prior to operation, left to clot, and centrifuged at 800 x g for 10 minutes at room temperature. The circulating levels of PRL, total T_3, total T_4, and thyroid stimulating hormone (TSH) were determined by means of mini-VIDAS (ELFA; Enzyme Linked Fluorescent Assay) using a Prolactin Kit (Biomerieux Inc., Durham, North Carolina, USA).

The patients were followed up after their surgical treatment, and serum PRL, total T_3, total T_4, and thyroid stimulating hormone (TSH) were re-estimated again 3 weeks after surgery to avoid the effect of operation stress and to compare their levels with those estimated before. The same kits and instruments were used to measure all samples.

Their weight (Kg) and height (m^2) were measured to calculate their body mass index (BMI) in Kg/m^2. Ethical approval and patient permission were obtained prior surgery for the local ethics committee and to conduct the study.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 17 (SPSS Inc., Chicago, IL., USA). Descriptive statistics such as mean, standard deviation (SD) and one-way ANOVA were used to evaluate the significance (*p*-value) between study variables before and after surgery. A *p*-value of <0.01 was considered statistically highly significant.

Results

Patient's serum total T_3, T_4, TSH and prolactin were estimated before and after surgery. Thyroid hormones level (mean ± standard deviations) were found normal before and after surgery in both primary and secondary infertility groups. Serum prolactin level was found elevated about 9 folds in primary infertile women and 8 folds in those with secondry infertility before surgery more than after. This elevated level returns to its normal range after removing fibroids from their uterus. There mean± standard of body mass index was within the overweight range(25-29.9 Kg/m^2) as shown in table-1.

Table 1. Clinical presentation of study patients before and after surgery

		Infertility		P value
		Primary (n=45)	Secondary (n=58)	
Age (years)		26.2±2.35	25.5±1.16	
BMI(Kg/m) ▲		25.37±1.71	29.74±0.89	
Serum total T_3 (nmol/l)	B	0.98±0.95	0.97± 0.95	NS
NRR=(0.95-2.5)	A	0.97±0.93	0.97± 0.94	
Serum total T_4(nmol/l)	B	88.12± 1.5	91.01±1.1	NS
NRR=(60-120)	A	84.93± 0.97	89.12±1.2	
Serum TSH(µIU/ml)	B	1.1 ±0.14	0.91±0.16	NS
NRR=(0.25-5)	A	1.0±0.21	1.02±0.11	
Serum PRL(µIU/ml)**	B	3785.5±1796.5	2921.8± 756.4	<0.001
NRR=(106-742)	A	400.9± 44.3	361.2± 36.66	

▲Reference range for BMI (normal BMI=18.5-24.9Kg/m^2, Over weight BMI=25-29.9 Kg/m^2, Obese BMI=30-34.9 Kg/m^2), B= before surgery, A=after surgery, NRR= normal reference range, NS=not significant, **= P<0.001.

No significant difference was found between thyroid hormones before and after surgery in both infertile groups, unlike prolactin hormone which was found increased with highly significant p value (<0.001) in both infertile groups.

Discussion

Fibroids are benign (that is, non-cancerous) tumors of the uterus. They are also called uterine leiomyomas, or simply myomas. They grow from the muscle cells of the uterus and may protrude from the inside or outside surface of the uterus or they may be contained within the muscular wall. They may cause infertility in a number of different ways. Some studies have suggested that fibroids in the muscle portion of the uterus may cause an alteration or reduction of blood flow to the uterine lining making it more difficult for an implanted embryo to grow and develop. Another theory suggests that even small fibroids that grow inside of the uterine cavity may act as a foreign body and result in an inflammatory reaction that makes the uterine environment hostile for an embryo to implant [(6)]. It is known that hyperprolactinemia is a common problem encountered in reproductive disorders. The understanding that prolactin hypersecretion

not only causes galactorrhea and amenorrhea but also gonadal dysfunction and infertility led to the wider use of prolactin estimations [7]. Indinnimeo *et al* [8] reported that serum concentrations of PRL, which is a trophic hormone produced by the pituitary gland, have been shown to be raised in certain groups of patients with cancer. It was detected in 0-20% of the colon cancer by immunohistochemistry and in the plasma in 6-53% of the patients. Also, Hsu *et al* [9] concluded that surgical removal of cervical carcinoma resulted in normalization of serum PRL concentrations. This explains the increase of PRL concentration level in patient's sera, and its decline to its normal level after surgery. It should be mentioned that all patients in this study were examined by MRI and/or CT scan to exclude the presence of pituitary adenoma. This step was important for each patient before removing her fibroid(s).

In addition to its production by the pituitary gland and the decidualized endometrium of the late luteal phase, the human myometrium has been proposed as a second source of uterine PRL, since immunoreactive PRL was found in supernatants from myometrial explants cultures [10]. Prolactin can function as a circulating hormone and as a cytokine. The explanation of this function is based on PRL production and its distinct regulation in extrapituitary sites, it's binding to membrane receptors of the cytokine receptor super family, and activation of signaling pathways that promote cell growth and survival. Many studies showed increasing evidence of PRL and said that PRL plays a role in several types of cancer in the reproductive and non-reproductive tissues via local production, or accumulation. Considering PRL as an active participant in tumorigenesis should inspire and encourage the development of novel therapies aimed at reducing tumor growth by suppressing PRL production, or by blocking its receptors [11]. In a previous study, it was found that prolactin level in patients with uterine fibroids was increased with a significant positive correlation with fibroid's size [12]. Another study done by Abdulla and Baban 2010 reported that the highest serum prolactin mean was found among patients with uterine fibroids presented with site of pain while tissue prolactin was found at its highest mean among women presented with irregular menstrual flow and menorrhagia while asymptomatic were 15% and 25% of them presented with infertility [13].

Hyperprolactinemia adversely affects fertility potential by impairing GnRH pulsatility and thereby ovarian function [14,15]. Most obstetricians and gynecologists check serum levels of TSH and PRL in every female patient undergoing an infertility evaluation regardless of their menstrual rhythm [16].

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 [7]. Hyperprolactinemia in this study is due to the ectopic production of prolactin from patient's fibroid(s), and this ectopic prolactin has different profiles and bioactivity. So, the theory of interference which causes infertility [7] cannot be supposed in this study. Because of absence of pituitary adenoma, the main reason for their hyperprolactinemia was the fibroids and this cause when removed the level of their prolactin returned to normal. This explanation agreed with several studies that demonstrated prolactin production by uterine tissues in addition to pituitary gland, including the endometrium, myometrium, and uterine fibroids. The interest in this hormone has been stimulated by the finding that prolactin acts as a mitogen for vascular smooth muscle [17].

Measurement of prolactin and thyroid hormones, especially thyroid stimulating hormone (TSH), has been considered an important component of infertility work up in women [18]. Several articles have highlighted the association of hyperthyroidism or

hypothyroidism with menstrual disturbance, anovulatory cycles, decreased fecundity and increased morbidity during pregnancy. For example, Goswami *et al*. 2009 mentioned that a hormonal disorder of female reproductive system is comprised of a number of problems resulting from aberrant dysfunction of hypo-thalamic-pituitary-ovarian axis [(19)]. These relatively common disorders often lead to infertility. While Nasima 2009 reported that although her study results reflect some clinical findings of women with primary and secondary infertility such as irregular menstruation, oligomenorrhea, acne, hirsutism, obesity, goiter, and poly cystic ovary, but the difference was not statistically significant, and no correlation was observed between TSH and PRL levels [(16)].

During our articles survey, no one has studied thyroid hormones and TSH levels in patients with uterine fibroids. All articles explained the relation between infertility and thyroid dysfunction [(20,21)].

Since thyroid hormones and TSH were within the normal ranges before and after surgery in the present study, and the increase in patient's prolactin before surgery is due to the presence of fibroid(s), it can be concluded that, first, the increase in prolactin level was due to an ectopic production from uterine fibroid(s), and second, there was no effect or role of this prolactin on their thyroid hormones function. Third, their infertility could be due to the presence of prolactin secreting fibroid(s).

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