

## Dysfunctional Uterine Bleeding

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### HISTORY

#### Menstrual

- a. Cyclicity—cycle length, regularity (preferably exact dates over 3-4 cycles)
  - i. If irregular, presence of pre- or postmenstrual spotting
  - ii. If acyclic, postcoital bleeding
- b. Flow—amount (change of diapers/pads in a day; if heavy, need for change at night, passage of clots)

This information will help to know the pattern of bleeding (Table 35.1).

**Table 35.1:** Patterns of abnormal uterine bleeding and their causes

Cycle length	Bleeding	Pattern	Cause(s)
Normal	Prolonged/ excessive	Menorrhagia	Fibroids, adenomyosis, tuberculosis, DUP
Normal	Reduced	Hypomenorrhea	Tuberculosis, DUP
Shortened	Normal	Polymenorrhea	Pelvic inflammatory disease, endometriosis, DUP
Shortened	Excessive	Polymenorrhagia	
Prolonged	Normal/reduced	Oligomenorrhea	Polycystic ovarian syndrome, DUP, tuberculosis, long acting progestins
Acyclical	Irregular, may be excessive	Metrorrhagia	Uterine growth on cervix, ca cervix/uterus/ovary, irregular ovarian hormone intake
Normal	Spotting	Premenstrual spotting; menorrhagia	(Irregular) luteal phase corpus luteum deficiency
Normal	Spotting	Postmenstrual spotting; menorrhagia	(Irregular) shedding; prolonged corpus luteum activity

Presence of postcoital or acyclical or contact bleeding would indicate lesion on or in the cervix and/or vagina like cancer of cervix or vagina, erosion or ulcer on cervix, atrophic vaginitis.

- c. Last menstrual period and exposure to pregnancy is important. With a sudden change from a regular menstrual history to abnormal bleeding pattern, pregnancy related causes are a possibility.

Anovulatory bleeding is typically non-cyclical with an unpredictable pattern ranging from prolonged bouts of spotting to outright hemorrhage. Conversely, predictable cyclic menses, especially with premenstrual melioria (suggestive of progesterone secretion) provide the possibility that a woman is ovulating.

#### Associated Problems

##### a. Lower abdominal pain (dysmenorrhea)

- i. In relation to menstruation—before, during, after, midcycle
- ii. Intensity—vague, increasing with each cycle.

Anovular DUB is usually painless. Congestive dysmenorrhea is associated with endometriosis and pelvic inflammatory disease. Spasmodic type is suffered by adolescents where no cause is found and also the women with submucous fibroid and those using intrauterine device. Patients with endometriosis may have progressive dysmenorrhea.

##### b. Dyspareunia—is a common accompaniment with endometriosis and pelvic inflammatory disease.

##### c. Symptoms/features/indicators suggestive of:

- i. Hypothyroidism
- ii. Bleeding diathesis
- iii. Tuberculosis.

#### Other Attributes

- a. Age—some causes are more common in some age groups. In reproductive age group pregnancy related and causes secondary to pelvic infection are more common. DUB will be the consideration in extremes of ages. However, one needs to exclude blood dyscrasias and endocrine mediated etiologies in adolescents. In perimenopausal and women of later age emphasis should be in excluding genital malignancies (Table 35.2).

**Table 35.2:** Causes of abnormal uterine bleeding in order of their occurrence in different age groups

<20	20-40	> 40
Coagulation defects	Pregnancy states	DUB
Endocrinal defects	DUB	Iatrogenic
DUB	Infections	Neoplasm
Infections	Endometriosis, fibroid	Pregnancy states
Endometriosis	Iatrogenic	Infections
Iatrogenic	Coagulation defects	Chronic liverrenal dis.
Pregnancy states	Endocrinal defects	Endocrinal defects
Neoplasm	Neoplasm	Coagulation defects

- b. Parity—adenomyosis and cancer cervix is more common in women with high parity, while fibroid, endometriosis and endometrial hyperplasia/cancer are associated with low parity.

- Contraceptive use—IUCD, ovarian steroidal hormones
- Other drug use—extraneous ovarian steroidal hormones, anticoagulants, salicylates.

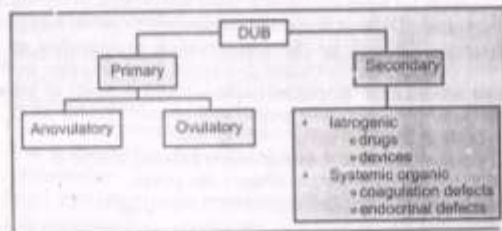
#### FREQUENTLY ASKED QUESTIONS (FAQS)

##### 1. What is dysfunctional uterine bleeding?

Dysfunctional uterine bleeding (DUB) is best defined as 'abnormal uterine bleeding due to disorder in the endocranial mechanisms of menstruation or physiological mechanisms responsible for arrest of menstruation'. It is an abstract definition and the diagnosis of the entity is by process of exclusion of the causes of abnormal uterine bleeding. The working definition considered by many is 'abnormal uterine bleeding not due to organic disease or the atrogenic cause.'

##### 2. How is it classified? What is the basis for classification?

Having taken 'absence of clinically detectable pelvic cause for abnormal uterine bleeding' as the working definition, some authors have classified DUB as primary and secondary. The assumption is that causes like hypothyroidism, thrombocytopenia, coagulation factor defects and those due to contraceptive usage or intake of ovarian steroidal hormones, salicylates or anticoagulants which are without pelvic abnormality should warrant inclusion under secondary DUB. Primary DUB is in fact the DUB and could be due to aberration in hypothalamo-pituitary-ovarian axis resulting in abnormality in ovulation and is classified as either anovulatory or ovulatory. Since abnormality in hypothalamo-pituitary-ovarian axis would logically mean anovulation, many use the terms DUB and anovulatory DUB interchangeably.



Classification of Dysfunctional Uterine Bleeding

##### 3. Ovulation indicates functioning hypothalamo-pituitary-ovarian axis. Then despite ovulation why do some women have abnormal uterine bleeding?

The mechanism of DUB in ovulatory and anovulatory states is not fully understood. It is likely that local endometrial mechanisms are important in the pathophysiology of DUB. These local mechanisms probably involve uterine vasculature possibly influenced by prostaglandins and other vasoactive substances, altered mechanism of hemostasis, and changes in the process of

tissue breakdown and remodeling. The influence of ovarian steroids upon these processes is likely to be indirect. Apart from the local mesostatic mechanism, it is the function and longevity of corpus luteum that results in abnormal uterine bleeding (AUB) patterns.

4. What could be the mechanism for anovulatory DUB?

Menstrual cycles become irregular because of acyclic estrogen production and absence of progesterone withdrawal which leads to endometrial proliferation and eventual erratic breakdown. Estrogen may also stimulate excessive endothelial production of nitric oxide in endometrium.

5. Specify local endometrial mechanisms implicated in DUB

- a. Vasculature—Morphometric analysis of uterine spiral arteriole density has shown no correlation with mean blood loss, but myometrial venous density can be increased in DUB. However, it can be functional rather than anatomical changes in the endometrial vasculature that are mainly responsible for excessive menstrual bleeding.
- b. Vasoactive substances—prostaglandins, endothelins and nitric oxide are the substances that could have a role in hemostasis.
  - i. Prostaglandins—Ovulatory DUB is associated with a shift in the ratio of endometrial vasoconstricting PGE2 alpha to vasodilatory PGI and an increase in endometrial concentration of prostaglandins. In persistently proliferative endometrium seen in anovulatory DUB, the availability of arachidonic acid is reduced and prostaglandin synthesis is impaired. Endometrial tissues could be more responsive to the action of vasodilatory prostaglandins in DUB.
  - ii. Endothelins—Receptors for endothelins are predominantly located at the endomyometrial junction and are present in increased concentration just before the menstruation. Sertal estradiol and progesterone reduce receptor concentrations.
  - iii. Nitric oxide (endothelium derived relaxing factor)—Factors which modulate the synthesis and action of nitric oxide could lead to an increase in menstrual bleeding and might be an important mechanism in anovulatory bleeding.
- c. Abnormalities of tissue breakdown and remodeling—may contribute to changes in the quantity and quality of menstrual loss. Endometrial breakdown and repair are largely controlled by local factors like lysosomes, matrix metalloproteinases, intercellular adhesion molecules, macrophages and other migratory leukocytes.
  - i. Lysosomes—Tissue hypoxia following spiral artery coiling and endometrial regression and vascular stasis stimulates lysosomal activation. Lysosomal enzyme activity in the endometrium is increased in women with ovulatory DUB and that secondary to use of intrauterine devices.
  - ii. Matrix metalloproteinases—are a highly regulated enzymes that can degrade most components of extracellular matrix and are expressed cyclically consistent with ovarian steroid hormones. Menstruation is

- associated with change in balance between expression of these substances and their tissue inhibitors leading to tissue degradation.
- iii. Macrophages and other migratory leukocytes—are increased premenstrually. Macrophages contain lysosomes and can release platelet activating factor and PGE2 that augment menstrual bleeding. Mast cells degranulate premenstrually to secrete heparin, histamine and other vasoactive substances. In DUB, endometrial secretion of heparin-like substances is increased.
  - iv. Inter cellular adhesion molecules and platelet-endothelial adhesion molecules are thought to control binding of leukocytes to endothelial cells and breakdown these bonds may contribute to DUB.
  - d. Endometrial repair and regeneration seems to be governed by local factors like cytokines through neutrophil chemotaxis, epithelial regeneration through vascular endothelial growth factor and endometrial hemostasis through balanced fibrinolysis. Over activation of the fibrinolytic system may unbalance the hemostatic system, causing early breakdown of thrombi in the endometrial vessels and excessive blood loss.

6. Diagnosis of DUB is based on the assumption that there is no detectable pelvic pathology. If there is a detectable fibroid, can the patient still have DUB?

Fibroid, like anovulatory DUB is a result of hyperestrogenic condition. Cervical, broad ligament and subserous fibroids do not produce menstrual abnormality through structural changes in uterus. AUB in such conditions could be considered as DUB. Studies on myomata related bleeding suggest that it is not the increased surface area of the endometrium or local compression of vessels that causes bleeding. Nor does it seem that myomas have any effect on the hypothalamic pituitary ovarian axis. Instead the likely cause of the problem appears to be growth factor dysregulation causing uterine vascular dysfunction. It may then be argued that such dysfunction and dysregulation occurs because of fibroids and hence the AUB can not be considered as DUB.

7. If a patient of uterine prolapse without decubitus ulceration has AUB, could it be considered as DUB?

Apart from the obvious decubitus ulceration and vascular erosion, pelvic congestion in the early stages of prolapse following altered uterine and ovarian circulation (venous congestion) due to anatomic change may influence ovarian steroidogenesis and cause AUB. In the menopausal older age group, atrophy could result in DUB.

8. What are the necessary investigations for the workup of a case thought to be of DUB?

Investigations are ordered with the intention to know the effect, the type and to exclude other causes of abnormal uterine bleeding (AUB).

- a. Hemogram—at least hemoglobin estimate with hematocrit, in all cases. Anemia could be effect as well as the cause. Local tissue anoxia may interfere with tissue regeneration and vascular hemostatic activity.

- b. Pelvic ultrasonography—will be of value for all cases in any age group to exclude pelvic causes of AUB and to note the endometrial pattern. Sonohysterogram will be an additional aid for ruling out intrauterine pathology.
- c. Coagulogram—restricted to bleeding/clotting time studies with platelet counts especially in adolescents will reveal the cause for abnormal uterine bleeding patterns.
- d. Thyroid function tests—the estimation of thyroid stimulating hormone for adolescents and perimenopausal groups will help to exclude subtle hypothyroid state which is not an uncommon cause for AUB.
- e. Uterine curettage—should be carried out in all cases of perimenopausal and menopausal age groups to over rule underlying neoplastic lesions. It will provide insight into type of endometrium and ovulatory status for specific hormonal manipulation when empirical treatment has failed in the mid reproductive age groups. It will not be required for adolescents since anovulatory DUB is more of a norm in them. Microbiologic analysis of menstrual blood of first day may help exclude genital tuberculosis in the latter.
- f. Other endocrine studies—like assay of follicular stimulating and luteinizing hormones are to be carried out if the patient is obese or features of hirsutism, infant cycles are present in adolescents and early reproductive age. Prolactin estimation is ordered when the patient fails to respond to medical management or has galactorrhea.

9. If uterine curettage is advised, what is the basis?

Uterine curettage is advised in perimenopausal and menopausal women with recurrent episodes of AUB to rule out uterine adenocarcinoma. In younger women not responding as anticipated to the medical management, the curettage is timed to precede next menstrual period to obtain information about ovulatory status (type of DUB) and the pattern of endometrium. In patients with continuous excessive bleeding, thorough curettage may have a therapeutic benefit. When carried out, curettage may curette out endometrial mucosal polyps, help diagnose submucous fibroid during the procedure and genital tuberculosis on histopathology.

10. Does the knowledge of type of endometrium in DUB influence the management?

The histological type of the endometrium will reflect the hormonal influence and mostly helps in tailoring the management for the case. Anovulatory endometrial patterns can be undone by mimicking the ovulatory effect through supplementation of progestins in the latter half of menstrual cycle or in cases where fertility is also a concern by inducing ovulation. The ovulatory patterns may be set right by inhibiting ovulation or through altering the local microstatic mechanism (e.g. PGs, antifibrinolytics, vessel wall stabilizers, hematinics, etc.) It should be remembered that atrophic endometrium though is of anovulatory type would require estrogen supplementation; where as,

ovulatory endometrial patterns due to deficient corpus luteum activity would require progestins (Table 35.3).

**Table 35.3:** Endometrial type, hormonal status and treatment

Type of endometrium	Estrogen	Progesterone	Directed treatment
1. Anovulatory a. Proliferative	normal	absent	progestins (from D15-25) or ovulation induction (when infertility is a concern)
b. Cystic glandular hyperplasia	?	absent	as above
c. Adenomatous hyperplasia— simple	??	absent	option 1 progestins (from D15-25) and follow up option 2 hysterectomy if menopausal or perimenopausal with positive history *family *hypertensive status *obese/hypertensive, diabetic)
d. Adenomatous hyperplasia— complex	???	absent	
e. Atrophic/ threshold	?	absent	estrogen
2. Ovulatory a. Secretory	normal	present	local macrostatics
b. Irregular opening (from D15-25)	normal	?	progestins
c. Irregular shedding	normal	persistent CL	estrogen-progestin combination pills

CL = corpus luteum

11. What is the mechanism of action?

It is the irregular bleeding because of thin endometrium due to poorly developed proliferative phase. In such cases amount of estrogen is less—enough to reach threshold for bleeding, but not enough to produce a full proliferative phase. It is seen in young girls and in perimenopausal phase.

12. What is the mechanism of action of progestins for use in anovulatory DUB?

Apart from it being logical (the patient has AUB because she has not ovulated and mimicking or inducing ovulation should set it right), the use of progestins

- help convert potent estradiol to less estrogenic estrone through stimulation of 17 beta hydroxyl steroid dehydrogenase and sulfotransferases.

- ii. hinder estrogen receptor replenishment by inhibiting estrogen's induction of its own receptor
- iii. suppress estrogen mediated transcription of oncogenes, which property is harvested for reversing premalignant/malignant changes.

13. How do estrogens act to reduce bleeding?

Estrogens are used in the management of DUB because of their effect

- i. on capillary/small vessel bleeding by increase in fibrinogen, factors V and IX, and platelet aggregation
- ii. on tissue reactions to bradykinin, mucopolysaccharides and capillary permeability
- iii. of endometrial proliferation.

14. What is/are the indication/s for hysterectomy in DUB.

The following could be considered as cases for hysterectomy

- a. Women not responding to medical management, showing significant effect of bleeding and are beyond 35-40 years of age in whom fertility is not a concern
- b. Perimenopausal women who are at risk of endometrial carcinoma
  - i. family/ personal history of adenocarcinoma
  - ii. known cases of chronic anovulation—polycystic ovarian syndrome, endometriosis
  - iii. obese with hypertension and/or diabetes, even if with simple endometrial hyperplasia
  - iv. complex and/ or atypical adenomatous hyperplasia
- c. Postmenopausal women with
  - i. thick endometrium or hazy endomyometrial junction
  - ii. repeated episodes of vaginal bleeding.

15. What is the risk of progression of anovulatory endometrial patterns to endometrial carcinoma?

As the extent of unopposed estrogenic action increases, the risk of endometrial carcinoma increases (Table 36.4).

Table 36.4: Type of anovulatory endometrium and risk of endometrial carcinoma

Endometrial pattern	Risk of endometrial carcinoma (%)
Simple hyperplasia	1
Complex hyperplasia	3
Simple hyperplasia with atypia	8
Complex hyperplasia with atypia	25

16. When will you consider that a patient has failed to respond to medical management?

A patient of DUB is started and continued for 3 to 6 cycles on the initially planned medical management, hormonal or otherwise. They are then observed



for about 3 cycles without any drugs. If the irregularity persists while on drugs or recurs after several attempts at the medical management, it can then be considered as treatment failure.

**17. Can hysterectomy be avoided in patients not responding to medical management?**

Levonorgestrel intrauterine systems (LNG-IUS), endometrial ablation methods and in some situations uterine artery embolization may help avoid resorting to hysterectomy.

**18. Intrauterine devices are thought to cause AUB and LNG-IUS is found to be useful in women who failed to respond to progestins. What is the basis for the claim?**

The daily dose of levonorgestrel (20 micrograms) causes desexualization of endometrial stroma, atrophy of endometrial glands, a surface papillary pattern, and a stromal inflammatory infiltrate. The drug being released directly at the endometrium makes these effects effective.

**19. What is endometrial ablation? Who are the candidates for the procedure? What are the different methods used?**

Endometrial ablation is destruction of endometrium. It could be considered for women with no intrauterine pathology not responding to medical therapy and having length of uterine cavity not bigger than 12 cm. Patients with anovulatory DUB are not good candidates for endometrial ablation. There are varieties of global endometrial ablation devices using different energy sources like hot water, cryocautery, microwave, laser, and radio frequency electricity.

**20. How will you manage a patient reporting with continuous excessive bleeding?**

In extreme circumstances, parenteral therapy with intravenous conjugated estrogens (25 mg) will usually arrest an acute bleeding episode. GnRH agonists have also been used because of their effect of initial stimulation of endogenous estrogen. Intravenous doses of tranexamic acid and/or etamsylate may also help in reducing the bleeding. Parenteral therapy should be followed by 2 to 3 weeks of oral progestins. In such patients where hysterectomy is planned, to tide over the bleeding episode tablets of danazol or injection of testosterone are used successfully while awaiting fitness/preparedness for surgery.

**21. Is it possible to correlate pattern of DUB to endocrine and histological changes?**

DUB can have its origin in an endocrine imbalance or can occur in normal menstrual cycles (ovulatory DUB).

**Table 35.5:** Correlation between menstrual patterns with ovarian and endometrial changes in menstruation

Ovulation	Phase changes	Endometrial histology	Menstrual pattern
Normal	Short FP	Normal	Polymenorrhagia, menorrhagia
Normal	Long FP	Normal	Oligomenorrhea, menorrhagia
Abnormal CL	Short LP	Normal with luteal lag or deficient secretory (irregular ripening)	Premenstrual spotting, menorrhagia
Persistent CL	Long LP	Well developed secretory	Prolonged cycles
Anovulation (insufficient follicles)	Short cycle	Deficient proliferative	Polymenorrhagia, metrorrhagia
Anovulation (polycystic ovaries)	Prolonged cycle	Proliferative or hyperplastic	Oligomenorrhea, metrorrhagia, hemorrhagic

CL = corpus luteum, FP = follicular phase, LP = luteal phase

#### MULTIPLE CHOICE QUESTIONS—ONE BEST ANSWER (MCQs)

- Which of the following is not the characteristic of anovulatory DUB?
  - Noncyclic bleeding
  - Painless bleeding
  - Premenstrual melasma
  - Spotting alternating with heavy flow
  - Unpredictable bleeding
- The nonsurgical treatment of choice for DUB when effectiveness, side effects, and acceptability are considered:
  - Danazol
  - Levonorgestrel intrauterine system
  - Nonsteroidal anti-inflammatory agents
  - Oral contraceptive pills
  - Tranexemic acid
- Most likely cause of abnormal uterine bleeding in a nulligravida, obese, hirsute woman with normal pelvic examination:
  - Estrogenation
  - Medications
  - Mucosal polyp

- D. Persistent corpus luteum
  - E. Theca cell tumor.
4. The most appropriate next step in the management of irregular, scanty vaginal bleeding, in a lactating woman who is taking depot medroxy progesterone, is:
- A. Combination oral contraceptives
  - B. Endometrial biopsy
  - C. Intravenous estrogens
  - D. Observation for 3 months
  - E. Progesterone supplementation.
5. Which of the following is not the side effect of Danazol?
- A. Deepening of voice
  - B. Hirsutism
  - C. Leucopenia
  - D. Tinnitus
  - E. Visual disturbance.
6. Which is the treatment option for a woman who returns 6 months after the endometrial ablation with amenorrhea, severe cyclical abdominopelvic pain described by her as cramps?
- A. Combined oral contraceptives
  - B. Hysterectomy
  - C. Levonorgestrel intrauterine system
  - D. Nifedipine acid
  - E. Repeat endometrial resection.
7. Which of the following statements about norethisterone are correct?
- A. Is found to be no more effective than placebo in the short term treatment of menorrhagia
  - B. Is not recommended for medical treatment of menorrhagia
  - C. It is a 19-carbon atom containing synthetic progestin derived from testosterone
  - D. It is a 21-carbon atom containing naturally occurring progesterone
  - E. It is the most prescribed (50%) medical treatment for menorrhagia.
8. Complication that is not commonly associated with endometrial ablation is:
- A. Fluid overload
  - B. Hematometra
  - C. Infection
  - D. Thermal damage
  - E. Uterine perforation.
9. The rationale for the therapeutic use of conjugated estrogens for the immediate treatment of DUB is that estrogen:
- A. Causes decasualization
  - B. Leads endometrial proliferation

- C. Reduces platelet adhesiveness
- D. Stabilizes endogenous clotting factors
- E. Withdrawal results in uniform endometrial slough.

10. An obese woman aged 45 years who has fibroids reports with irregular heavy vaginal bleeding in the last 6 months. What is the most appropriate next step in the management of this patient?

- A. Combination oral contraceptives
- B. Endometrial biopsy
- C. Hysterectomy
- D. Myomectomy
- E. Reassurance and observation for 3 months.

**Answers**

1.C; 2.B; 3.A; 4.D; 5.D; 6.B; 7.C; 8.C; 9.B; 10.B