INTRODUCTION

Uterine fibroids are monoclonal tumors of the uterine smooth muscle cells and consist of large amount of extracellular matrix that contain collagen, fibronectin and proteglycan ***(Sankaran and Manyonda, 2008).***

Leiomyomas of the uterus are one of the most common pathologic abnormalities of the female genital tract. Their occurrence increase with age, and they are found in 20- 50% of women older than 30 years. Leiomyomas of the uterus are the most common indication for hysterectomy ***(Neuwirth, 2008).***

Leptin is a product of the ob gene, which is expressed primarily in adipocytes. Leptin acts on leptin receptors (LEPRs), which are widely distributed and account for its pleitropic effects on energy homeostasis, neuroendocrine function, and immune function ***(Procaccini et al., 2012).***

Leptin receptors are expressed in many organs and tissues, including those related to the control of reproductive physiology (e.g., the hypothalamus, pituitary gland, and gonads). In the last decade, it has become clear that leptin receptors located in the brain are major players in most leptin actions, including reproduction. Leptin is an adipocyte-derived hormone involved in a myriad of physiological process ***(Elias and Purohit, 2012).***

Dietary fat intake, high body mass index (BMI), estrogen, and progesterone are well-known risk factors for myoma uteri ***(Marshall et al., 1998).*** These risk factors may also affect serum leptin levels ***(Fried et al., 2000).***

It is one of the most important adipose-derived hormones, encoded by the ob gene and appears to play an important role in energy expenditure, neuroendocrine- reproductive systems, and immune response ***(Brennan et al., 2006).***

Its concentration is related to the mass of adipose tissue ***(Margetic et al., 2002).*** There are several factors influencing circulating leptin levels. Gender and menopause related differences in leptin levels have been reported ***(Rosenbaum et al., 1996).***

The production of leptin is under a complex hormonal control. Some studies have found that estrogens both *in vivo* ***(Ambrosius et al., 1998),*** and in vitro ***(Machinal et al., 1999)*** increase serum leptin, whereas androgens may show the opposite effect ***(Nowicki et al., 2001).***

Leptin gene is expressed both in myomas and in the surrounding myometrium but not in the myometrium of healthy women ***(Markowska et al., 2005).***

It was reported that there is a decrease in serum leptin levels in women with myoma uteri ***(Chan et al., 2003).*** On the other hand, another recent study did not find any significant difference in serum leptin level between women with myoma and women without myoma ***(Dingiloglu et al., 2007).***

Both estrogen and androgen levels have been found to correlate with leptin levels ***(Perry et al., 1997). Shimizu et al. (1997)*** and ***Cella et al. (2000)*** reported correlation between leptin and estradiol levels throughout the menstrual cycle, while ***Paolisso et al. (1999)*** indicated correlation with plasma progesterone, but not with estradiol.

Most human studies that show a link between leptin and estradiol are cross-sectional ***(Perry et al., 1997)*** or observational ***(Baumgartner et al., 1999).***

In this study, Serum leptin level changes estimated before and after surgical hysterectomy.

AIM OF THE WORK

The purpose of this study is to:

- Serum leptin level changes before and after surgical hysterectomy.

Chapter One

UTERINE LEIOMYOMA

Uterine fibromyoma, more correctly termed leiomyomata but variously referred to as myomas, leiomyofibromas, fibroleiomyomas and myomas, are the commonest pelvic tumour in women ***(Parker, 2007).***

Uterine fibroids are monoclonal tumors of the uterine smooth muscle cells and consist of large amount of extracellular matrix that contain collagen, fibronectin and proteglycan ***(Sankaran and Manyonda, 2008).***

Leiomyomas of the uterus are one of the most common pathologic abnormalities of the female genital tract. Their occurrence increase with age, and they are found in 20- 50%of women older than 30 years. Leiomyomas of the uterus are the most common indication for hysterectomy ***(Neuwirth, 2008).***

The gold standard diagnostic modality for uterine fibroids appear to be gray scale ultrasonography, with magnetic resonance imaging being a close second option in complex clinical circumstances ***(Khan et al., 2014).***

The management of uterine fibriod can be approached medically, surgically, and even minimal access techniques. The recent introduction of selective progesterone receptor modulators (SPRMs) and aromatase inhibitors has added more armamentarium to medical option of treatment. Uterine artery

embolization (UAE) has now been well-recognized as a uterine-sparing (fertility-preserving) method of treating fibroid. More recently the introduction of ultrasound waves MRgFUS or radiofrequency for uterine fibroid ablation has added to the option of minimal access treatment. More definite surgery in the form of myomectomy or hysterectomy can be performed via the minimal access or open route method ***(Khan et al., 2014).***

A leiomyoma arises from a single neoplastic cell within the smooth muscle of the myometrium. Neoplastic transformation probably involves somatic mutation of normal myometrial cells and the complex iteraction of sex steroid and local growth factors. Somatic mutations such as translocation, duplication, and deletion have been identified in almost one half of leiomyoma studied by cytogenic analysis ***(Neuwirth, 2008).***

Incidence

Uterine leiomyomas are found in 20- 50%of women older than 30 years ***(Neuwirth, 2008).***

Risk Factors Associated with Leiomyomas

A. Menarche:

Most of the studies had reported an increased risk of fibroid with earlier age of menarche and newer data confirm these findings ***(Schwartz, 2006).***

B. Parity

Parity has been inversely associated with a risk of fibroid development in the earlier studies and the newer studies confirm these findings ***Parazzini (2006).*** A relative risk of fibroids among parous women of 0.5, compared with nulliparae, and a progressive decline in risk relative to the number of births have been reported ***(Sato et al. 2000a).***

An explanation for these findings is that pregnancy reduces the time of exposure to unopposed estrogens, whereas nulliparity or reduced fertility may be associated with anovulatory cycles characterized by long-term unopposed estrogens.

C. Age:

The cumulative incidence (based on both ultrasonogrphic detection of fibroid in women with an intact uterus and evidence of prior fibroids among women who have had hysterectomy) increases with age, but the rate of increase slow at older age. This suggest that the older premenopausal uterus is less susceptible to fibroid development ***(Laughlin et al., 2010).***

D. Menopause

Uterine leiomyomas are steroid-hormone dependent and have high estrogen concentrations, elevated numbers of estrogen receptors and more bound estrogen. UL increase in size when exposed to high estrogen levels, such as during the reproductive years and diminish in the presence of low estrogen levels, following menopause or during GnRH agonist therapy ***(Christian Nordqvist, 2014).***

E. Obesity

Fibroid are more common in women with a higher body mass index ***(Stewart, 2001).***

F. Exercise

The possibility of a relationship between exercise and the occurrence of fibroids has been addressed by comparing prevalences among a large group of former college athletes and non athlete. Former non athletes were found to be 1.4 times more likely than former athletes to develop benign uterine tumors ***(Flake et al., 2003).***

G. Hormone Replacement Therapy

Fibroids are expected to shrink after menopause, but hormone replacement therapy (HRT) may prevent this shrinkage and may even stimulate growth ***(Flake et al., 2003).***

Addition of progestins does not appear to reduce risk. One large ***(Polatti et al., 2000)*** and several small ***(Colacurci et al., 2000; Fedele et al., 2000;*** clinical trials demonstrated increased fibroid size during treatment with transdermal estrogen when progesterone was included.

H. Tamoxifen

Tamoxifen is a partial estrogen agonist that binds to ERs in receptive cells, thereby antagonizing the effects of estrogen by competitively binding to target organ receptors. Because

tamoxifen is effective adjuvant therapy for ER positive breast cancer, it might be expected to induce regression of estrogen-responsive uterine fibroids.

Epidemiology and Etiology

Leiomyomas are the most common female reproductive tract tumors. They are probably of unicellular origin, and their growth rate is influenced by estrogen, growth hormone, and progesterone. Although studies have not clarified the exact process, uterine fibroid tumors arise during the reproductive years and tend to enlarge during pregnancy and regress after menopause. The use of estrogen agonists is associated with an increased incidence of fibroid tumors, and growth hormone appears to act synergistically with estradiol in affecting the growth of fibroid tumors. Conversely, progesterone appears to inhibit their growth ***(Chalas et al., 2005).***

Clinical Features

Uterine fibroids are the cause for some of the most common gynecological problems among women presenting to gynecology emergency and outpatient department in UK. They are often asymptomatic but they can cause multitude of symptoms such as abnormal uterine bleeding, a feeling of pelvic pressure, urinary incontinence or retention, or pain. They may also be associated with reproductive problem such as infertility and miscarriage ***(NICE, 2010).***

Diagnosis

The bimanual examination is often the first indication that a patient may have uterine fibroid tumors. Several studies, including transvaginal ultrasonography, sonohysterography, hysteroscopy, and magnetic resonance imaging (MRI), may be helpful in evaluating these tumors. MRI is preferred when precise myoma mapping is required (usually for surgical purposes), but it is the most expensive modality for evaluating fibroid tumors. Sonohysterography and hysteroscopy can be used to evaluate the extent of submucosal fibroid tumors, but these tests are relatively invasive ***(Griffin et al., 2005).***

Management

Leiomyoma symptoms should be carefully elicited because this influences treatment choice. For women whose only symptom is heavy bleeding, there are several options after pregnancy, endometrial, and hormonal causes of bleeding have been ruled out.

Larger submucosal leiomyomas may be amenable to shrinkage with gonadotropin-releasing hormone analogs to improve the chances of complete resection and maximize preoperative iron stores. For heavy or prolonged menses in a woman without a submucous leiomyoma, a number of medical options exist, including steroidal therapies such as oral contraceptive pills and the levonorgestrel intrauterine system. Contraceptive patches and vaginal rings likely work in a similar

fashion. The levonorgestrel intrauterine system has been shown to work effectively in women with leiomyomas, although expulsion of the levonorgestrel intrauterine system may be more common ***(Zapata et al., 2010).***

Endometrial ablation is a minimally invasive surgical option for menorrhagia when there is not a significant uterine cavity distortion and no desire for future pregnancy. Several devices are Food and Drug Administration-approved for use in the myomatous uterus, but most studies have been performed with minimally enlarged and distorted uteri. In a retrospective study, leiomyomas did not increase the failure rate of endometrial ablation, but a cavity measuring over 9 cm in depth increased chance of continued menses ***(El-Nashar et al., 2009).***

For women with pressure symptoms attributable to myomas (bladder discomfort, constipation, back or pelvic pressure) with or without menorrhagia, there are several alternatives to hysterectomy, including myomectomy, uterine artery embolization and magnetic resonance-guided focused ultrasonography. Advanced preoperative imaging, including magnetic resonance imaging (MRI) or sonohysterogram may help determine the best treatment for each patient. MRI with gadolinium may demonstrate leiomyoma devascularization which limits treatment by focused ultrasound or uterine artery embolization. MRI may also help identify lesions suspicious for sarcoma ***(Tanaka et al., 2004).***

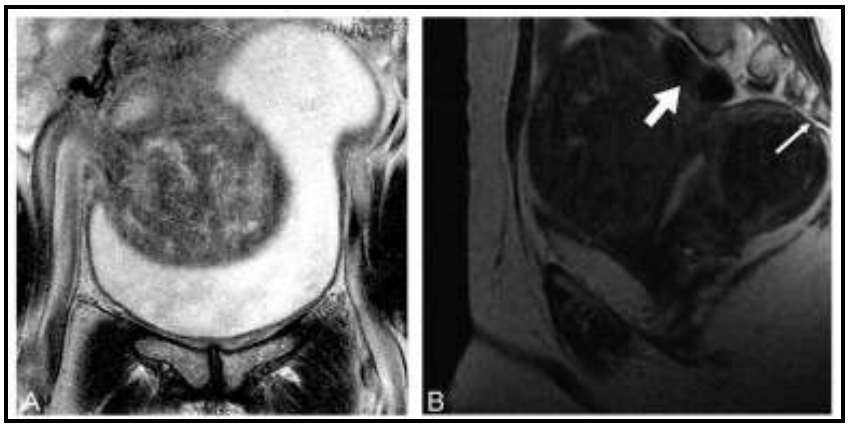

Figure (1): Magnetic resonance imaging (MRI) demonstrating leiomyoma compressing (A) the bladder and (B) the spine (*thin arrow*) and colon (*thick arrow*) ***(Laughlin and Stewart, 2011).***

The number of treatment options is increasing and includes expectant management, surgery, uterine artery embolization, ablative techniques, and medical management. Clinical guidelines have been created to assist patients and physicians in choosing appropriate management options ***(Lefebvre et al., 2003).***

A) Medical Treatments

Medical therapy is available for women with symptomatic fibroid tumors who prefer conservative management.

I) Gonadotropin-Releasing Hormone Agonists:

GnRHA (gonado-tropin-releasing hormone) administrated by injection. GnRHAs make the woman'body produce much lower quantities of estrogen, which makes the fibroids shrink ***(Christian Nordqvist, 2014).***

II) Hormone Therapy:

Hormone therapy with cyclic or non-cyclic estrogen–progestin combinations appears to be ineffective in alleviating the symptoms of fibroid tumors and limiting tumor growth. Studies have found no evidence that low-dose contraceptives cause the growth of uterine fibroid tumors; thus, these tumors are not a contraindication to the use of these contraceptives ***(Evans and Brunsell, 2007).***

A small study found significant improvement in bleeding after treatment with depot medroxy-progesterone acetate (Depo-Provera) in 20 African women with menorrhagia attributed to uterine fibroid tumors ***(Venkatachalam et al., 2004).***

B) Surgical Treatments

When medication have not worked the patient may have to undergo surgery ***(Christian Nordqvist, 2014).***

III) Hysterectomy

Hystrectomy is the definitive procedure and carries an outstanding good outcome and guarantees complete cessation of periods with no risk of fibroid recurrence. Hysterectomy can be done vaginal, abdominal, or laparoscopic (total or laooutaroscopic-assisted vaginal) route ***(Salama SS, 2013).***

IV) Myomectomy

A recent observational study has suggested that abdominal myomectomy might improve reproductive outcomes in patients with myoma. The reproductive performance was particularly good when the patients were younger and had previous pregnancy prior to surgery ***(Machuplli et al., 2013).***

V) Uterine Artery Embolisation

Uterine artery embolisation (UAE) has been shown to be both effective (for short-and medium –term symptom relief) and safe for women who may wish to have children at some time in the future NICE International procedure Guideline ***(November, 2010).***

Uterine artery embolisation treatment stop the fibroid from getting its blood supply. UAE is generally used for women with large fibroids. UAE effectively shrink the fibroid.

Chapter Two

LEPTIN AND SERUM LEPTIN LEVELS IN WOMEN WITH UTERINE LEIOMYOMAS

Leptin Hormone:

Leptin, the product of the obesity gene (ob) predominantly secreted from adipocytes, plays a major role in the negative control of feeding and acts via a specific receptor (Ob-R), six isoforms of which are known at present. Evidence has been accumulated that leptin, like other peptides involved in the central regulation of food intake, controls the function of the hypothlamic-pituitary-adrenal (HPA) axis, acting on both its central and peripheral branches ***(Malendowicz et al., 2007).***

Leptin is a plausible regulator of aromatase, given the coexpression of leptin and aromatase by adipocytes. Leptin also stimulates collagen production and may therefore play a role in leiomyoma formation. Treatment of primary leiomyoma cells in culture with lepton resulted in increased aromatase expression. Furthermore, leptin treatment resulted in phosphorylation of JAK-2 and STAT3, while cotreatment with a JAK-2 phosphorylation inhibitor prevented the leptin-regulated increase in aromatase promoter I.4, suggesting a possible mechanism for leptin regulation of aromatase in leiomyomata ***(Fertil Steril, 2011).***