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## Research Article

# HISTOMORPHOLOGICAL PATTERNS OF DYSFUNCTIONAL UTERINE BLEEDING ON ENDOMETRIAL BIOPSIES- REVISITED

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### ABSTRACT

**Background-**Dysfunctional Uterine Bleeding (DUB) is defined as abnormal uterine bleeding not caused by pelvic pathology, medications, systemic disease or pregnancy. It is a diagnosis of exclusion. Endometrial biopsy is a simple, cost effective procedure which helps in ruling out organic causes and establishing the changes in endometrium. **Objectives-**To analyse the endometrial histomorphological patterns in cases of DUB and to correlate with clinical presentations. **Methodology-**Endometrial biopsy samples fixed in 10% formalin were processed, embedded, sections cut, stained with H& E stain and hisopathological features were noted. **Results-** Out of 500 endometrial biopsies studied, 225 were Proliferative, 69 Secretory, 127 Simple hyperplasia without atypia, 27 Complex hyperplasia without atypia, 10 Mixed endometrium, 07 disordered proliferation, 07 chronic endometritis, 05 Partial mole, 05 luteal phase defect, 05 atrophic, 04 Arias stella reaction, 04 inadequate, 02 Endometrial adenocarcinomas, 01 endometrial stromal sarcoma and 01 Endometrial polyp. Majority of patients were in the age group of 31-40 years. Most common presenting complaint was menorrhagia. **Conclusion-**The study helps in detecting and differentiating functional causes from organic lesions, thereby facilitating appropriate patient management.

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## INTRODUCTION

Dysfunctional uterine bleeding (DUB) is the clinical term used to describe abnormal uterine bleeding not associated with a clinically detectable organic cause, in women of child bearing age.<sup>1</sup>

DUB is one of the frequently encountered and perplexing conditions. The prevalence increases with age, peaking just prior to menopause. Since most cases are associated with anovulatory menstrual cycles, adolescent and peri-menopausal women are particularly vulnerable. About 20% of affected individuals are in the adolescent age group and 50% are aged between 40-50 years.<sup>2</sup> Contrary to this, the revised concept indicates increased incidence of DUB in reproductive age group.

Endometrial biopsy is the chosen method to evaluate DUB because of its advantages over other diagnostic methods. It is a simple, cost effective, out patient procedure which is pivotal in studying the endometrium and helps in differentiating the organic from functional causes of DUB, thus helping in customizing the treatment accordingly. Endometrial biopsy has

the additional advantage of having the ability to detect even the non-hormonal conditions resulting in DUB.<sup>3,4</sup>

Normal menstruation is defined as the bleeding from secretory endometrium, associated with an ovulatory cycle, not exceeding a length of 5 days. Any bleeding not fulfilling these criteria is referred to as abnormal uterine bleeding. Dysfunctional uterine bleeding is defined as abnormal uterine bleeding not caused by pelvic pathology, medications, systemic disease or pregnancy. Thus, if on bimanual examination, the uterus and appendages are found to be normal, this term is used.<sup>1,5</sup>

40- 55% cases of DUB occur in the age of 20-40 years.<sup>6</sup>The common causes of DUB in different agegroups are as shown in the table

**Table 1** Causes of DUB by age group<sup>7</sup>

Age group	Causes
Prepuberty	Precocious puberty (hypothalamic, pituitary, or ovarian origin)
Adolescence	Anovulatory cycle

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Reproductive age	Complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy), organic lesions (polyps, endometrial hyperplasia, carcinoma, leiomyoma, adenomyosis), anovulatory cycle, ovulatory DUB
Perimenopausal	Anovulatory cycle, irregular shedding organic lesions
Postmenopausal	Organic lesions (carcinoma, hyperplasia, polyps) endometrial atrophy

Endometrial biopsies obtained by dilatation and curettage (D&C) provide a sample of endometrium for histopathological study. It has been reported that, histology assists in diagnosing the cause of abnormal uterine bleeding in 48.5% of cases, intrauterine lesions in 25.5% and anovulatory cycles in 22.9%.<sup>8</sup>

The histomorphological patterns seen on endometrial biopsies in cases of DUB include

1. In a ovulatory cycle: Inadequate proliferative phase, Inadequate secretory phase (Underdeveloped secretory endometrium, Luteal phase defect), Irregular shedding of the endometrium, Irregular ripening and Dysmenorrhoea membranacea<sup>1,9,10</sup>
2. In a anovulatory cycle: Disordered proliferative phase<sup>11</sup>
3. Endometrial hyperplasia<sup>11,12</sup>:classified by Kurman and Norris (1986), approved by WHO a). Hyperplasia without atypia (Simple/ complex) b). Atypical hyperplasia(Simple/ complex)

Treatment of functional and organic causes of DUB are different and call for a correct diagnosis and appropriate management, thus reducing the morbidity and mortality associated with this common entity<sup>1,6</sup>, hence underlining the importance of endometrial examination in these cases.

In a study of 104 cases of abnormal uterine bleeding, it was found that proliferative (30.8%) type of endometrium was the commonest, followed by secretory (25.8%), hyperplastic (20.2%), irregular shedding (7.7%), malignancy (5.8%) and tuberculosis (3.8%).<sup>13</sup>

In a study of 7000 endometrial curettings, 88.14% had histological signs of oestrogen influence in the form of an anovulatory or an ovulatory endometrium with simple hyperplasia which was the most common form of hyperplasia.<sup>14</sup> Findings in a study of 100 cases of DUB- DUB was common in reproductive &peri-menopausal age, multiparous(87%), menorrhagia was the commonest symptom(34%) and hyperplastic endometrium the commonest pattern(44%).<sup>15</sup>

In a study of 260 cases of DUB, menorrhagia(51.9%) was the commonest symptom, common age was 41-50 years(48%), with endometrial hyperplasia(24.7%) being the commonest pattern. The study revealed that, 40% of the curettings detected endometrial pathology rendering D&C as an important diagnostic procedure.<sup>16</sup> In a study of 2295 cases, secretory endometrium(24.9%) was the most common followed by proliferative (21.7%). Uterine malignancies & complex hyperplasia with atypia were common in the age group of 52 years & above (3.3% &1.2% respectively).<sup>17</sup>

The present studied was carried out to document the various histopathological patterns seen on endometrium in DUB cases inorder to rule out organic causes and to correlate it with the clinical profile.

### Objectives of the Study

To study the histomorphological patterns of endometrial biopsies in dysfunctional uterine bleeding and to correlate the clinical presentations with the histopathological diagnosis

### MATERIALS & METHODS

The study was undertaken in the Department of Pathology, Mysore medical college & research institute between December 2010 and May 2012. All the endometrial biopsy samples received in the department were included in the study. The endometrial biopsy material fixed in 10% formalin was processed routinely and 3-4 micron sections were prepared from paraffin embedded tissue. These sections were stained with haematoxylin and eosin and studied for the following findings to detect the cause of bleeding – glandular changes, stromal changes, spiral arterioles, peri arteriolar predecidualization, predecidualization upto sub surface zonacompacta, haemorrhage, leucocytic infiltration, chronic endometritis, granuloma formation, lymphoid follicles and atypical changes. Appropriate special stains like Periodic acid Schiff was done as and when required. A detailed histological study was carried out and the findings noted. Details of the clinical history and relevant investigations were collected. Statistical analysis was done using Frequencies, Descriptives, Contingency coefficient test and Chi square test.

**Inclusion Criteria-** Endometrial samples of DUB patients of less than 50 years age were included in the study.

Institutional ethical committee clearance was obtained.

### RESULTS

The present study comprised of evaluation of 500 cases of DUB over a period of 18 months and the data was analysed in the following ways.

1. Age distribution pattern (Table 2)
2. Relationship of DUB with Parity (Table 3)
3. Bleeding patterns in DUB patients. (Table 4).
4. Patterns of distribution of histopathological findings among various age groups
5. Histopathological findings in the present study (Table 7)
  - A. Reproductive age group (21-40 years) (Table 5)
  - B. Perimenopausal age group (Table 6)
6. Study of histopathological findings in correlation with different types of abnormal bleeding
7. Duration of symptoms (Table 8)

**Table 2** Age distribution pattern

Age group	Number	Percentage
<20	25	5.0
21-30	120	24.0
31-40	190	38.0
41-50	165	33.0
Total	500	100.0

The age of patients ranged from 17 to 48 years with maximum number of cases seen in the age group of 31-40 years (38%).

**Table 3** Relationship of DUB with parity

Parity	Number	Percentage
Nulliparous	55	11.0
Multiparous(1-3)	380	76.0
Grand-multiparous(>3)	65	13.0
Total	500	100.0

The parity ranged from 0 to 4 with the highest incidence of DUB in multiparous (76%) women.

**Table 4** Distribution of bleeding patterns

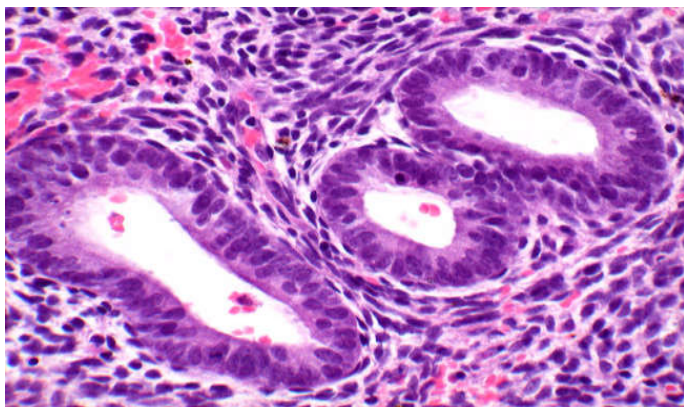
Bleeding patterns	Number	Percentage
Menorrhagia	370	74%
Metrorrhagia	60	12%
Menometrorrhagia	40	8%
Polymenorrhagia	30	6%
Oligomenorrhea	0	0%

Menorrhagia was the most common symptom accounting for 74%.

**Table 5** Pattern of distribution of histopathological findings in patients of the reproductive age group(21-40 years)

Histopathological findings	Number	Percentage
Proliferative phase	180	58
Secretory phase	46	14.8
Simple hyperplasia without atypia	38	12.2
Complex hyperplasia without atypia	13	3.8
Mixed endometrium	9	2.6
Partial mole	5	1.5
Luteal phase defect	5	1.5
Disordered proliferation	4	1.1
Chronic endometritis	4	1.1
Arias stella reaction	3	0.8
Inadequate	1	0.3
Endometrial adenocarcinoma	2	0.5
<b>Total</b>	<b>310</b>	<b>100%</b>

Out of the 310 cases belonging to the reproductive age group, proliferative phase(Fig 1) was the dominant histopathological pattern with 2 cases of endometrial adenocarcinoma.

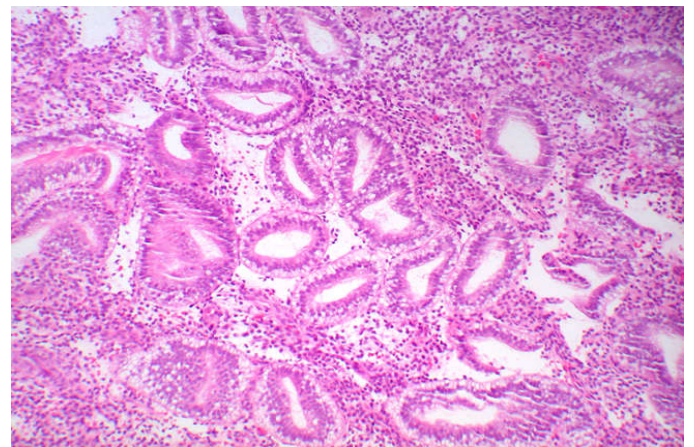


**Figure 1** H& E stain showing Proliferative phase with tubular glands lined by pseudostratified epithelium, surrounded by cellular stroma.

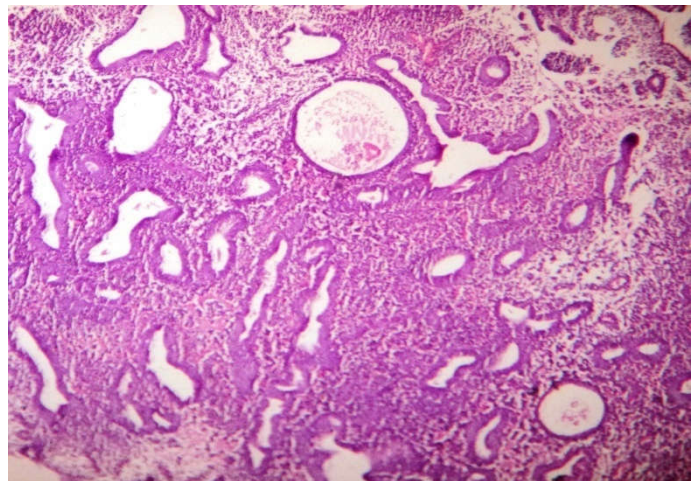
There were 190 patients belonging to the perimenopausal age group with a predominance of simple hyperplasia without atypia pattern(Fig 3) with a one case each of endometrial stromal sarcoma and endometrial adenocarcinoma(Fig 4).

**Table 6** Pattern of distribution of histopathological findings in patients of the peri-menopausal age group

Histopathological findings	Number	Percentage
Proliferative phase	45	23.6
Secretory phase(Fig 2)	23	12.1
Simple hyperplasia without atypia	89	46.8
Complex hyperplasia without atypia	14	7.3
Atrophic endometrium	5	2.6
Endometrial stromal sarcoma	1	0.5
Inadequate	3	1.5
Disordered proliferation	3	1.5
Mixed endometrium	1	0.5
Chronic endometritis	3	1.5
Endometrial adenocarcinoma	1	0.5
Arias stella reaction	1	0.5
Endometrial polyp	1	0.5
Total	190	100%

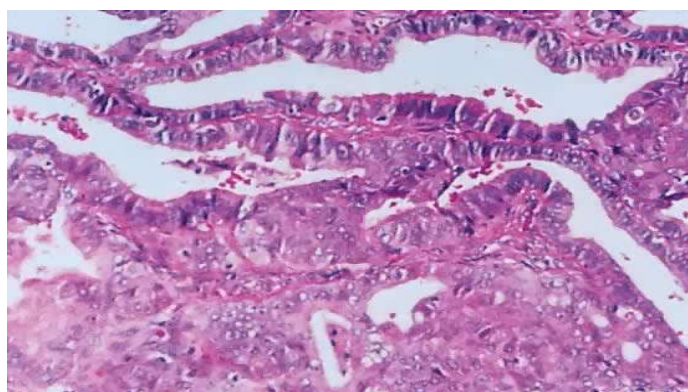


**Figure 2**-H&E stain- Secretory phase with tortuous glands showing subnuclear vacuolation and oedematous stroma



**Figure 3** H& E stain -Simple hyperplasia without atypia with large cystically dilated glands against compact stroma





**Figure 4** H & E stain- Endometrial adenocarcinoma showing overcrowding of glands, intraglandular bridging, papillary projections with nuclear atypia& mitoses

**Table 7** Analysis of histopathological patterns

Histopathological findings	Number	Percentage
Proliferative phase	225	45
Secretory phase	69	13.8
Simple hyperplasia without atypia	127	25.4
Complex hyperplasia without atypia	27	5.4
Mixed endometrium	10	2
Partial mole	5	1
Luteal phase defect	5	1
Disordered proliferation	7	1.4
Chronic endometritis	7	1.4
Arias stella reaction	4	0.8
Inadequate	4	0.8
Endometrial adenocarcinoma	3	0.6
Atrophic	5	1
Endometrial stromal sarcoma	1	0.2
Endometrial polyp	1	0.2
<b>Total</b>	<b>500</b>	<b>100%</b>

Proliferative phase was the most common histopathological finding accounting for 45% followed by Simple hyperplasia without atypia accounting for 25%.

**Correlation between types of bleeding and histopathological findings**

Irrespective of the type of bleeding, proliferative phase was the commonest histopathological finding in all types of abnormal bleeding.

**Table 8** Duration of symptoms in the patients

Duration	Number	Percentage
<1wk	20	04%
1wk-4wk	50	10%
1m-6m	255	51%
6m-1yr	90	18%
>1yr	85	17%
Total	500	100%

Maximum number of patients presented with symptoms for a duration of 1 to 6 months, accounting for 51%. 04% of patients presented with symptoms of less than a week.

**Incidence of organic lesions detected histopathologically in clinically diagnosed DUB cases**

In the present study, there were 05 cases of organic lesions detected on histopathological examination, out of which 01 was an endometrial polyp, 01 endometrial stromal sarcoma, and 03 endometrial adenocarcinomas. Diagnosis of these cases stresses the importance of endometrial examination in DUB cases.

**DISCUSSION**

Dysfunctional uterine bleeding continues to be one of the most frequently encountered and perplexing problems in Gynaecological practice. It may present at any age between puberty and menopause and it may be associated with kinds of histopathological findings in the endometrium. Below is a table which compares the results of present study with other studies.

**Table 9** Comparative study of age incidence

Authors	Number	<20		21-30		31-40		41-50		51 and above	
		Total	%	Total	%	Total	%	Total	%	Total	%
Sutherland <sup>18</sup> (1950)	100	36	3.6	242	24.2	343	34.3	362	36.2	17	1.7
AnusuyaDas <sup>19</sup> (1964)	117	17	14.5	24	20.5	33	28.2	38	32.5	5	4.3
Bhattacharji <sup>20</sup> (1964)	164	14	8.5	50	30.5	56	34.2	44	26.8	--	--
Wagh&Swamy <sup>21</sup> (1964)	552	97	17.6	215	39	143	25.9	94	17	3	0.5
Mehrotra <sup>22</sup> (1972)	150	15	10	72	48	35	23.3	25	16.7	3	2
Muhammad <sup>16</sup> (2005)	260	0	0	33	12.7	102	39.2	125	48.1	--	--
Present study(2012)	100	5	5	24	24	38	38	33	33	--	--

The highest incidence of DUB was noted in the 31-40 years age group in the present study which is in concordance with the results of the studies by Das and chugh<sup>19</sup>(1964), Bhattacharji<sup>20</sup>(1964), Narula<sup>22</sup>(1964) and Maheshwari *et al*<sup>13</sup>(1996) whereas, Sutherland<sup>18</sup>(1950), Mac Gregor, MuhammedMuzaffar<sup>16</sup>, Anusuya Das(1964) reported maximum incidence in 41-50 years age group and Mehrotra *et al*<sup>22</sup>(1972), Wagh and Swamy<sup>21</sup>(1964) reported maximum incidence in 21-30 years age group.

Considering these discrepant observations, one may conclude that, any age after menarche is not exempt from DUB.

The highest incidence of DUB was seen in the reproductive age group in the present study(62%) which is in concordance with the results of the studies by Sutherland<sup>18</sup>(56.8%), V.G.Mehrotra *et al*<sup>22</sup>(71.33%) and Pillai *et al*<sup>15</sup>(58%).

**Relation between parity and dysfunctional uterine bleeding**

In the present study, the highest incidence of DUB was seen in multiparous(76%), which is in concordance with the results of the studies by Bhattacharji<sup>20</sup>(46%), Pillai<sup>15</sup>(87%) and V.G.Mehrotra *et al*<sup>22</sup>(46%).

The lowest incidence was seen in nulliparous women in the present study which is in concordance with the results of the studies by Mehrotra *et al*<sup>22</sup>(20%), Das & Chugh<sup>19</sup>(18%) and Bhattacharji<sup>20</sup>(18.8%).

By these observations, it may be implied that incidence of DUB is highest in parous women.

**Bleeding patterns in DUB**

**Table 10** Comparative study of types of bleeding and DUB

Type of bleeding	V.G.Mehrotra		Present study	
	Number	Percentage	Number	Percentage
Menorrhagia	78	52	370	74
Metrorrhagia	29	19.33	60	12
Menometrorrhagia	0	0	40	8
Polymenorrhagia	39	26	30	6
Postmenopausal bleeding	4	2.67	0	0
Total	150	100%	100	100%

In the present study, menorrhagia was the commonest type of bleeding (74%) followed by metrorrhagia(12%), menometrorrhagia(08%) and polymenorrhagia(06%). In comparison, in the study by V.G.Mehrotra, while menorrhagia was the commonest(52%) type of bleeding, polymenorrhagia was the next common type followed by metrorrhagia and postmenopausal bleeding.

### Endometrial hyperplasia in cases of DUB

**Table 11** Comparative study of incidence of endometrial hyperplasia in DUB

Authors	Year	Number	Percentage with endometrial hyperplasia
Keene and Payne <sup>19</sup>	1934	500	23%
Traut <i>et al</i> <sup>19</sup>	1936	---	58%
Jones <sup>19</sup>	1938	---	25%
Hones <i>et al</i> <sup>19</sup>	1949	104	66.33%
Sutherland <sup>23</sup>	1950	1000	15.5%
Shah & Cave <sup>19</sup>	1958	60	58.6%
Bhattacharji <sup>20</sup>	1964	164	29.2%
AnusuyaDass <sup>19</sup>	1964	117	30.6%
Mehrotra <sup>22</sup>	1972	150	19.4%
Veena <sup>13</sup>	1996	104	20.2%
Pilli <sup>15</sup>	2002	100	44%
TalatMirza <sup>24</sup>	2012	1000	13%
Present Study	2012	154	30.8

Majority of the studies including the present study indicate that, the incidence of hyperplasia in DUB ranges from 19.4 to 31.25% whereas, a few other studies reported a higher incidence at 55 to 68% range while the lowest incidence (07%) was reported by Mirza<sup>24</sup>.

In the present study, the two important observations which were made regarding endometrial hyperplasia in DUB were that Endometrial hyperplasia was highest in the age group of 41-50 years and that it was highest in patients with history of menorrhagia.

In a study of 552 cases of DUB, it was observed that iron deficiency anaemia was the commonest end result of prolonged bleeding (37.4%) and the role of Emotional factors was proposed in the causation of DUB as normal endometrial pattern was seen in 20% of cases.<sup>21</sup>

In a review of 150 cases, an incidence of 8.32% of functional uterine bleeding was obtained, which was lower when compared with other studies. 48% of cases fell in the age group of 21-30 years.<sup>22</sup>

In a study of 1000 cases, 57% were functional and the rest 43% had organic lesions. Proliferative endometrium(35%) was the commonest pattern & hyperplasia(30%) was the commonest in organic lesions followed by chronic endometritis(13%) & polyps in 12%. Maximum cases were in the peri-menopausal age group.<sup>24</sup>

### CONCLUSION

DUB is one of the common gynaecological problems encountered in clinical practice.

Endometrium is a mirror of histopathology for the hormone dependant and non-hormone dependant causes of DUB in different age groups and is important in detecting the cause, clinching the diagnosis and managing the patient.

In the present study, menorrhagia was the commonest presenting symptom and multiparous women were the most affected by DUB. The commonest histopathological finding encountered was proliferative phase which was true for all the agegroups except for 41-50 years agegroup in which endometrial hyperplasia of the simple type without atypia was the commonest. The next common findings in the order of prevalence in the present study were secretory phase of endometrium and simple hyperplasia without atypia.

The importance of endometrial biopsy, histopathological study coupled with clinical correlation is invaluable in understanding the disease process in order to determine the underlying functional or organic cause and to plan appropriate patient management.

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