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EFFECT OF MIFEPRISTONE ON UTERINE FIBROIDS- COMPARATIVE STUDY

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Abstract:

INTRODUCTION :

Mifepristone (RU 486) is a progesterone receptor modulator with antagonistic properties. It binds strongly to endometrial progesterone receptors, minimally to estrogen receptors, and upregulates androgen receptors. In a placebo-controlled trial low dose mifepristone (RU 486) has been shown to decrease myoma size as well as symptoms. An increase in androgen receptors also contributes to antiproliferative effects. Mifepristone also delays or inhibits ovulation, which may produce amenorrhoea. Direct suppressive effects on endometrial vasculature as well as on reducing stromal vascular endothelial growth factor (VEGF) have also been suggested for reducing menstrual blood loss.

OBJECTIVES :

To determine the efficacy and safety of mifepristone for the management of uterine fibroids in pre-menopausal women.

MATERIAL AND METHODS :

The study was conducted in the tertiary care center. This hospital-based study was conducted between September 2023 and February 2024 for 6 months. 30 consecutive cases were studied based on inclusion criteria. All patients were treated with mifepristone 25mg once daily for 3 months. A pictorial blood loss assessment chart (PBAC) score was used to assess menstrual blood loss. A haemogram, liver function test, and ultrasound were performed.

RESULTS: In this study, we observed there was a significant improvement in the hemoglobin (Hb)level, a significant reduction in uterine volume, fibroid size, and heavy menstrual bleeding.

CONCLUSION :

Mifepristone was able to significantly improve the patient outcome by reducing the amount of blood flow during menstruation increasing the Hb levels and significantly reducing the size of myoma.

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Key words: Mifepristone, uterine fibroid, size, blood loss

Introduction:

The most common benign gynecological tumor is uterine leiomyoma, which affects up to 25% of women who are of reproductive age and 40% of whom have symptoms severe enough to require treatment.[1] Surgery has always been the only option for treating symptomatic myomas, and in premenopausal women, myomas can be the cause of up to 40% of hysterectomies.[2] There are limits to nonsurgical options for treating symptomatic myomas. Danazol decreases uterine volume by 18–23%, but it also causes liver damage and prominent androgenic side effects. In three months, gonadotrophin-releasing hormone agonist (GnRH) can reduce leiomyoma size to roughly 50%, but it comes at a high cost, requires parenteral administration, and is linked to hypoestrogenism, which can cause hot flashes, dry vagina, and bone loss.[3-5]

GnRH withdrawal results in myoma regrowth and symptom recurrence.[6] While uterine artery embolization has been demonstrated to improve menorrhagia, lessen pain, and reduce leiomyoma size by 35–69%, there are possible side effects, including uterine synechia and premature ovarian failure.[7]

While conventional wisdom maintains that estrogen plays a critical role in fostering the growth of leiomyoma, new research indicates that progesterone is more important for the upregulation of progesterone receptors and is necessary for the maintenance and expansion of uterine leiomyoma.[8] As a result, a large number of studies were conducted to assess the effectiveness of antiprogestogens such as asoprisnil, ulipristal (PEARL Study), and progesterone receptor modulator CDB-2914 in the nonsurgical treatment of uterine myomas[9,10].

Progesterone receptor modulator mifepristone (RU 486) primarily has antagonistic effects. It upregulates androgen receptors and binds minimally to estrogen receptors and strongly to endometrial progesterone receptors.[11] It has been demonstrated that low-dose mifepristone (RU 486) reduces both the size and symptoms of myomas.[12] Mifepristone's direct effect on reducing the number of progesterone receptors may account for the size reduction. Furthermore, a hormonal environment akin to the early follicular phase may also prevent the steroid-dependent growth of myoma due to the ovarian acyclicity observed with mifepristone. The antiproliferative effects are also facilitated by an increase in androgen receptors. Additionally, mifepristone suppresses or delays ovulation, which can result in amenorrhea.
It has also been proposed that direct suppression of the endometrial vasculature and stromal vascular endothelial growth factor (VEGF) can minimize menstrual blood loss.[13, 14]

Although they are a well-researched option, GnRH analogs are not commonly used in the medical management of myomas. In contrast, mifepristone is cheaper than GnRH analogs, has a few side effects, and is taken orally. If it turns out to be a successful medical treatment for uterine myoma, it might be a more affordable alternative to GnRH analogs in environments with limited resources.

In this context, this study is conducted to determine the efficacy and safety of mifepristone for the management of uterine fibroids in pre-menopausal women.

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Methodology:

The study was conducted in the tertiary care center. This hospital-based study was conducted between September 2023 and February 2024 for 6 months. 30 patients by convenience sampling were studied based on inclusion criteria.

Inclusion criteria: The perimenopausal age group (40–45 years) includes women who have symptomatic fibroids larger than 2 cm in size, parous women who have finished having children and who gave consent for the study, and women who agreed to have endometrial sampling, and ultrasounds (USGs) both before and after treatment.

Criteria for exclusion: Infertile women, as well as women who have not finished their families and have used hormonal contraceptives. women who have had hormonal therapy within the last three months, women who have antiprogesterone contraindications, women with active liver disease, severe respiratory disease, renal disease, coagulation defect, and thromboembolic disease, and women who declined to consent to the study

All patients were treated with mifepristone 25mg once daily for 3 months. A pictorial blood loss assessment chart (PBAC) score was used to assess menstrual blood loss at 0, 1, and 3 months. A haemogram, liver function test, and ultrasound were performed at 0 and 3 months.

Data were recorded on the patient's demographics, baseline clinical profile, menstrual cycle details, and the severity of their symptoms. The pictorial blood loss assessment chart (PBAC) scores, a semiquantitative measure that considers the number of soaked pads, their level of soakage, clot passage, and flooding episodes, were used to measure menstrual blood loss. If the score is 100 or higher, menorrhagia is the result.[16]

A thorough gynecological and general examination was performed. Serum oestradiol levels, liver and kidney function tests, and hemoglobin were measured in the blood. An ultrasound was performed to confirm the diagnosis of leiomyomas, measure endometrial thickness, determine the number, location, and volume of myomas, and rule out other pelvic pathologies. In cases where there were multiple myomas, the volume of each one was calculated and added. The ellipsoid method was utilized to calculate the fibroid volume, and the formula $V=0.5233(D1\times D2\times D3)$ was applied. The fibroid's longitudinal, transverse, and cross-sectional diameters are represented by the numbers D1, D2, and D3, respectively.

After three months the hemoglobin level, LFT, and ultrasound are repeated. The data collected were entered in the Epi info 7 version and analyzed. Fisher’s exact and paired t-tests were used to compare proportion and mean. The $p<0.05$ is considered significant.

Results:

The results of the study post-three-month follow-up show mean age is 42.1+/-0.81 years and the majority were of parity 2. Also, backache, dysmenorrhea, and HMB were seen in 40%, 70 and 73.3% of participants. (Table 1&2)

Table 1: Age and Parity Distribution

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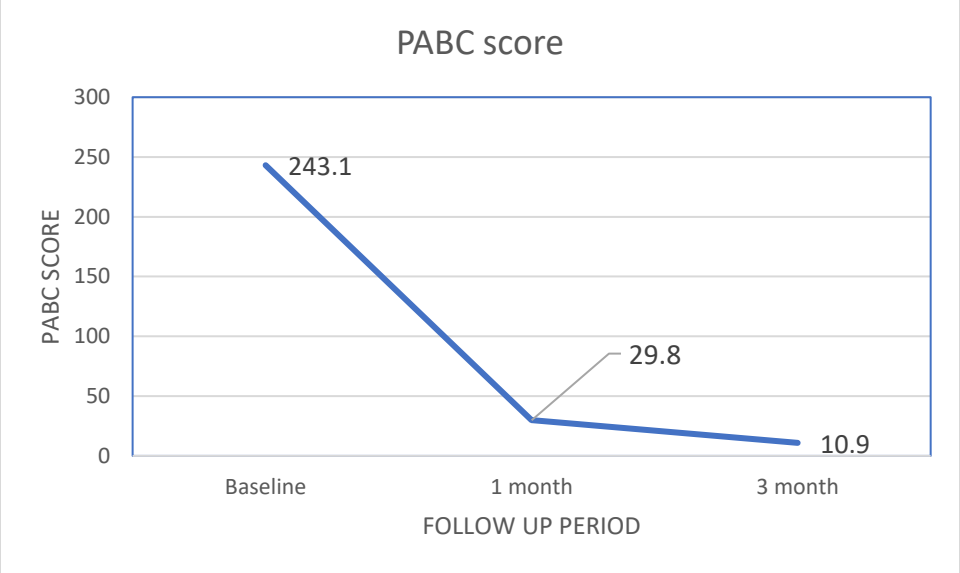
Variables	**n,%**
Age in mean+/-s.d	42.1+/-0.81
Parity 1 2 3 and above	 6, 20 19, 63.4 5, 16.6

Table 2: Distribution of symptoms

Symptoms	N	%
Dysmenorrhea	21	70
Heavy menstrual bleeding	22	73.3
Backache	12	40



P<0.001

Figure 1: PBAC Score

The mean PBAC score at 0, 1, and 3 months is 243.1+/-18.33, 29.8+/-8.22, and 10.9+/-3.43. The results were significant. This suggests the mean PBAC score has been reduced by the use of mifepristone which is a good prognosis. (Fig.1)

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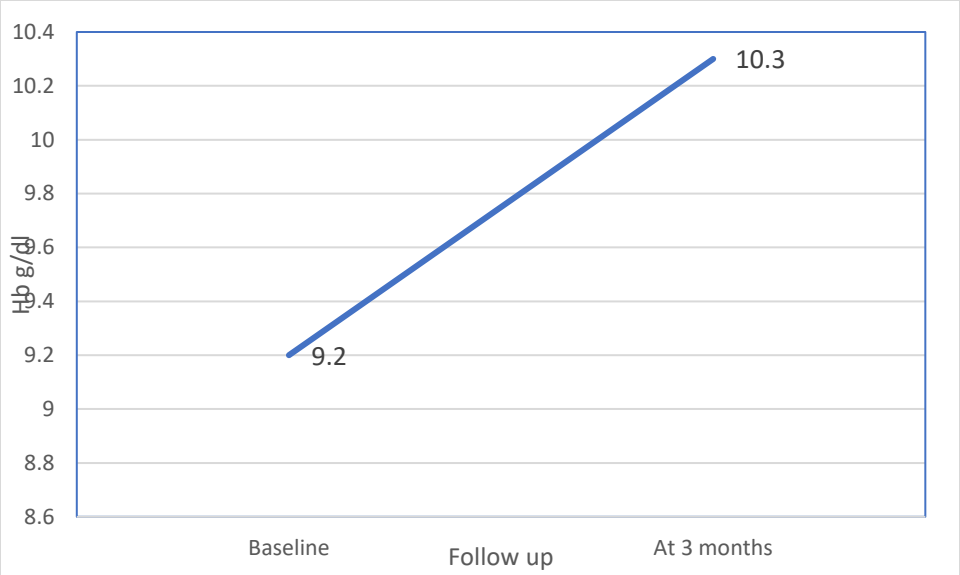

P value =0.008

Figure 2: Hemoglobin comparison

The hemoglobin level was 9.1+/-1.1 g/dl whereas at 3 months is 10.3+/-1.09 g/dl. The results were significant showing use of mifepristone has improved the hb level(Fig.2)

Table 3: Uterine volume, endometrial thickness, and fibroid size comparison

Variables	**At baseline Mean+/-s.d**	**3 months follow up Mean+/-s.d**	**P value**
Uterine volume	193.7+/-89.6	100.6+/-43.3	<0.001
Endometrial thickness	7.7+/-1.6	6.16+/-1.3	<0.001
Fibroid size	13.8+/-8.3	9.04+/-6.7	0.017

The uterine volume, endometrial thickness, and fibroid size have significantly reduced post mifepristone treatment suggesting a good prognosis of the use of mifepristone on fibroid.

Discussion:

The most prevalent benign tumors discovered in up to 70% of women during their reproductive years are uterine myomas or fibroids.[17] Three out of every four hysterectomies are performed for leiomyoma. Therefore, the expense of healthcare to society as a result of uterine leiomyomas is significant. Medical therapy and hysterectomy are two possible treatments for uterine myomas.[17] Ongoing research is being done to determine the best course of

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treatment for uterine leiomyoma. In the future, mifepristone might end up being the medication of choice among the many medications available for the medical treatment of myomas. The goal of the current study is to investigate this strategy for the treatment of uterine myoma

The majority of the study's patients fell into parity II, then parity I, and parity II. In a similar study, Shaikh et al. found that the majority of the female participants in the mifepristone 25 mg and 50 mg groups belonged to para 2 (31 versus 24 patients).[18] Additionally, Singh et al. reported that the majority of cases in their study were married and in para-2 status.[19]The majority of the women in this study reported having dysmenorrhea and heavy menstrual bleeding (HMB). In a similar study, Arora et al. reported that HMB was the primary symptom reported by all 120 patients in their study, with severity graded using the PBAC scoring system.[20] Upon observing that every single patient experienced amenorrhea while on mifepristone, this score was reduced to 'zero'. Furthermore, According to Singh et al., the most common complaints were pelvic pain/pelvic mass (36% versus 42%), dysmenorrhea (40% versus44%), dyspareunia (10% versus12%), and back pain (20% versus 18%). [19]

According to the results of our study, the hemoglobin level significantly improved after the third month of follow-up. Similar to this, Sathyanarayanan et al. reported that following three months of treatment and iron supplementation, hemoglobin increased from 8.86 gm% to 10.88 gm%.[21] The mean hemoglobin levels in the ulipristal acetate and mifepristone groups decreased from 9.346 and 9.508, respectively, before therapy to 10.186 and 10.164, following three months of treatment, according to Singh et al., although the increase in levels was not statistically significant.[12] Mifepristone was initially reported to be used in the treatment of uterine fibroids by Englund et al in 1998. They demonstrated that uterine fibroids are hormone-dependent steroid tumors with progesterone and estrogen receptors (PR and ER). In comparison to pre-treatment measurements, the authors observed that fibroid volume (mean±SE) decreased by 21.9±4.8% after 4 weeks, 39.5±6.6% ($p<0.001$) after 8 weeks, and 49.0±9.2% after 12 weeks of treatment. [22]

Similar to the above study, our study found that the mean reduction in fibroid volume after treatment was also reported, as was the significant reduction in uterine volume at three months after treatment. When the fibroid was checked three months after treatment, it had greatly shrunk in size. One patient did not react to the treatment, despite a 13.6 cm increase in uterine volume. Additionally, Singh et al. noted a noteworthy decrease in the fibroid volume between the mifepristone and ulipristal acetate groups after treatment. [12]

According to Arora et al., the average fibroid area was 8.95 cm2 at the start of the investigation. Following a 6-month course of mifepristone tablets, a noteworthy decrease was noted in every dimension of the fibroid, resulting in a reduction in area overall ($p=0.001$).[20] Similar results were reported by Kirsty et al. in 2009 reports, where a size reduction of 50% was seen with a dose of 5 mg or 10 mg mifepristone for 6 months.[23] In our study, in the third month after treatment, ET was significantly lower. In response to the complaints, every woman experienced amenorrhea while undergoing treatment. After receiving mifepristone treatment for

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six months, Arora et al. found that the average endometrial thickness decreased at follow-up when compared to baseline.[20] This study shows that the mifepristone antiprogesterone component has a significant effect on the treatment of uterine myoma or fibroid. This study has limitations like a small sample size and convenience sampling.

Conclusion:

By lowering blood flow during menstruation and raising hemoglobin levels, mifepristone was found to be able to considerably improve patient outcomes when the medication's management was assessed. Mifepristone was able to significantly shrink the size of the myoma and provide symptomatic relief for the patients. The medication also caused reversible proliferative endometrial changes. Therefore, mifepristone was found to be a better medication in the medical management of myoma in our study; however, larger study populations with longer or more treatment cycles are recommended for more accurate comparisons.

Conflict of interest: Nil

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