Original Research Article

Assessing response of perimenopausal abnormal uterine bleeding after treatment

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ABSTRACT

Background: *Abnormal Uterine Bleeding (AUB) is caused by either Organic lesions such as genital tract infections, tumors, adenomyosis, pregnancy and its complications, systemic disorders or Dysfunctional Uterine Bleeding (DUB). In women ≥ 40 years, and certainly in menopausal patients, it mandates evaluation to confirm benign nature of the problem, by ruling out endometrial carcinoma, so that medical treatment or conservative surgery can be offered and unnecessary radical surgery can be avoided.*

Objectives: *Categorizing of Perimenopausal women with AUB for further management according to histo-pathological report and to study the efficacy of medical management (Mainly Progestins).*

Material and Methods: *A total of 60 patients were selected who presented with symptoms of abnormal uterine bleeding at perimenopausal age group (40-54 years). Histopathological results were evaluated after obtaining endometrial tissue and patients are treated accordingly. Treatment response was assessed and tabulated. Statistical Analysis has done by danielsoper.com using chi-square test.*

Results: *Abnormal uterine bleeding was mostly seen in multiparous women with parity >2 about 63.3%. Among menstural irregularities, 45% of cases presented with menorrhagia. Most of the patients were diagnosed as Anovulatory DUB about 60%. Out of 11 hyperplasia patients, 2 (18.1%) patients diagnosed as complex hyperplasia without atypia. No progression of AUB has seen after MPA treatment among all patients with endometrial hyperplasia.*

Conclusion: *Cyclical oral progestogens are effective in regulating and reducing irregular bleeding due to Oligo/Anovulation. Majority of the cases of endometrial hyperplasia without atypia can be successfully treated with progestogen therapy.*

Keywords:

Introduction

Abnormal Uterine Bleeding (AUB) is defined as any bleeding that does not correspond with the frequency, duration or amount of blood flow of a normal menstrual cycle [1] and could be a sign of simple hormonal imbalance or a serious underlying condition necessitating aggressive treatment including a major surgical procedure. [2] Menstruation is the cyclic uterine bleeding experienced by almost all women of reproductive age. Normal menstruation is defined as "the bleeding from secretory endometrium associated with an ovulatory cycle, not exceeding a length of five days". AUB is caused by either organic lesions such as genital tract infections, tumors, adenomyosis, pregnancy and its complications, systemic disorders or Dysfunctional Uterine Bleeding (DUB).

Perimenopause, also called the menopausal transition, generally occurs at around 40-50 years of age. During climacteric, ovarian activity declines. The

premenopausal menstrual cycles are shortened, often anovulatory and irregular. The irregularity in menstrual cycle during perimenopause can be due to anovulation or to irregular maturation of follicles. [3] In women ≥ 40 years, and certainly in menopausal patients, it mandates evaluation to confirm benign nature of the problem, by ruling out endometrial carcinoma, so that medical treatment or conservative surgery can be offered and unnecessary radical surgery can be avoided. A study reports that on histopathology only 10% of these are found to have endometrial carcinoma. [4] Medical treatments of perimenopausal abnormal uterine bleeding include non steroidal anti-inflammatory drugs, or antiprostaglandins, tranexamic acid, the progestogen releasing intra-uterine devices, combined oral contraceptives pills, and other hormonal therapies. As no medical treatment is superior to another, each woman should be individually assessed as to appropriate management. [5]

The aim of the present study was Categorizing of Perimenopausal women with AUB for further management according to histo-pathological report and to study the efficacy of medical management (Mainly Progestins).

Material and Methods

This was a prospective study done in a private Obstetrics and Gynaecology hospital for 2 years from 2014 to 2015. Informed consent has taken from all patients. A total of 60 patients were selected for doing this study who presented with symptoms of abnormal uterine bleeding at perimenopausal age group (40-54 years). Patients presenting with AUB due to pregnancy related complications, having coagulation abnormalities and less than 40 yrs and more than 54 yrs age group were excluded from the study. Detailed clinical history is obtained from the patient with specific relevance to parity and bleeding pattern, thorough clinical examination including general, gynaecological and systemic examination was carried out. A clinical diagnosis of abnormal uterine bleeding was made. Endometrial tissue obtained from Dilatation & curettage under local anesthesia in the late luteal phase. Endometrial tissue was sent to Department of Pathology, where the endometrial tissue is fixed in 10% formalin for 12-24 hours and the entire tissue was taken for routine processing. 5µ thickness sections taken from paraffin blocks were stained with Haematoxylin and Eosin (H&E) and studied under light microscopy. Histopathological results were evaluated, and patients are treated accordingly. Treatment response was assessed and tabulated. Analysis was done to know the p value by danielsoper.com using chi square test.

Results

Out of 60 patients in the age group of 40-54 years, abnormal uterine bleeding was mostly seen in multiparous women with parity >2 about 63.3%. In the present study commonest menstrual irregularity was menorrhagia (45%) (Table: 1). Among others, 18.3% presented with polymenorrhoea, 16.6% had menometrorrhagia, 15% had polymenorrhagia, and 5% had oligomenorrhoea. Endometrial thickness of 4-5.9 mm was observed in most number of AUB patients about 26.6%, followed by 8-9.9 mm thickness, 6-7.9 mm thickness about 16.6% and 15% respectively. (Table: 2) All the patients (60) were treated

according to histo-pathology report and response to treatment were depicted in Table No.3.

Table: 1 Distribution of patients according to symptoms

Symptoms	No. of patients	Percentage (%)
Polymenorrhoea	11	18.3
Polymenorrhagia	9	15
Menorrhagia	27	45
Menometrorrhagia	10	16.6
Oligomenorrhoea	3	5
Total	60	100

Table: 2 Distribution of patients according to endometrial thickness

Endometrial thickness (in mm)	No. of patients	Percentage (%)
<2	0	-
2-3.9	8	13.3
4-5.9	16	26.6
6-7.9	9	15
8-9.9	10	16.6
10-11.9	6	10
12-13.9	5	8.3
14-15.9	2	3.3
>16	4	6.6
Total	60	100

Table: 3 Distribution of patients according mode of treatment given

S.No	Causes of AUB	No. of patients	Treatment Given	No. of patients responded	No. of patients not responded
1	Anovulatory DUB (36)	31 5	Cyclic progestins LNG-IUCD	29 (96.6%) 4 1(80%)	2 (6.4%) 1 (20%)
2	Ovulatory DUB	8	Tranexamic acid	7 (87.5%)	1 (12.5%)
3	Uterine fibroids	2 2	Cyclic progestins LNG-IUCD	2 (100%) 1(50%)	0 1 (50%)
4	Adenomyosis	1	Cyclic progestins	-	1 (100%)
5	Hyperplasia without atypia	9	MPA 10mg/day for 14 days	7 (77.7%)	2 (22.2%)
6	Hyperplasia with atypia	2	MPA 30mg/day for 3 months	1 (50%)	1(50%)

DUB - Dysfunctional Uterine bleeding, LNG-IUCD - Levonorgesterol Intrauterine contraceptive device, MPA-Medroxy Progesterone Acetate

Table: 4 Efficacy of 3 months of progestin therapy in hyperplasia

Diagnosis	No. of patients	Regression No. (%)	Persistence No. (%)
Simple hyperplasia (SH)			
• **Without atypia**	7	6 (85.7)	1 (14.2)
• **With atypia**	2	1 (50)	1 (50)
Complex hyperplasia (CH)			
• **Without atypia**	2	1(50)	1 (50)
• **With atypia**	-	-	-
Total	11	8 (72.7)	3 (27.2)

Most of the patients were diagnosed as Anovulatory DUB about 60% followed by Hyperplasia without atypia and Ovulatory DUB about 15% and 13.3% respectively. On assessing treatment response, cyclic progestins shown better response than LNG-IUCD among Anovulatory DUB and Uterine fibroids patients. Among 36 Anovulatory DUB patients, assessing treatment response with cyclic progestins and LNG-IUCD showed sensitivity of 93.5%, specificity of 20%. Response of Medroxy Progesterone Acetate treatment in patients with endometrial hyperplasia was tabulated in Table no. 4. Out of 11 hyperplasia patients, 2 (18.1%) patients diagnosed as complex hyperplasia without atypia.

Discussion

Once malignancy and significant pelvic pathology have been ruled out, medical treatment should be considered as the first line therapeutic option for abnormal uterine bleeding. Targeted treatment for an underlying medical condition that can affect menstrual bleeding, such as hypothyroidism, should be initiated prior to the addition of any of the medical agents. [6] Regular, heavy menstrual bleeding can be successfully treated with both hormonal and non-hormonal options. Irregular or prolonged bleeding is most effectively treated with hormonal options that regulate cycles, decreasing the likelihood of unscheduled and potentially heavy bleeding episodes. The decision to proceed with a trial of medical treatment should be based on a patient choice of drugs by assessing benefits and side effects of drugs, desire of fertility or contraception, underlying medical conditions or contraindications, presence of dysmenorrhea.[6]

In the present study commonest menstrual irregularity was menorrhagia about 45%. Among others, 18.3% presented with polymenorrhoea, 16.6% had meno metrorrhagia, 15% had polymenorrhagia, and 5% had oligomenorrhoea. Our findings are consistent with studies by Sajitha K et al,[7] Aseel Ghazi Rifat et al,[8] Rajshri P. Damle et al,[9] Usha G. Doddamani et al,[10] 2013 in which the most common symptom was menorrhagia.

In the present study Endometrial thickness of 4-5.9 mm was observed in most number of AUB patients about 26.6%, followed by 8-9.9 mm thickness, 6-7.9 mm thickness about 16.6% and 15% respectively. Mean endometrial thickness of <8mm is less likely to be associated with malignant pathology in perimenopausal age group which is consistent with the study by Getpook C et al,[11] they found that endometrial thickness of 8 mm or less is

less likely to be associated with malignant pathologies in perimenopausal uterine bleeding. Most of the patients were diagnosed as Anovulatory DUB about 60% followed by Hyperplasia without atypia and Ovulatory DUB about 15% and 13.3% respectively. Bhoomika Dadhania and Gauravi Dhruva et al,[12] 2013, observed the commonest pattern in these patients was proliferative endometrium. The commonest pathology was simple cystic hyperplasia (25.3%). They concluded that there is an age specific association of endometrial bleeding, with highest incidence in perimenopausal age group.

Outcome in anovulatory DUB

31 were treated with MPA, among them 96.6% were relieved from AUB and 6.4% were not relieved from AUB. Fraser et al[13] showed a reduction in menorrhagia in six women with objectively demonstrated anovulation who were treated with oral progestogens. 5 were treated with LNG-IUCD, 80% were relieved from the symptoms, and remaining 20% were not responded for treatment these results are consistent with the results of study by Kriplani A, Singh BM et al[14] in which menorrhagia was cured in 35 (77.7%) out of 45 patients at 3 months.

Outcome in ovulatory DUB

8 patients were treated with Tranexamic acid 500mg TID, 87.5% attained regular bleeding with normal flow and the remaining 12.5% showed abnormal bleeding pattern. These results are same as that of a study by Kriplani A et al [15] in which lack of response was seen in 6.1% with Tranexamic acid.

Outcome in uterine fibroids

2 patients were treated with progestins, response was 100%. In study by Ayse Kavasoglu Tosun et al [16] after six months treatment, the reduction of bleeding determined in oral progestin (norethisterone) group is 56%. 2 were treated with LNG IUCD, 1 patient attained regular cycles and remaining 1 patient had irregular bleeding. However in study by Ayse Kavasoglu Tosun et al[16] 2014, after three months of treatment the ratio of satisfaction in LNG-IUD group was 80% and after six months 73%.

Outcome in adenomyosis

1 patient was not responded even after treatment with LNG-IUCD. In study by Nina manasukani et al[17] cases with adenomyosis seemed to respond very well and most of the patients were asymptomatic (52.63%) and 26.3% had amenorrhea at 6 months and 31.57% at 12 months. In many studies, though it was found that LNG IUCD is very effective in treatment of abnormal uterine bleeding, very few patients opting for IUCD in our setup as most of the patients are belonging to low socioeconomic status.

In the present study, regression rates were 85.7% for SH without atypia, 50% for SH with atypia, 50% for CH without atypia after 3 months of hormone therapy. Progression rates were 7.7% for SH without atypia, no progression was identified in case of SH with atypia and CH without atypia. SD Reed et al, [18] was found that among women with complex hyperplasia without atypia only 28.4% of women treated with progestin had persistence/progression. Tasci et al, [19] evaluate the treatment of simple endometrial hyperplasia without atypia with different progestogens it was found that none of the cases progressed. Chiara Marra et al [20] 197 patients with

simple or complex hyperplasia were treated with progesterone at different dosages (100 versus 200 versus 300 mg daily). Endometrial biopsies were performed at 6, 12, 18 months Out of 60 women with simple hyperplasia, remission was observed in 81.8% , 97.5% and 100% patients treated, respectively, with progesterone 100, 200 and 300 mg daily. Out of 72 women with complex hyperplasia, remission was observed in 60%, 92.4% and 85.7% patients treated with progesterone 100, 200 and 300 mg daily, respectively. In conclusion, progesterone increased the regression rate of both simple and complex hyperplasia. Horn et al [21] concluded that endometrial hyperplasia without atypia is likely to respond to hormonal treatment. In study by Simender mesci et al [22] regression rates were 77.1% for SH; 80% for CH, and 100% for CAH after 3 months of hormone therapy. Regression rates after 6 months of hormone therapy were 72.7%, 100%, and 100% for SH, CH, and CAH, respectively. persistence and progression rates were 22.9% for SH, 20% for CH, and 0% for CAH after 3 months of therapy, and no persistence or progression in patients after 6 months of therapy

The SH regression rate has been reported to be 74- 80%, with a 1% progression rate (Tabata et al [23], Montgomery et al [24]). In a recent study, complete resolution was found in 72% of 60 cases after 3 months of progestin therapy, with no progression (Tasci et al [19]) The duration and type of progestin therapy, and the optimal biopsy time, remain controversial in females with endometrial hyperplasia. A follow-up biopsy at 3 months following the initial treatment has been suggested as it corresponds to the average response time. A lack of response at the first biopsy (8-12 weeks after initiating treatment) suggests treatment failure (Simpson et al [25]). However larger randomized studies are needed to confirm this role and to compare progestogen types, regimes, dosages and routes of administration.

Histopathological diagnosis is useful for diagnosis, to assess therapeutic response and to know the pathological incidence of organic lesions in cases of dysfunctional uterine bleeding prior to treatment. This study suggests that cyclical oral progestogens are effective in regulating and reducing irregular bleeding due to Oligo/Anovulation. Majority of the cases of endometrial hyperplasia without atypia can be successfully treated with progestogen therapy. Even in cases with atypia progestogen therapy can be a safe alternative if women are high risk for surgery. But careful monitoring of the endometrium is needed. This can be achieved with periodical endometrial biopsy, transvaginal ultrasonography, and evaluation of the symptoms. Ultimately, good patient selection and long-term follow-up are the most important factors in success and safety of treatment.

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