INTRODUCTION

Uterine leiomyomas (fibroids or myomas) are benign, smooth muscle tumors of the uterus ***(Stewart, 2001).*** Uterine leiomyomas are the most common benign tumors among women. Although most of them are asymptomatic and are discovered accidentally during a routine pelvic examination or imaging studies, 20% to 50% of them can cause menorrhagia, pelvic pain, pressure symptoms, also colorectal and urinary complaints ***(Flake et al., 2003).***

Myomas can be single or multiple and can vary in size, location, and perfusion. Myomas are commonly classified into subgroups based on their location: subserosal (projecting outside the uterus), intramural (within the myometrium), and or submucosal (projecting into the cavity of the uterus). Recognized risk factors for development of uterine fibroids include null parity, early menarche, increased frequency of menses, history of dysmenorrhea, family history of uterine fibroids, African descent obesity, and age (peak incidence at 40 to 50). Clinical conditions that seem to increase risk of fibroids include hypertension and diabetes ***(Flake et al., 2003).***

Treatment of women with uterine leiomyomas must be individualized, based on symptomatology, the size and location of fibroids, age, the needs and desires of the patient for preservation of fertility or the uterus, the availability of therapy, and the experience of the therapist. Symptomatic uterine

fibroids may be treated medically, surgically, or with a combination of both ***(Myers et al., 2002).***

The standard treatment of symptomatic leiomyomas is myomectomy for women who wish to preserve fertility. Myomectomy can be accomplished by laparotomy, laparoscopy, or hysteroscopy. Myomectomy by laparotomy involves the surgical removal of the fibroids through an incision in the abdominal wall. Where there is a small number of sub-serous or intramural myomas and the uterine size is less than that of 16 weeks gestation, laparoscopic myomectomy may be an option ***(Hurst et al., 2005).***

Other Treatment modalities of myoma include:

- Expectant Management: 3% to 7% of untreated fibroids in premenopausal women regress over 6 months to 3 years**.** Most women experience shrinkage of fibroids and relief of symptoms at menopause; therefore, depending on the severity of their symptoms, women who are approaching menopause may choose to wait for the onset of menopause before deciding on treatment ***(Peddada et al., 2008)***.

- Medical treatment to control the symptoms as AUB and reduce size of myoma: Oral Contraceptives, Progestins/ Levonorgestrel Intrauterine System, GnRH agonists, Gonadotropin-Releasing Hormone Antagonists, Danazol, Aromatase inhibitors, The estrogen receptor antagonist,

Selective Estrogen Receptor Modulators, Mifepristone and Ulipristal acetate ***(Sohn et al., 2018).***

- Surgical treatment: Hysterectomy (abdominal/vaginal/ laparoscopic) in women who have completed childbearing, hysterectomy is indicated as a permanent solution for symptomatic leiomyomas ***(Falcone and Parker, 2013).***

Complications of abdominal myomectomy include bleeding, fever, infection and visceral damage. A requirement for transfusion in up to 20% of cases following abdominal myomectomy has been reported in the literature ***(Schüring et al., 2011).***

Blood loss during myomectomy can be intra-operative or postoperative and with haematoma formation. The average volume of blood loss during abdominal myomectomy is 200 to 800 ml. Massive blood loss associated with the dissection of huge fibroids renders myomectomy a more technically challenging procedure than hysterectomy. Sometimes myomectomy is converted to hysterectomy intra-operatively when bleeding becomes heavy and uncontrollable or when it is impossible to reconstruct the uterus because of the many defects left by removal of multiple myomas ***(Chiang et al., 2014).***

Many techniques are used to reduce blood loss during myomectomy; preoperative measures such as correction of preoperative anemia associated with menorrhagia may be

treated with iron supplementation, use of gonadotropin (GHG) triggers prior to surgery. Intra-operative measures as use of tourniquet around the uterus during the operation, injections of Vasopressin or other vasopressors as epinephrine in the uterine muscle and use of ecbolics (misoprostol, oxytocin, etc.). Uterine artery ligation, embolization, or internal iliac artery ligation may also be used to avoid hysterectomy when heavy bleeding is anticipated or occurs during myomectomy **(*Kongnyuy et al., 2014).***

Misoprostol is a synthetic prostaglandin E_1 analogue. Prostaglandins increase myometrial contractions and lead to a reduction in myometrial hemorrhage ***(Prata and Weidert, 2016).***

Misoprostol has become an important drug in obstetrical and gynecologic practice because of its uterotonic and cervical-ripening actions. It is commonly used for medical abortion, cervical ripening, and the management of miscarriage, induction of labor and prevention of postpartum hemorrhage. It can be given orally, sublingually, vaginally and rectally. It has the advantage of being cheap, widely available, and stable at the room temperature. The most common adverse effects of misoprostol are nausea, vomiting, diarrhea, abdominal pain, chills, shivering, and fever, all of which are dose-dependent ***(Tang et al., 2007).*** Misoprostol, which is employed in the treatment and prevention of postpartum hemorrhage in obstetrics, may decrease intra-operative hemorrhage in myomectomies ***(Tang et al., 2007).***

AIM OF THE WORK

The aim of this work is to assess the effect of using misoprostol in abdominal myomectomy operations on blood loss, duration of the operation.

Research question

In women undergoing myomectomy, Does vaginal Misoprostol reduce intra-operative blood loss?

Research hypothesis

In women undergoing myomectomy, vaginal Misoprostol may reduce intra-operative blood loss.

UTERINE MYOMAS

Uterine fibromyoma, more correctly termed leiomyomata but variously referred to as myomas, leiomyofibromas, fibroleiomyomas and fibromas, are the commonest pelvic tumor in women. It is benign, monoclonal tumor of the myometrium smooth muscle cells. They are consisting of great quantities of extracellular matrix (ECM) consist of collagen, fibronectin, and proteoglycan. Collagen type I and III are numerous, but the collagen fibrils are created abnormally and are in disruption, similar to the collagen found in Keloid formation ***(McWilliams and Chennathukuzhi, 2017).***

Incidence:

Myomas are remarkably common. Fine serial sectioning of uteri from 100 consecutive women who underwent hysterectomy found myomas in 77%, including some as small as 2mm ***(Parker, 2007).***

Recent Cochrane review study showing a random sampling of women aged 35 to 49 who were screened by self-report, medical record review, and sonography found that by age 35 the incidence of myomas was 60% among African-American women; the incidence increased to over 80% by age 50. Caucasian women have an incidence of 40% by age 35, and almost 70% by age 50 ***(Hodgson et al., 2017).***

Etiology:

Although the exact causes of myomas are unknown, advances have been made in the understanding of the hormonal factors, genetic factors, growth factors, and molecular biology of these benign tumors ***(Isah et al., 2018)***.

Pathogenesis:

In the recent years, significant progress has been made in our understanding of fibroid tumor genesis. A current model suggests that a distinct stem/reservoir cell-enriched population, designated as the leiomyoma-derived side population (LMSP), is responsible to sustain proliferation and tumor growth ***(Ono et al., 2012)***. Hormones have been considered as the major promoter of fibroid growth. In addition, several pathogenic factors such as genetics, microRNA, growth factors, cytokines, and chemokines have a role in the fibroid development and growth ***(Tinelli et al., 2018).***

Both estrogen and progesterone appear to promote the development of myomas. Myomas are rarely observed before puberty, are most prevalent during the reproductive years, and regress after menopause. De novo production of estrogen within myoma tissue is suggested by increased levels of aromatase, an enzyme that converts androgens to estrogen. Levels of estradiol within myomas are higher than in normal myometrium with low levels of enzymes that convert estradiol

to estrone which may promote accumulation of estradiol within the cells, leading to up regulation of estrogen and progesterone receptors, hyper responsiveness to estrogen, and myoma growth. Consistent with this idea, myomas show a higher proliferative index than normal myometrium throughout the menstrual cycle. Myomas have increased concentrations of progesterone receptors A and B compared with normal myometrium ***(Parker, 2007).***

Uterine fibroid is a multifactorial and still enigmatic pathology. The genetic background seems to play an important role, with cytogenetic anomalies observed in about 40% of uterine fibroids. Abnormal ECM expression, increased growth factors, cytokine and chemokine concentrations, and an extracellular disorganized matrix have been implicated in development and growth of uterine fibroids. Estrogens may exert their growth stimulatory effects on such tumors through the action of a complex network of cytokines, growth factors, or apoptosis factors and through different cellular mechanisms ***(Grings et al., 2012).***

Growth factors, proteins or polypeptides produced locally by smooth muscle cells and fibroblasts control the proliferation of cells and appear to stimulate myoma growth, primarily by increasing extracellular matrix. Some of the identified myoma related growth factors are transforming growth factor-b(TGF-b), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), platelet derived growth factor

(PDGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), and prolactin ***(Ciebiera et al., 2018).***

Biochemical and clinical studies also suggested that progesterone, progestin, and progesterone receptors (PR-A and PR-B) might increase proliferative activity in fibroids by enhancing the expression of growth factors (EGF, IGF-I) and apoptosis-related factors (TNF alpha, Bcl-2 proteins) ***(Vergara and Daniele, 2015).***

Uterine fibroid cells typically show a high expression of cell-cycle regulator and anti-apoptotic proteins. This can trigger tumor growth and make cells resistant to apoptosis ***(Islam et al., 2013).***

The ratio between PR-A and PR-B is similar in normal myometrium and fibroids, while p53 and p21 mRNA and protein levels are increased in fibroids. ***(Lora et al., 2012).*** Bcl-2 (B-cell lymphoma) protein, an apoptosis-inhibiting gene product, was abundantly expressed in fibroids compared with normal myometrium. Bcl-2 protein expression in fibroid cells is up regulated by progesterone but down regulated by estradiol. Up regulation of expression of proliferating cell nuclear antigen (PCNA) in fibroids is done by progesterone and estradiol ***(Tinelli et al., 2018).***

Protein and mRNA expression of basic fibroblast growth factor (bFGF) and T-cadherin in uterine fibroid were present

with significantly higher expression than that in adjacent normal myometrium and control normal myometrium. In addition, T-cadherin correlated well with bFGF ***(Wang et al., 2013).***

Uterine Sarcoma Genetics:

Genetic differences between myomas and leiomyosarcomas indicate they most likely have distinct origins, and leiomyosarcomas do not result from malignant degeneration of myomas. Although myomas are proliferative tumors, they remain differentiated and have chromosomal rearrangements similar to other benign lesions. In contrast, leiomyosarcomas are undifferentiated and have complex chromosomal rearrangements and aneuploid karyotypes. Cluster analysis of 146 genes in leiomyosarcomas has shown that the majority is down-regulated, but in myomas or myometrium they are not ***(Chen et al., 2018).***

Risk Factors:

1- Age:

Women are most likely to be diagnosed with myomas during their forties; however, it is not clear whether this is because of increased formation or increased myoma growth secondary to hormonal changes during this time ***(Parker, 2007).***

2- Race:

Black race was the only factor that was shown to be consistently associated with an increased risk of uterine fibroids, black women were found to have a two–three folds greater risk of developing uterine fibroids than white women ***(Stewar et al., 2017).***

3- Hormonal:

Early menarche (<10 years) has been found to increase the risk of future myoma and late menarche (>16 years) has been found to decrease the risk of uterine myomas. No studies have investigated the relation between late age at menopause and risk for uterine fibroid ***(Wise et al., 2016).***

4- Family history:

First-degree relatives of women with myomas have a 2.5 times increased risk of developing myomas ***(Baez et al., 2017).***

5- Body mass index:

A prospective study found that the risk of myomas increased 21% with each 10 kg increase in body weight and with increasing body mass index. Obesity increases conversion of adrenal androgens to estrone and decreases sex hormone–binding globulin. The result is an increase in biologically available estrogen, which may explain an increase in myoma prevalence and/ or growth ***(Parker, 2007).***

6- Oral contraceptives:

There is no definite relationship between oral contraceptives and the presence or growth of myomas. One study found an increased risk of myomas with oral contraceptives, but a subsequent study found no increased risk with use or duration of use, although another study found a decreased risk ***(Wise et al., 2016).***

7- Parity & null-parity:

The inverse association between myoma risk and parity is well known and an increasing number of term pregnancies decreases myoma risk. Both hormonal and non-hormonal mechanisms may also explain this association. Parity means decreased menstrual cycling and term pregnancies cause changes in ovarian hormones, growth factors and estrogen receptor levels, and changes in the uterine tissue. Thus, myomas are more common in nulliparous women. The reduction in risk ranges from 20–50% when comparing parous with nulliparous women. Older age at first term birth has been associated with a lower risk of Uterine fibroid but the longer the time since the last birth, the higher the risk of Uterine fibroid ***(Sparic et al., 2016).***

The postpartum myometrium returns to normal weight, blood flow, and cell size via apoptosis and dedifferentiation. This remodeling process may be responsible for the involution

of myomas. Another theory postulates that the vessels supplying myomas regress during involution of the uterus, depriving myomas of their source of nutrition ***(Parker, 2007).***

8- Diet:

Fibroids are believed to be a hormone-related disease. Therefore, consuming foods that impact hormone levels are thought to pose a risk. A diet high in meat, especially red meat, is naturally higher in saturated fat than a diet limiting these foods. Diets higher in saturated fat have been linked to higher estrogen levels, which could worsen existing fibroids. Diets high in meat were also seen to be low in fruits, vegetables and thus fiber. Although commonly associated only with healthy digestion, fiber aids in regulating hormone levels by carrying excess estrogen out of the body through bowel movements ***(Murray and Pizzorno, 2013).***

9- Physical activity:

Athletic women are noted to have a 40% lower prevalence of myomas compared with non-athletes. It is not clear whether this difference represents the effects of exercise or lower conversion rates of androgens to estrogens due to lean body mass ***(Parker, 2007).***

10- Menopausal hormone therapy:

For the majority of postmenopausal women with myomas, hormone therapy will not stimulate uterine growth. If

the uterus does grow, it is more likely related to the dose of progesterone than estrogen. Postmenopausal women with myomas were given 2 mg of oral estradiol daily and randomized to 2.5 or 5.0 mg of medroxyprogesterone acetate (MPA) per day. Myomas were measured sonographically before and 1 year after treatment. 77% of women taking 2.5 mg of MPA had either no change or a decrease in myoma diameter, and 23% had a slight increase. However, 50% of women taking 5 mg of MPA had an increase in myoma size ***(Parker, 2007).***

11- Smoking:

Smoking may reduce the incidence of myomas. A number of factors decrease bioavailability of estrogen at the target tissue; reduced conversion of androgens to estrone secondary to inhibition of aromatase by nicotine, increased 2-hydroxylation of estradiol, or stimulation of higher sex hormone–binding globulin levels ***(Parker, 2007).***

12- Tissue injury:

Cellular injury or inflammations resulting from an environmental agent, an infection or hypoxia have been proposed as mechanisms for initiation of myoma formation ***(Parker, 2007).***

13- IGF-1, Diabetes, and Polycystic Ovary Syndrome (PCOS):

There is a link between IGF-1 and leiomyoma cell proliferation and gene expression. Studies of human uterine