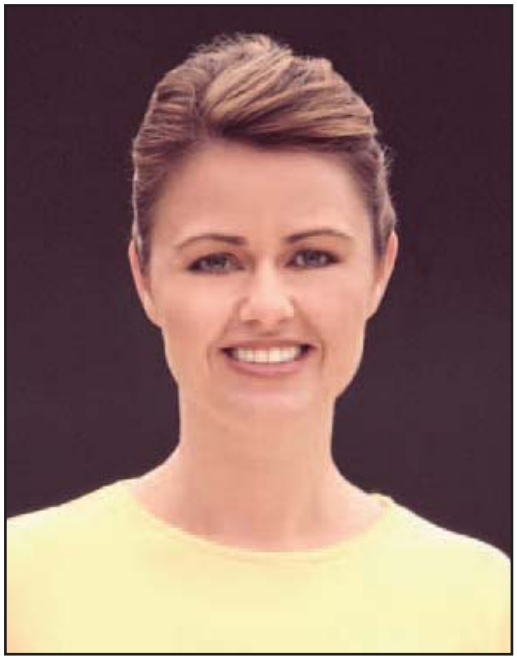
Is Your Patient Bleeding Too Much?

What to do about DUB



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In this article:

1. What is dysfunctional uterine bleeding (DUB)?
2. What are the specific and non-specific causes of DUB?
3. How do I treat DUB?

Patient investigations:

Head & Neck: Essentially normal with no thyromegaly. There was a scar from a previous thyroidectomy.
Chest & cardiovascular system: Essentially normal.
Abdomen: No hepatosplenomegaly. No masses palpable per abdomen.
Speculum: Moderate amount of old blood in the posterior fornix. The vagina walls looked normal. The cervix also looked normal. No Pap smear done. Pipelle endometrial biopsy performed. (Biopsy was done after negative stat urine pregnancy test).
Bimanual: Bulky uterus but no adnexal masses.

Case

A 48-year-old woman was referred for management of irregular, prolonged bleeding of five-month duration. She was started on oral medroxyprogesterone acetate, 10 mg once daily for 10 days, by the primary physician, while waiting for the consultation. She developed acute exacerbation of the bleeding on completing the 10-day therapy. After going to the emergency department for assessment, the emergency physician phoned the gynecologist to request urgent consultation for the patient. She was seen that day.

She has no significant past medical history. She has had a partial thyroidectomy for a thyroid nodule, which was found to be benign on histology. Her post-operative thyroid function tests have been normal. She does not have any other significant gynecologic history. The patient has not used contraception for the past 11 years. She does not have any significant peri-menopausal symptoms, and is not taking any medication.

What is the cause of her menorrhagia?
For case discussion, see page 78.

Dysfunctional Uterine Bleeding

Dysfunctional uterine bleeding (DUB) is a common problem in gynecologic and general practice. Most patients usually go to their primary physician first. Therefore, the goal for the primary physician would be to initiate workup, institute therapy, and know when to refer urgent and non-urgent cases.

What is DUB?

DUB is defined as abnormal uterine bleeding with no specific cause.[1] To make a firm diagnosis of DUB, one must rule out specific causes of abnormal genital tract bleeding. It is, therefore, a diagnosis of exclusion.

What are the types of DUB?

Abnormal uterine bleeding, associated with DUB, involves abnormality in quantity, duration, and frequency. The quantity can be described as heavy (with or without clots), scant, or spotting. The duration of bleeding may be prolonged or short. The frequency may be increased (one- to two-week interval between periods, or inter-menstrual bleeding), or decreased (two- to six-month interval between periods, or no periods for up to a year or more).

In the current climate of medical practice, where health information is shared with patients and other allied health personnel, the nature of abnormal uterine bleeding should be described in simple terms, instead of medical terminology like menorrhagia, metrorrhagia, menometrorrhagia, oligomenorrhea, or amenorrhea.[1]

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Practice Pointer

The aim of the workup for abnormal uterine bleeding is:

To rule out specific causes of uterine bleeding as noted in the differential diagnoses.

Differential diagnosis of abnormal genital tract bleeding

The etiology of abnormal genital tract bleeding is extensive, but some of the common causes found in general practice are listed in Table 1.

Table 1
Differential diagnoses of abnormal uterine bleeding

- Pregnancy
- Exogenous hormones
- Endocrine causes
- Anatomic causes
- Coagulopathies
- Infections
- Genital tract malignancy
- Drugs
- Anovulatory cyles associated with:
  - post-menarche
  - peri-menopause
  - polycystic ovary syndrome (androgen excess)
  - renal failure

Workup of abnormal uterine bleeding

The aim of the workup is to rule out specific causes of genital tract bleeding. A detailed history, with extensive review of the systems using information from the differential diagnosis, as well as a complete general examination, can narrow the differential diagnoses and direct the nature and extent of the investigation.

What are the specific causes of DUB?

Pregnancy

It is important to rule out pregnancy in all cases, using either a urine pregnancy test, or a serum qualitative or quantitative beta-human chorionic gonadotropin test.

Exogenous hormones

The most common exogenous hormones are oral contraceptives, progestational agents, and medications used for hormone replacement therapy (HRT).

Oral contraceptive therapy is associated with a 30% to 40% risk of abnormal bleeding within the first three months of use.[2,3] Progestational agents (*e.g.,* levonorgestrel implant, or depo-medroxyprogesterone acetate) are invariably associated with abnormal bleeding within the first year of use.[4,5]

When HRT is initiated in a peri-menopausal patient with a history of irregular bleeding, there is usually worsening of the abnormal bleeding, especially if a cyclical HRT regimen is followed. Post-menopausal patients using HRT also experience abnormal bleeding, but the risk is reduced with the continuous-combined regimen.

Exogenous hormones can also be found in differing concentrations in over-the-couner herbal or "natural" sources of post-menopausal formulations.

Endocrine causes

Some of the common endocrine causes of abnormal bleeding are hypothyroidism, hyperthyroidism, adult-onset congenital adrenal hyperplasia, Cushing's syndrome, hyperprolactinemia, hormone-producing ovarian tumours (thecomas, Sertoli's cell), and diabetes mellitus.

Anatomic causes

The benign anatomic causes of abnormal bleeding include uterine leiomyomas, endometrial or endocervical polyps, cervical lesions, such as ectropion, and lacerations of the cervix and/or vagina following con-

sensual sex, use of sex toys, or sexual assault. Foreign bodies in the vagina can also lead to abnormal bleeding, especially in the pediatric age group. In perimenopausal and post-menopausal patients, atrophic vaginitis can lead to post-coital spotting and/or bleeding.

Genital tract malignancies

The common gynecologic malignancies causing abnormal bleeding include cancers of the cervix, cancers of the uterus, and, to a lesser extent, functional ovarian cancers. Vaginal carcinomas are a rare cause of bleeding.

Genital tract infections

Patients with cervicitis of any etiology, but particularly chlamydial cervicitis, can present with intermenstrual bleeding and post-coital spotting. This should be ruled out, especially in teenagers or patients at risk for sexually transmitted infec-

Case Discussion

Plan:
1. Comprehensive blood work.
2. Control of the acute bleeding.

The patient was given the option of birth control pills for control of the acute bleeding, as well as for long-term therapy while waiting for workup results, or the use of birth control pills for control of the acute bleeding, followed by depo medroxyprogesterone acetate for long-term therapy. The patient opted to have the birth control pill for initial control and to decide on further therapy after the workup had been completed.

Treatment Given:
Ovral™ two tablets, three times a day for three days, followed by two tablets, twice a day, for three days, then one tablet daily to complete two packs of Ovral™ 21. The patient was advised to use dimenhydrinate for control of nausea.

Followup:
The patient was seen in three weeks. The acute bleeding had subsided within three days of the high-dose BCP therapy. The patient was on the second pack of the Ovral™. A pap smear was performed, since bleeding had subsided. The workup results were normal. The Pipelle endometrial biopsy result was also normal, showing secretory endometrium with no hyperplasia or malignancy.

Definitive Diagnosis:
Dysfunctional uterine bleeding

Further Management Options:
1. Birth control pill
2. Depo-medroxyprogesterone acetate
3. Endometrial ablation

The patient opted to continue on birth control pill therapy for the meantime, but may consider balloon ablation in the near future.

tions. Other causes of cervicitis to consider include condyloma (human papillomavirus), herpes simplex virus, Neisseria gonorrhoea, and other bacteria.

Endometritis of any cause (post-partum, post-abortal, spontaneous, therapeutic, or as part of pelvic inflammatory disease) can also predispose a woman to irregular bleeding.

Coagulopathies

Any condition predisposing to bleeding diathesis can cause abnormal bleeding. Such conditions include thrombocytopenia, leukemia, hepatic dysfunction (alcohol induced or secondary to chronic liver disease), and von Willebrand's disease.

The mechanism of bleeding associated with liver disease is related to decreased prothrombin (dependent factors II, VII, IX, and X). With Von Willebrand's disease, however, the bleeding is secondary to abnormal platelet function and decreased synthesis of factor VIII.

Drugs

Some examples of drugs that can cause abnormal uterine bleeding include anti-coagulants (heparin or warfarin sodium), some types of antidepressants, citalopram, or drugs affecting dopamine concentration (anti-psychotics, alpha-methyldopa), and certain classes of antidepressants (amoxapine, imipramine, amitriptyline).

Most physicians review the teratogenic potential of new drugs before prescribing to reproductive-age women. It would be advisable to consider the effects of any new drug on the patients' menstrual cycles during the same search.

It is now common practice to use warfarin sodium for patients with chronic atrial fibrillation, to prevent thrombo-embolic sequelae. If these patients are not closely monitored to keep the international normalised ratio in the therapeutic range of two to three, they may present to the emergency department with significant uterine bleeding. Consequently, they may require discontinuation of warfarin sodium, Vitamin K therapy, transfusion of blood, and sometimes, fresh-frozen plasma for management.

What are the non-specific causes of DUB?

Once the specific causes of abnormal bleeding have been ruled out through the workup, one would be left with the non-specific causes of abnormal uterine bleeding—the true DUB. This bleeding is related to anovulatory cycles, typically found in the post-menar-

Dysfunctional Uterine Bleeding

Table 2
Anovulatory mechanism for DUB

- Dysfunction of hypothalamus-pituitary-ovarian axis.
- No progesterone production.
- Continuous stimulation of endometrium by estrogens.
- Increased proliferation of endometrial tissues.
- Absence of periodic shedding causing breakdown of fragile endometrial tissues.
- Healing irregular and dysynchronous in endometrium.

che and peri-menopausal periods, as well as in association with polycystic ovary syndrome/androgen excess and chronic renal failure (Table 2).

The nature of the abnormality may be irregular and prolonged bleeding. This bleeding is usually secondary to continuous stimulation of the endometrium by sustained low levels of estrogens, associated with post-menarche and perimenopause. The other typical pattern of bleeding involves varying periods of amenorrhea followed by acute heavy bleeding. This pattern results from the sustained high levels of estrogens found in polycystic ovary syndrome/androgen excess.[1]

What are the investigations for DUB?

Table 3
Investigations of DUB

Blood Work

- Complete blood cell count (CBC) ideal (hemoglobin, platelets, white blood cell count if no CBC).
- PTT, international normalised ratio (if taking heparin or warfarin sodium).
- Coagulative studies if high suspicion of von Willebrand's disease.
- Hormonal assay: thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, prolactin, total testosterone, free androgen index, sex hormone binding globulin, dehydroepiandrosterone sulfate, 17-OH progesterone.
- Screen for diabetes mellitus, lipids (obesity, polycystic ovary).

Anatomic

- Pap smear (if no bleeding/macroscopic lesion).
- Biopsy of abnormal macroscopic lesion of vulva, vagina, or cervix.
- Screen for sexually transmitted infections, *Candida*, *Trichomonas*.
- Endometrial biopsy (Pipelle, Novak): satisfactory specimen correlates well with dilatation and curettage specimen.
- Imaging studies: ultrasound best.

The next step in the workup involves comprehensive laboratory investigations and anatomic investigations. The investigations may be tailored to the specific patient situation, and an additional workup would be dictated by the final diagnosis (Table 3). The workup is usually negative in patients with DUB.

How do I treat DUB?

The treatment would depend on the results of the workup. If specific etiologies were found, then the treatment would be directed by the normal management of the specific condition, with or with-

out additional medical therapy for abnormal bleeding (Table 4). The specific causes may also require specific surgical management.

The management of nonspecific causes of DUB is mainly medical, with surgical treatment reserved for cases where medical therapy fails. Patients who have completed their families can elect to have surgical management after a short course of medical therapy, or as the primary therapy. The surgery is usually elective, but sometimes can be done as an emergency procedure in life-threatening situations. In the adolescent patient, or patients requiring fertility, medical therapy is the only choice.

It is important to note that intravenous (IV) conjugated estrogens therapy is associated with risk of deep vein thrombosis or pulmonary embolism, especially in obese patients. Once treatment has been initiated for acute bleeding [using either IV conjugated estrogens or tapering high doses of monophasic birth control pills (BCP), or oral medroxyprogesterone acetate], the treatment should be continued using a normal dosage of the BCP or depomedroxyprogesterone acetate, otherwise there would be a recurrence of acute bleeding.

The definitive treatment for the bleeding associated with chronic renal failure is renal transplant. Medical therapy has not been very effective. Surgical therapy may be considered, if renal transplant is not planned, or while awaiting the transplant.

The treatment of abnormal bleeding related to polycystic ovary syndrome (PCO)/androgen excess depends on whether the patient requires immediate fertility or not. If immediate fertility is not required, then BCP can be used for both cycle control and contraception. Depomedroxyprogesterone acetate can also provide contraception, control the bleeding problem, and protect the endometrium from hyperplasia or malignancy associated with prolonged amenorrhea. In patients requiring fertility, the role of the primary physician would be to control the abnormal bleeding, then stop therapy to allow the patient to attempt pregnancy, as spontaneous ovulation can sometimes occur. If pregnancy were not achieved after a period of time, then referral to a gynecologist or reproductive endocrinologist would be advisable, since the patient may require ovulation induction using

Dysfunctional Uterine Bleeding

Table 4
Medical therapy for DUB

Non-acute bleeding

Birth control pills (BCP).

Oral or depo-medroxyprogesterone acetate.

Nonsteroidal anti-inflammatory drugs.

Others (such as GnRH analogue (Depot Lupron), Danazol, or Tranexamic Acid).

Acute bleeding

Airway, breathing, circulation.

Intravenous conjugated estrogens 25 mg (4 hourly, 4 doses, or until bleeding subsides).

- high risk of deep venous thrombosis or pulmonary embolism **OR** High dose BCP in tapering doses **OR** Depo-medroxyprogesterone acetate (150 mg +/- oral medroxyprogesterone acetate, 10mg once daily for 10 days).

References

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clomiphene citrate alone, or in combination with metformin.

When should I refer my patient to a specialist?

In the primary practice setting, the indication for referral may be urgent or non-urgent. Urgent referrals are usually required for patients with acute bleeding, with hemodynamic instability, or if the bleeding was not controlled by initial therapy. Most referrals, however, are non-urgent. The indications for such referrals are ineffective medical therapy, completion of workup (endometrial biopsy/imaging studies), anatomic causes/malignancy, or PCO requiring fertility. CME

Take-home message

Diagnosis

- To make a firm diagnosis of DUB, one must rule out specific causes of abnormal genital tract bleeding.
- It is advisable to consider the effect of any new drugs on a patient's menstrual cycle.

Workup

- The workup for DUB involves both laboratory and anatomic examinations.

Management

- The management of DUB is mainly medical, with surgical treatment reserved for when medical therapy fails.