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EFFECT OF LOW DOSE MIFEPRISTONE ON THE ENDOMETRIAL HISTOPATHOLOGY IN PATIENTS WITH SYMPTOMATIC LEIOMYOMA

Gynaecology

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ABSTRACT

Mifepristone is a selective progesterone receptor modulator (PRM) with antiprogesterone activity and it is nowadays commonly used in the cases of leiomyoma as it causes a significant reduction in the leiomyoma size. It causes cystic glandular dilatation in the endometrium without any hyperplasia or atypia and these are designated as PRM-associated endometrial changes. We have conducted the prospective interventional study in a tertiary care hospital including sixty four patients with symptomatic uterine leiomyoma. Study evaluated the effect of the low dose mifepristone on the endometrial histopathology. Mifepristone therapy significantly reduced the menstrual bleeding days (P = 0.000) in all the patients by causing absolute amenorrhoea (100%) and endometrial biopsy showed cystic glandular dilatation in 25% (16/64) cases without any premalignant changes (p value=0.005). Thus, concluding that the mifepristone is a promising agent and offers an effective conservative treatment for the uterine leiomyoma with almost no side effects. It causes certain changes in the endometrial histopathology but they are benign without any evidence of hyperplasia and atypia.Thus, confirming the safety of the drug over a period of observation.

KEYWORDS

Mifepristone, Leiomyoma, Endometrial biopsy, Amenorrhoea

Introduction:

Mifepristone is a synthetic steroid and a selective progesterone receptor modulator with the antiprogesterone, antiglucocorticoid, and weak antiandrogenic activity. [1] Mifepristone primarily having antagonistic activity and antagonizes endometrial and myometrial progesterone receptors. It binds strongly to endometrial progesterone receptors, very minimally to estrogen receptors and causes up-regulation of androgen receptors. [2,3] In the presence of progesterone it acts as a competitive antagonist while in the absence of progesterone it acts as a partial agonist.

Mifepristone is the thoroughly studied antiprogestin and is being used over two decades for different clinical indications. Different functions and effect of mifepristone on the endometrium, ovulation and follicular development is dependent on the dose and the time of exposure of drug. [2]

Mifepristone causes a reduction in fibroid size by several mechanisms. [3] Many clinical trials have been done till now which showed the clinical use of mifepristone in cases of leiomyoma causing leiomyoma reduction, symptomatic improvement, and improvement in the quality of life. [4,5,6,7,8] As a result of progesterone antagonistic activity mifepristone treatment leads to unopposed estrogen activity and the further effects on the endometrium. It causes cystic glandular dilatation in the endometrium without any evidence of endometrial hyperplasia or cellular atypia. There is no change or increase in the mitotic activity or index. These changes are designated as PRM-associated endometrial changes (PAEC).

It also inhibits or probably delay ovulation and thus leading to amenorrhoea. [1,3] It has been previously reported that 90% of women who have received low-dose mifepristone ranging from 2-10 mg per day were anovulatory and amenorrhoeic in spite of the fact that the levels of estradiol (E2) remained within the mid-follicular range. Mifepristone act as a suppressive agent directly on the endometrial vasculature as well as reduces the level of vascular endothelial growth factor which has been suggested as a mechanism for decreasing the menstrual blood loss. [9]

The generalized changes of progesterone receptor modulators have been described previously in many studies in detail. [10] However, the frequency of these changes in exposed and non- exposed endometrium is not studied in detail. This data is very important to follow the endometrial changes according to the dose and the timing schedule of the drug. It is very important to study the changes after cessation of the therapy also. In the present study, we have evaluated the effect of low-dose mifepristone on the endometrial histopathology.

MATERIAL AND METHODS:

The current study is a prospective interventional study and conducted in the tertiary care center over a span of six months. Institutional Ethical Committee has given the ethical clearance.Total of 64 women in the age group between 20-45 years, presented in the OPD with symptomatic leiomyoma, who met the inclusion criteria were recruited in the study.

Exclusion criteria included:

1) Rapid increase in the fibroid size
2) Any associated co-morbid condition (HTN, DM, Heart disease, hypothyroidism or coagulation disorder
3) Pregnancy
4) Lactating mother
5) Any hormonal therapy use
6) Severe bleeding
7) Adnexal or ovarian mass
8) Histopathological evidence of endometrial hyperplasia

Patients were explained about the study and informed consent was taken. A complete history, examination, and investigations were done for all the patients. Menstrual history was recorded in detail and blood loss quantification was done with the pictorial blood loss assessment chart. Menorrhagia was taken as score > 100. [11] Other symptoms were also recorded like a low backache, rectal pressure, urinary frequency, dysmenorrhoea, dyspareunia, pelvic pressure, and infertility.

Complete general and gynecological examination were done to rule out any contraindications to the study and also assessing the size of the uterus. Baseline ultrasound examination was done to confirm the presence of the leiomyoma, its site and to exclude any pelvic pathology. Baseline investigations were done including complete blood count, liver function test, kidney function test and paps smear. A premenstrual endometrial biopsy was done in all the patients. Endometrial biopsy was done on the OPD basis with the pipelle curette and sample was sent in the formalin for the histopathological examination. Patients with any evidence of hyperplasia, any pre-malignant condition or malignancy were excluded.

Mifepristone is available as a 200 mg of dose for abortion purposes in India, therefore 10 mg of the dose was prepared by the Sun

pharmaceuticals by crushing the mifepristone in the powdered form and fill in the empty capsules according to the weight. Capsules of 10 mg of mifepristone were prepared without adding any inert substance. Patients were started on mifepristone 10 mg daily OD dose for three months. All the patients were followed monthly and the menstrual bleeding pattern was noted. Repeat endometrial biopsy was taken at the end of the therapy.

Statistical analysis:
Pre and post-therapy variables were measured by chi-square test. A P value less than 0.05 was taken as significant. ANOVA test was done for assessing repeated measures like changes in the hemoglobin.

Results:
Sixty-four patients were recruited for the study. All the patients completed their follow-up and evaluated monthly for their menstrual bleeding pattern and repeat endometrial biopsy was done at the end of three months of mifepristone therapy. Patient's demographic details were shown in Table 1.

Table 1: Population distribution on the basis of demographic details

Characteristics	n=64n	(%)
Age group (years)		
< 25	4	(6.25)
25-29	10	(15.62)
30-34	38	(59.37)
35-39	4	(6.25)
40-45	8	(12.5)
Religion		
Hindu	40	(62.50)
Muslim	24	(37.50)
Christian	0	(0)
Sikh	0	(0)
Socioeconomic class*		
Upper class	0	(0)
Upper middle class	24	(37.50)
Lower middle class	20	(31.20)
Upper lower class	20	(31.20)
Lower class	0	(0)
Educational status		
Illiterate	6	(9.4)
Primary	16	(25)
Secondary	12	(18.80)
Graduate	16	(25)
Postgraduate	14	(21.9)
Diagnosis		
Primary infertility	10	(15.62)
Secondary infertility	2	(3.12)
Multiparous	40	(62.50)
Nulliparous	8	(12.5)
Unmarried	4	(6.25)

*Patients were divided into social classes according to Modified Kuppuswamy scale taking into account, education and occupation of the head of the household and per capita income

Table 2 is showing the population distribution on the basis of leiomyoma-related symptoms.

Table 2: population distribution on the basis of leiomyoma related symptoms

SYMPTOMS	n=64n	(%)
Menstrual*	42	(65.62)
No menstrual complaints	22	(34.37)
Menorrhagia	22	(52.38)
Polymenorrhagia	10	(23.80)
Polymenorrhoea	10	(23.80)
Irregular	0	(0)
Infertility	12	(18.75)
Primary infertility	10	(15.62)
Secondary infertility	2	(3.12)
Dysmenorrhoea	18	(28.12)

***Sum of patients with menstrual symptoms is not 42 because many patients had more than one menstrual complaint or associated dysmenorrhoea**

At the time of recruitment mean value of pictorial blood loss assessment chart score was 150±83.00, mean hemoglobin was <12gm% with the mean value of 10.04±1.32 and none of the patients had abnormal liver or kidney function tests.

Total 72 leiomyomas were there as some patients had multiple leiomyomas. 66.66% (48/72) patients had intramural leiomyoma, 30.55% (22/72) submucosal leiomyoma and 2.77% (2/72) subserosal leiomyoma. Mean leiomyoma volume was 56.61±69.74 cm3.

Effect on Haemoglobin level:
Mean value of hemoglobin pre-therapy was 10.04±1.32 gm% and post-therapy was 12.84±1.23 gm%. Mean value of hemoglobin increases after 3 months of mifepristone therapy.

This observation is the result of absolute amenorrhoea achieved within one month of mifepristone therapy and this effect continued till the therapy was given. Mean Haemoglobin level was increased by 2.8 gm% after three months of mifepristone therapy which was a significant finding.(p value=0.005).

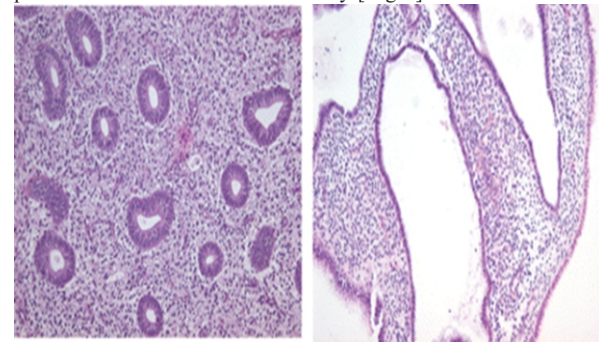
Effect on menstrual bleeding pattern:
Absolute amenorrhoea was the most prominent finding in these patients. All of them had amenorrhoea starting from the first month and this effect continued till the patient was on the therapy. This finding was highly significant. (p value=0.00).

Effect on the endometrium:
Almost 45% of patients had proliferative endometrium at the time of recruitment and none of the patients had hyperplasia with or without atypia. 25% (16/64) of patients had cystic glandular dilatation without hyperplasia or atypia at the end of the therapy.This finding was highly significant. (p value=0.005) Table 3 is showing pre and post-therapy endometrial histopathology of all the patients.

Table 3: Showing endometrial histopathology pre and post-therapy

Endometrial histopathology	Pre-therapy n(%)	Post-therapy (After 3 months)n(%)	P-value
Proliferative	30(46.9)	8(12.5)	**0.001(S)**
Secretory	14(21.90)	26(40.6)	0.542(NS)
Late secretory	18(28.10)	14(21.90)	0.287(NS)
Hormonal imbalance	2(3.10)	0(0)	O.542(NS)
Cystic glandular dilatation withou hyperplasia or atypia	0(0)	16(25)	**0.005(S)**
Total (n)	64	64	

The hallmark of the cystic glandular dilatation was the presence of numerous cystic glands which were lined by an inconsistent appearance of the epithelium.The glands were often lined by a pseudostratified epithelium identical to the normal proliferative pattern but with minimal mitotic activity. [Fig. 1]



Proliferative endometrium

Cystic glandular dilatation without hyperplasia/atypia

Fig 1: Comparing proliferative endometrium with cystic glandular dilatation without hyperplasia or atypia after three months of mifepristone therapy.

There were multiple apoptotic bodies present in the endometrium. Cytologically, these glands don't have the characteristics of atrophy, cystic hyperplasia or disordered proliferative endometrium, and displayed only feeble mitotic activity. The glandular part of the endometrium was the most persistently affected part by the mifepristone therapy.

Discussion:

Progesterone receptor modulators like mifepristone and ulipristal have an antiproliferative effect on the endometrium, absolute amenorrhoea and anovulatory effects, that advocates their use in the conditions like leiomyoma, endometriosis, and dysfunctional uterine bleeding. [12] Mifepristone is associated with the decreased levels of markers suggestive of proliferation in humans. [13]

Murphy et al in 1993 had first reported the use of mifepristone in cases of uterine leiomyoma followed by many other studies using different doses of mifepristone varying from 2.5 mg to 50 mg and showed the usefulness of this drug in leiomyoma cases. [3, 14]

In the present study, we have used 10 mg of dose as it was shown by many previous studies that the 10 mg dose was as effective as 25 and 50 mg. Vidushi et al have shown that the 10mg dose was as effective as the 25 mg dose. [3] In this study we have focused on the effect of the low dose mifepristone on the endometrial histopathology and the menstrual bleeding pattern.

The most eminent finding was the cessation of menstruation in 100% of the patients achieved in the very first cycle after mifepristone therapy which continued until the end of 2nd and 3rd month. On review of the literature, many studies have been done and showed the similar results at the end of 3 months with doses ranging from 5mg to 50mg of mifepristone. Bagaria et al [4] conducted a study with the same dose and for the same duration and showed a cessation of menstruation in almost 73.6% of the patients by the end of the first month and 84.2% of the patients at the end of 2nd and 3rd months versus none in the placebo group. In the same study amenorrhoea rates reduced from 65 % at three months to 32% at six months. [4] 88% of patients became amenorrhoeic at end of mifepristone treatment in the study conducted by Seema et al in 2016 with the 10mg dose for three months of duration. [2] In the study conducted by Vidushi et al in 2013, 95.7% with 10 mg and 90.4% of patients with 25 mg of mifepristone developed amenorrhoea. [3] The results of these studies are comparable to our study. Many studies have shown that when the duration of therapy increases the prevalence of amenorrhoea was decreased Mean Haemoglobin level was increased by 2.8 gm% after three months of mifepristone therapy in our study which was the result of the effect of mifepristone on the menstruation. Similar results were found in the study done by Vidushi et al in 2013. They have compared two doses of mifepristone 25 mg Vs 10 mg for the treatment of uterine leiomyoma over 150 patients and found a significant increase in the hemoglobin level with the p-value of < 0.05. [3] Similar results were found in the study conducted by Shikha Seth et al in 2013 [15] and Seema et al in 2016 [2] with the rise in hemoglobin level of 2.80 gm/dl and 2.38 gm/dl respectively.

In the many antecedent studies, there was a fear of endometrial hyperplasia with the mifepristone use which was approximately calculated as 28% with 5-10 mg dose but it was actually decreased to only 14 % after reviewing the cases as many of the findings of cystic glandular dilatation were mistaken as endometrial hyperplasia. Progesterone receptor modulators causes some specific changes in the endometrium which are designated as progesterone receptor modulator- associated endometrial changes (PAEC) which consist of cystic dilatation of endometrial glands with combination of oestrogenic (mitotic) and progestogenic (secretory) findings, non-synchronous endometrium, pseudostratification of epithelium, pseudo-decidualized stroma, abnormal, dilated thin blood vessels with almost no evidence of atypical hyperplasia. Despite a paucity of mitosis, PAEC may be mistaken for endometrial hyperplasia. [5,10,13] In the present study, 25% (16/64) patients had cystic glandular dilatation without hyperplasia or atypia and this finding was highly significant. (p value=0.005) None of the patients had this finding pre-therapy. These histopathological findings were similar to the findings seen in the study conducted by Julietta et al in 2012 with 2.5 and 5 mg of dose. [13] In the same study this change was seen in almost 86% of the exposed endometrium. [13] Bagaria et al conducted a study over 40 women with the same dose and duration of mifepristone and found endometrial hyperplasia in 63% women compared to none in the placebo group. [4] 4.7 % patients showed similar changes in the endometrium in the study conducted by Vidushi et al. Repeat endometrial-histopathology in the same study did not reveal any complex hyperplasia or atypia in either group.[3]

Conclusion:

It was concluded from the study that there are certain specific changes in the endometrium which is caused by the mifepristone therapy and these changes are designated as progesterone associated endometrial changes (PAEC) which consist of cystic glandular dilatation with no evidence of atypical hyperplasia. These PAEC can be confused with the hyperplasia but they are absolutely benign. Thus, mifepristone can be used safely in the cases of uterine leiomyoma even for the prolonged duration.

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