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Histopathological Study Of Perimenopausal Abnormal Uterine Bleeding In Formulating Treatment Modalities

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Abstract
Objectives:
1. Analyzing the histo-pathological pattern of endometrium in abnormal uterine bleeding.
2. Categorizing the patients according to histo-pathological report for further management.
3. To study the efficacy of medical management (Mainly Progestins).
Materials and methods: *A prospective and observational study was done in Department of Obstetrics and Gynaecology, Gandhi Hospital, Secunderabad, Telangana. Total 100 cases of perimenopausal women (40-54 yrs) with abnormal uterine bleeding were studied during the period of 2 years from NOV 2012 to SEP 2014. D and C was done after making a clinical diagnosis of AUB in these women,. They were treated medically depending on histopathology report. Patients with proliferative type of endometrium and cystic glandular hyperplasia were treated with oral cyclical progestogens for 14 days a month or Levonorgestrel intrauterine system. Patients with secretory endometrium were treated with antifibrinolytics. Later they were followed up for 3 months for response to treatment. Patients with simple hyperplasia were given 10 mg/d Medroxyprogesterone acetate orally 14 days in 2nd half of menstrual cycle for 3 months. Patients with atypia were given 30mg/day Medroxyprogesterone acetate orally continuously for 3 months. Endometrial Curettage was repeated after hormone therapy for 3months.*
Results: *69% of the cases presented with abnormal uterine bleeding were between the age group of 40- 45 year.97% of the total cases were multiparous. Menorrhagia (47%) was the main presenting complaint. According to histopathological reports 43% were showing proliferative type of endometrium, 22% were showing cystic glandular hyperplasia and 20% were showing endometrial hyperplasia .11% were of secretory type of endometrium. A few of them showed irregular shedding (2%), endometritis (1%), adenocarcinoma (1%). Out of 65 patients with anovulatory AUB which consisted of proliferative and cystic glandular hyperplasia type of endometrium, 55 were treated with oral cyclical progestogens of which 94.5% showed response. 10 were treated with LNG IUCD of which 80% showed response. In cases with endometrial hyperplasia regression rates were 84.6% for SH without atypia, 50% for SH with atypia, 66.7%% for CH without atypia after 3 months of hormone therapy. Persistence rates were 7.7% for SH without atypia, 50% for SH with atypia, 33.3% for CH without atypia. Progression rates were 7.7% for SH without atypia, No progression was identified in case of SH with atypia and CH without atypia. In cases with secretory type of endometrium, 92.8% attained regular bleeding with normal flow when treated with tranexamic acid.*
Conclusion: *Medical treatment can be considered as the first line therapeutic option for abnormal uterine bleeding with proliferative and secretory type of endometrium. Majority of the cases of endometrial hyperplasia without atypia can be successfully treated with progestogen therapy .Careful monitoring is needed if patients with endometrial hyperplasia with atypia are treated with progestogens.*

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List Of Abbreviations Used In The Text
AUB-Abnormal Uterine bleeding
SH-Simple hyperplasia
CH-Complex hyperplasia
NSAIDS- Non-steroidal anti-inflammatory drugs
DMPA-Depot-medroxyprogesterone acetate
MPA- Medroxyprogesterone acetate
GnRH Agonists- Gonadotropin-releasing hormone agonist
LNG-IUD-Levonorgestrel intrauterine device

COCPS-Combined oral contraceptive pills
SH-Simple hyperplasia
CH-Complex hyperplasia

I. 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]**.** Abnormal uterine bleeding is a commonly encountered gynecological problem in perimenopausal age group.

Endometrial assessment by endometrial biopsy or curettage is indicated in the peri and postmenopausal years in order to exclude endometrial hyperplasia or carcinoma**.** In addition to it, accurate histopathological diagnosis facilitates the implementation of optimal treatment strategies[3]

The endometrial biopsy is chosen to evaluate dysfunctional uterine bleeding because it has several advantages over other diagnostic methods. Endometrial curettage is relatively inexpensive and accurate as an office procedure. The only disadvantage of endometrial biopsy is that, it is an invasive procedure.

Medical treatments of perimenopausal abnormal uterine bleeding include nonsteroidal anti-inflammatory drugs or antiprostaglandins, tranexamic acid, the oral progestogen (norrethisterone acetate, megesol acetate, and medroxyprogesterone 17-acetate) progestogen releasing intra-uterine devices, combined oral contraceptives pills, and other hormonal therapy. However, there is no consensus on dose, treatment, duration, administration of route or the most effective type of progestin. As no medical treatment is superior to another, each woman should be individually assessed as to appropriate management[4].

Aims And Objectives Of The Study

The present study is done with following aims and objectives-
1. Analyzing the histo-pathological pattern of endometrium in abnormal uterine bleeding.
2. Categorizing the patients according to histo-pathological report for further management.
3. To study the efficacy of medical management (Mainly Progestins).

II. Patients And Methods

The present study was aimed to analyze the histological pattern of endometrium in patients with abnormal uterine bleeding and to study the various treatment modalities accordingly.

This study was carried out in the department of Obstetrics and gynaecology, Gandhi Hospital, secunderabad.100 women who were clinically diagnosed as cases of abnormal uterine bleeding during a period of 2 yrs were selected for the study.

Criteria for the selection of cases-

Inclusion criteria:

Patients of perimenopausal (40 to 54yrs) age group clinically diagnosed as AUB.

Exclusion criteria:

1. Patients presenting with AUB due to pregnancy related complications
2. Patients having Coagulation abnormalities
3. Patients less than 40 yrs and more than 54yrs age group.

Method-

Detailed clinical history was 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.

Histopathological results were evaluated, and patients were treated accordingly.

Patients with anovulatory AUB were treated with cyclical progestins 14 days a month or Levonorgestrel intrauterine system. Patients with small fibroids and adenomyosis were also treated with hormonal therapy then after 3 months patients were enquired about relief of symptoms.

Patients with secretory endometrium were treated with antifibrinolytics.

Patients with simple hyperplasia were given 10 mg/d Medroxyprogesterone acetate orally 14 days in 2nd half of menstrual cycle per month for 3 months. Patients with atypia were given 30mg/day Medroxyprogesterone acetate orally continuously for 3 months. Endometrial Curettage was repeated after hormone therapy for 3months.

III. Observation And Results

The analysis of age distribution, parity distribution and symptomatic distribution, type of endometrium in patients with AUB.

The total numbers of patients studied were 100 from Nov 2012 to Sep 2014.

Table No.1 - Distribution of patients according to age:

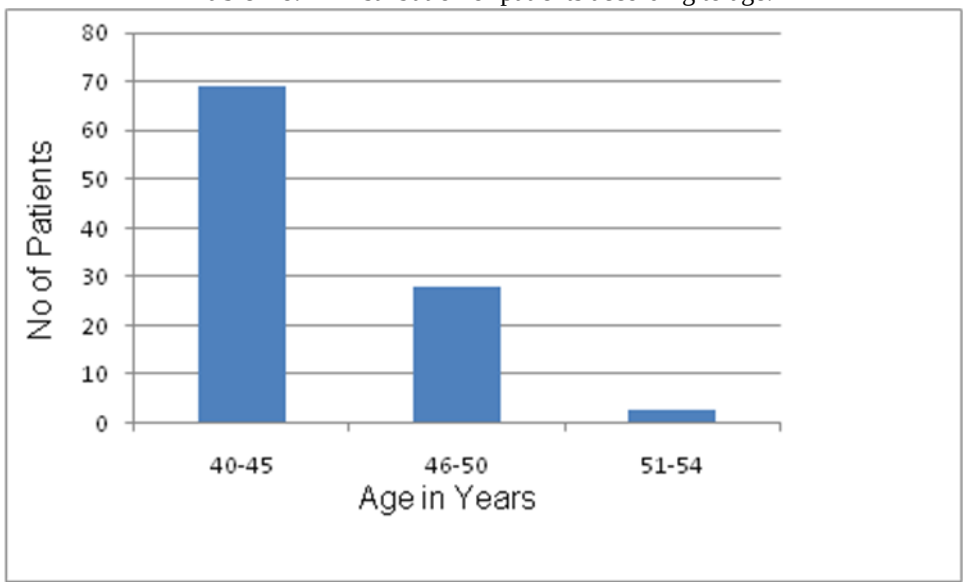

Fig. 1 Distribution of patients according to age

Maximum no. of patients in the study group belongs to the age group of 40-45 years.

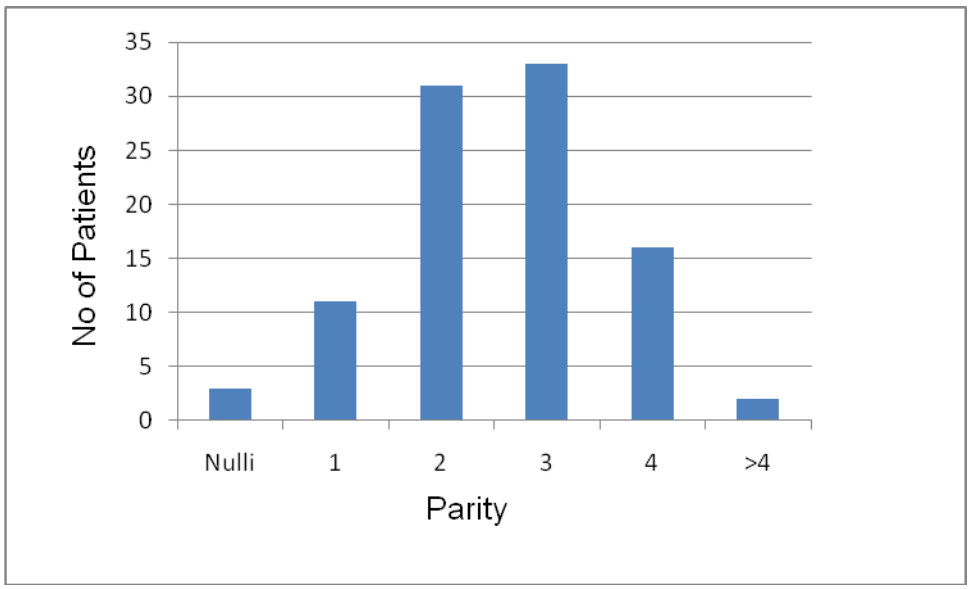

Fig.2 Distributionof patients according to parity

It is noted that multiparas who conceived 2 or more times had greater incidence of AUB.Among 100 cases of AUB 86 patients were of parity 2 or more. Nulliparous were only 3.

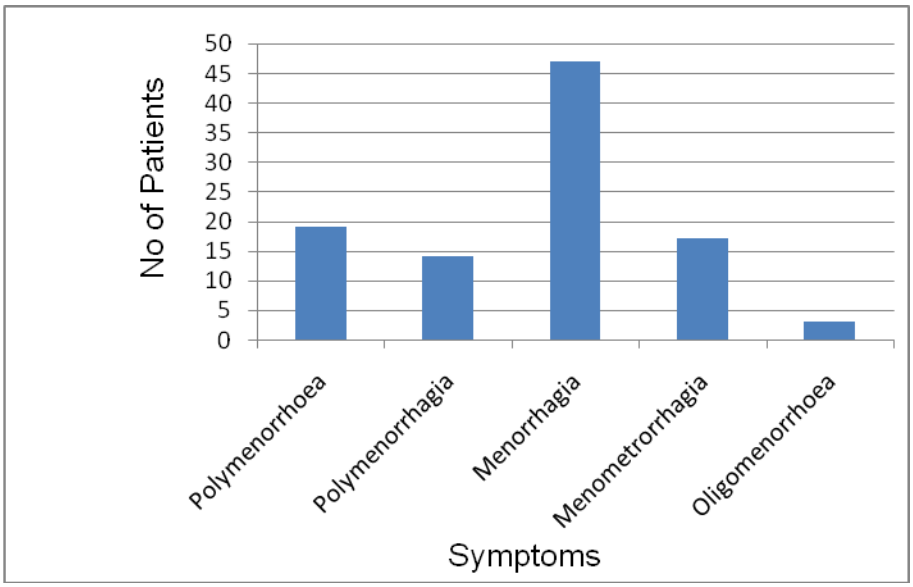

Fig.3 - Distribution of patients according to symptoms

In the present study commonest menstrual irrgiaegularity was menorrhagia which was observed in 47% of cases .Among others 19% presented with polymenorrhoea, 17% had menometrorrhagia, 14% had polymenorrhagia, and 3% had oligomenorrhoea.

Table No.1 - Distribution of patients according to histopathology:

Histopathological finding	No. of cases
Proliferative	43
Secretory	11
Endometrial hyperplasia • Simple hyperplasia Without atypia With atypia • Complex hyperplasia Without atypia With atypia • Cystic glandular hyperplasia	 13 4 3 0 22
Irregular shedding	2
Endometritis	1
Well differentiated adenocarcinoma	1

Table No.2- Distribution of patients according to cause of AUB:

Cause of AUB	No. of patients
Dysfunctional uterine bleeding	72
Organic lesions	28
Total	100

Among perimenopausal age group the most common cause of AUB was found to be dysfunctional in origin.

Table No. 3 Distribution of patients with organic lesions:

Organic lesion	No.of patients
Uterine fibroids	6 (2 cases with simple hyperplasia)
Endometrial hyperplasia	20
Endometrial adenocarcinoma	1
Endometritis	1
Adenomyosis	2

Table No.4 Distribution of patients according to response to medical management:

Cause of AUB	Total no. of patients	No. of patients responded	No. of patients not responded
Idiopathic	72	66	6
Uterine fibroids	6	3	3
Endometrial hyperplasia • Simple hyperplasia Without atypia With atypia • Complex hyperplasia Without atypia With atypia	 13 4 3 -	 11 2 2	 2 2 1
Endometrial adenocarcinoma	1	-	-
Endometritis	1	1	-
Adenomyosis	2	-	2

Table No.5 Distribution of patients according to the mode of treatment given:

Causes of AUB	No. of patients	Treatment Given	No. of patients responded	No. of patients not responded
1.Anovulatory AUB(65)	55 10	Cyclic progestins LNG-IUCD	52(94.5%) 8(80%)	3(5.5%) 2(20%)
2.ovulatory DUB	14	Tranexamic acid	13(92.8%)	1(7.2%)
3.uterine fibroids	3 3	Cyclic progestins LNG-IUCD	2(66.7%) 1(33.3%)	1(33.3%) 2(66.7%)
4.adenomyosis	2	Cyclic progestins	-	2(100%)
5.hyperplasia without atypia	16	MPA 10mg/day for 14 days	13(81.2%)	3(18.8%)
6. .hyperplasia with atypia	4	MPA 30mg/day for 3 months	2(50%)	2(50%)

In the present study,

Outcome in anovulatory DUB –(Proliferative and cystic glandular hyperplasia)

55 were treated with MPA, among them 94.5% were relieved from AUB and 5.5% were not relieved from AUB.10 were treated with LNG-IUCD, 80% were relieved from the symptoms, remaining 20% were not responded for treatment.

Outcome in ovulatory DUB –(secretory type 0f endometrium)

11 patients were treated with Tranexamic acid 500mg TID, 92.8% attained regular bleeding with normal flow and the remaining 7.2% showed abnormal bleeding pattern.

Outcome in uterine fibroids -

3 patients were treated with oral progestins, among them 2 attained regular bleeding and 1 patient did not respond to treatment.

3 were treated with LNG IUCD, 1 had spontaneous expulsion of IUCD during her first menstrual period, 1 patient attained regular cycles and remaining 1 patient had irregular bleeding.

Outcome in adenomyosis -

2 patients with adenomyosis were treated with LNG IUCD, both did not respond.

Response of treatment in patients with endometrial hyperplasia is as follows-

Table No.6 Efficacy of 3 months of progestin therapy in hyperplasia:

Diagnosis	No. of patients	Regression No. (%)	Persistence	Progression
Simple hyperplasia • Without atypia • With atypia	 13 4	 11 (84.6) 2 (50)	 1 (7.7) 2 (50)	 1 (7.7)
Complex hyperplasia • Without atypia • With atypia	 3 -	 2 (66.7) -	 1 (33.3) -	 - -
Total	20	15	4	1

In the present study, regression rates were 84.6% for SH without atypia, 50% for SH with atypia, 66.7%% for CH without atypia after 3 months of hormone therapy.

Persistence rates were 7.7% for SH without atypia, 50% for SH with atypia, 33.3% for CH without atypia.

Progression rates were 7.7% for SH without atypia and no progression was identified in case of SH with atypia and CH without atypia.

IV. Discussion

The present study includes patients of perimenopausal age group (40-54yr) presented with abnormal uterine bleeding.

In present study, most common menstrual disturbance found was menorrhagia in 47% cases. This may be explained as many patients in perimenopausal age group have anovulatory cycles resulting in menirrhagia.

Our findings are consistent with studies by **Sajitha K et al.,[5] 2014, Aseel Ghazi Rifat et al.,[6] 2013 ,Rajshri P. Damle et al.,[7] 2013Usha G. Doddamani et al.,[8] 2013** in which the most common symptom was menorrhagia.

In majorityof the patients AUB was idiopathic (72%) in origin followed by endometrial hyperplasia (20%), uterine fibroids (6%) and adenocarcinoma (1%).

In a similar study including patients of all ages, benign findings included disordered proliferation (93.4%), polyps (3.9%), hyperplasia (2.5%), and malignancy (0.7%) **Soleymani et al.,[9] 2013**. In a study by **SimenderMesci-Haftaci et al., [10] 2013** it was found that the majority of patients had benign findings (44.8%), followed by polyps (30%), endometrial hyperplasia (24%) and adenocarcinoma (1.2%).

In present study of perimenopausal age group, proliferative endometrium was observed in 43% of cases which is very much in alliance with study done by **Rajshri P. Damle et al., [7]** reported 34.09% while **Sujata Jetley et al., [11]** reported 30.6% of proliferative endometrium in peri-menopausal age group study.

The second most common lesion was Cystic glandular hyperplasia (22%),seen in metropathia hemorrhagica.

The third most common was endometrial hyperplasia(20%) which is in concordance with **Rajshri P. Damle et al.,[7]** (23.86%) **,Dangal G et al.,[12]** (23%) and **Slobada L et al.,[13]** (22.6%) ,**Khare et al.,[14]** (36.2%) .**Doroiswami S et al., [15]** (68%) observed high incidence of endometrial hyperplasia in 40-49 years of age group.

In the present study,

Outcome in anovulatory DUB -

55 were treated with MPA, among them 94.5% were relieved from AUB and 5.5% were not relieved from AUB. **Fraser et al[16] 1990** showed a reduction in menorrhagia in six women with objectively demonstrated anovulation and heavy menstrual bleeding who were treated with oral progestogens. This study suggests that cyclical oral progestogens are effective in regulating and reducing irregular bleeding due to Oligo/Anovulation. However larger randomized studies are needed to confirm this role and to compare progestogen types, regimes, dosages and routes of administration.

10 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[17] 2007** in which menorrhagia was cured in 35 (77.7%) out of 45 patients at 3 months.

Outcome in ovulatory DUB -

11 patients were treated with Tranexamic acid 500mg TID, 92.8% attained regular bleeding with normal flow and the remaining 7.2% showed abnormal bleeding pattern. These results were same as that of a study by **Kriplani A et al[18] 2006** in which lack of response during treatment was seen in 6.1% with Tranexamic acid.

Outcome in uterine fibroids-

3 patients were treated with progestins, among them 2 attained regular bleeding and 1 patient was not responded for treatment.In study by **Ayse Kavasoglu Tosun et al [19] 2014** after six months treatment, the reduction of bleeding determined in oral progestin (norethisterone) group is 56%.

3 were treated with LNG IUCD, 1 had spontaneous expulsion of IUCD during her first menstrual period, 1 patient attained regular cycles and remaining 1 patient had irregular bleeding. In our study the patient who had spontaneous expulsion and one with irregular bleeding underwent hysterectomy.

However in study by **Ayse Kavasoglu Tosun et al [19] 2014** after six months treatment, the reduction of bleeding determined in LNG-IUD group is 80%.After three months the ratio of satisfaction in LNG-IUD group was 80% and after six months 73%. The difference in results may be because few patients were given LNG IUCD when compared to author study.

Outcome in adenomyosis-

2 patients with adenomyosis were treated with LNG-IUCD both were not responded. Among them 1 patient requested removal of the IUCD 2 months after insertion because of persistent irregular blood loss. In study by **Nina manasukani et al [20] 2014** cases with adenomyosis seemed to respond very well and after the first 6 months 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.

Response of treatment in patients with endometrial hyperplasia is as follows-

When we evaluated the responses to progestin, regression rates were 84.6% for SH without atypia, 50% for SH with atypia, 66.7%% for CH without atypia after 3 months of hormone therapy.Persistence rates were 7.7% for SH without atypia, 50% for SH with atypia, 33.3% for CH without atypia. Progression rates were 7.7% for SH without atypia, no progression was identified in case of SH with atypia and CH without atypia.

In the study by **Simender mesci et al., [10] 2013**, 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., [21] 2001; Montgomery et al., [22] 2004**). 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., [23] 2014**). In a similar study of 31 females aged 30-70 years with endometrial hyperplasia, persistence was evident in 45% following MPA therapy; this was the highest rate reported in the literature. However, all endometrial hyperplasia types were evaluated, as in our study, which might explain the high rate of persistence (**Vereide et al., [24] 2003**).

The levonorgestrel-releasing intrauterine system, which has been advocated in many studies, has been found to be superior to oral progestins. However, no randomized studies of the efficacy of all types of oral progestins with an at least 5-year follow-up have been conducted **(Gallos et al., [25] 2013).**

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., [26] 2014).**

Limitations of the study:

1. The study was carried out in limited number of patients over a short period.
2. As the sample size was less many treatment options of AUB could not be studied.

V. Conclusion

Our study concludes that:

1. Abnormal uterine bleeding in perimenopausal women is most commonly dysfunctional in origin. However, a significant number show underlying organic pathologies. Hence a thorough histopathological work up and clinical correlation is mandatory in cases of abnormal uterine bleeding in this age group to find out organic pathology.
   .
2. Medical treatment can be considered as the first line therapeutic option for abnormal uterine bleeding.
3. Majority of cases of ovulatory AUB with secretory type of endometrium responded well to tranexamic acid
4. cyclical oral progestogens are effective in regulating and reducing irregular bleeding in anovulatory AUB with proliferative and cystic glandular hyperplasia type of endometrium.
5. Majority of the cases of endometrial hyperplasia without atypia can be successfully treated with progestogen therapy.
6. 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.
7. Ultimately, good patient selection and long-term follow-up are the most important factors in successful and safe treatment.

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