

Maria Creatsas and George K. Creatsas

Dysfunctional uterine bleeding (DUB) is an abnormal uterine bleeding (AUB) in the absence of organic cause. It is usually a painless, excessive, and irregular endometrial bleeding that may be prolonged, and it is not attributable to any underlying structural or systemic disease. The etiology of DUB arises out of continuing maturation of the hypothalamus, such that the eventual establishment of normal pulsatile gonadotropin release leads to normal menstrual cycle control. The European Society of Human Reproduction and Embryology (ESHRE) defined DUB as excessive bleeding (excessively heavy, prolonged, or frequent) of uterine origin, which is not due to a pelvic disease, complications of pregnancy, or systemic disease. According to ESHRE, DUB can be either ovulatory or anovulatory [1, 2].

Figure 2.1 shows the incidence of DUB in relation to the age of the patients and the seasonal distribution.

DUB is usually seen during adolescence. In about 95 % of cases DUB is due to the late maturation of the hypothalamic–pituitary–ovarian axis. Anovulation is considered the most common cause. However, other causes as pregnancy complications, coagulation disorders, systemic diseases, and anatomical lesions of the uterus should be excluded. The pathophysiology of the disease is related to the lack of maturation of the positive feedback, which results in anovulation, excess estrogen secretion, abnormal endometrial hyperplasia, and profuse bleeding, leading to endometrium apoptosis. Endometrium sampling shows proliferation, hyperplasia, and lack of progestagenic effect [3–5].

As endometrium is a known source of prostaglandin (PG) and especially of PGF_{2a} and PGE₂ production, the alteration of PGF_{2a} (vasoconstrictor) and PGE₂ (vasodilator) ratio have been also considered as a cause of the disease. DUB patients presented with anovulation exhibit a decreased availability of arachidonic acid, the precursor of PG synthesis. The PGF_{2a}/ PGE₂ ratio is found decreased,

M. Creatsas • G.K. Creatsas (✉)

2nd Department of Obstetrics and Gynecology, University of Athens-Aretaieio Hospital,
76 Vas Sofias Ave., Athens 11528, Greece
e-mail: geocre@aretaicio.uoa.gr

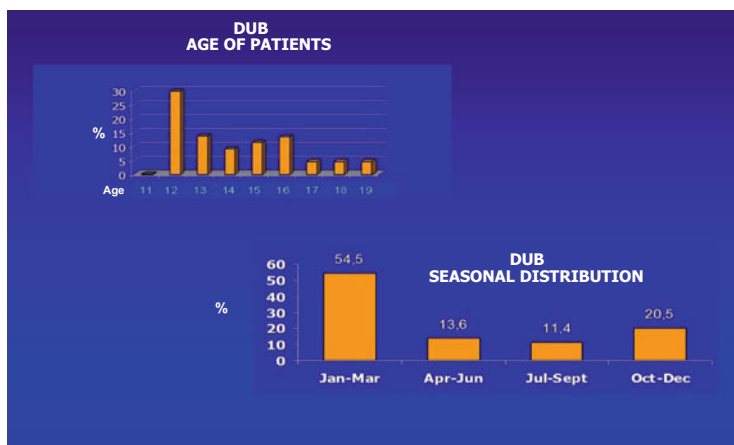


Fig. 2.1 Age of patients and seasonal distribution of DUB cases (personal data)

giving a predominance of vasodilation. Those patients with ovulatory DUB have an increased bioavailability of arachidonic acid that alters the PG ratios [3, 6].

The female reproductive organs are some of the few adult tissues that exhibit regular intervals of rapid growth. They are also highly vascular and have high rates of blood flow. Angiogenesis is therefore an important component of the growth and function of these tissues. Vascular endothelial growth factors (VEGFs) and fibroblast growth factors (FGFs) appear to be major angiogenic factors in the female reproductive organs. DUB, endometrial hyperplasia, carcinoma, and endometriosis are pathologies related to disturbances of the angiogenic process. Angiogenic or antiangiogenic compounds may prove to be effective therapeutic agents for the management of the above pathologies [7].

Cycling endometrium requires repeated, rapid, and short-term proliferation as well as rapid inhibition of neovascularization. Endometrial angiogenesis is regulated by growth factors and cytokines, which in turn are influenced by the levels of estradiol and progesterone during the menstrual cycle. Production of VEGF is stimulated *in vitro* by both E2 and PGs.

The evaluation of DUB cases includes a detailed family and personal history as well as a careful gynecological examination, including visualization of the cervix, even in virgin young girls (vaginocopy), laboratory studies: hematocrit (Hct) and hemoglobin (Hb) and others (mainly focused on the coagulation profile), pelvic ultrasonography (US), radiological imaging procedures, and rarely hysteroscopy or/and curettage. Endocrinological tests are not always necessary.

Differential diagnosis includes organic causes of AUB as: bleeding related to reproductive tract diseases, trauma and genital injury due to rape or sexual abuse. Young women can also cause injury to themselves when attempting to use tampons.

Infections due to endometritis and pelvic inflammatory disease can cause AUB accounting to less than 10 % of all AUBs. Vaginitis and cervical inflammation or erosion can also cause vaginal bleeding [3, 8–10].

AUB due to systemic–chronic diseases and endocrine disorders maybe related to renal or liver diseases. Patients with liver disease usually have deficiency of the vitamin K-dependent clotting factors (II, VII, IX, and X) or fibrinogen and plasminogen deficiency. Liver disease may also result in abnormal estrogen metabolism, which causes endometrial proliferation and estrogen breakthrough bleeding. Uremic patients with abnormal platelet function and decreased renal clearance of prolactin give rise to hyperprolactinemia and may also present anovulatory DUB. Nineteen percent of adolescents with persistent menorrhagia requiring hospital admission may have a coagulation disorder and more than 50 % of these young women may present a coagulopathy such as thrombocytopenia, von Willebrand's disease, or leukemia [1, 11, 12].

Systemic bleeding disorders are found in 7–20 % of women of all ages presented with menorrhagia [8, 12, 13]. Patients aged 10–19 years old examined for menorrhagia revealed that 13 % had thrombocytopenia, 55 % had immune thrombocytopenic purpura (ITP), and 22 % myelosuppression due to chemotherapy. Eight percent had abnormal platelet function and 11 % had coagulation disorders. Von Willebrand factor's deficiency is a common hereditary bleeding disorder. Among women with von Willebrand's disease, 65 % reported heavy bleeding at menarche. Factor's XI deficiency, Glassman's disease, aplastic anemia, and leukemia may also cause AUB [13–15].

Hypothyroidism may cause menorrhagia accompanied by metabolic symptoms. AUB is also related to abnormal function of corpus luteum, steroid-secreting ovarian tumors, and imminent premature ovarian failure. Differential diagnosis of AUB also includes side effects after treatment with hormonal medications such as implants, intrauterine devices, combined oral contraceptives (COCs), and transdermal patches. Anticoagulant, neuroleptic, and chemotherapeutic drugs can also give rise to AUB.

The disease is classified as mild, moderate, or severe. In mild DUB cases, the use of COCs is occasionally indicated as well as a careful follow-up. In cases of moderate degree, the use of the new-generation 17 β -estradiol COCs (E₂-COCs) or the cyclic use of progestagenic compounds are the treatment of choice. Cyclic oral progestogens are administered for the same 10 days every month to prevent the action of unopposed estrogens and stabilize the endometrium [1, 2, 9].

If the young patient has iron deficiency anemia, supplemental iron therapy is recommended. The use of nonsteroid anti-inflammatory medications may reduce the bleeding through the inhibition of prostaglandin synthase [6, 16]. Severe cases need hospitalization. Transfusion is usually indicated to restore hemodynamic balance. The hypovolemic cases need immediate resuscitation with intravenous administration of fluids. It is essential to obtain blood samples to exclude an underlying bleeding disorder before starting therapy.

Surgical procedures as dilation and curettage or hysteroscopy and insertion of mini intrauterine devices are not recommended unless the hemorrhage is heavy and the previous mentioned treatment is unsuccessful. Hemorrhage usually stops within 24 h and changeover of therapy is usually recommended. Alternatively intravenous (IV) administration of estrogen therapy has been used followed by COCs.

Nausea and vomiting are rare complications of IV therapy and can be managed with antiemetics. Tranexamic acid, a synthetic derivative of the amino acid lysine, exerts an antifibrinolytic effect through reversible blockade on plasminogen. Other therapies, such as the use of high doses of progestogens given per os or parenterally, gonadotropin-releasing hormone (Gn-RH) agonists, with add-back therapy, as well as levonorgestrel-impregnated intrauterine devices, are rarely used for the management of DUB during adolescence [6, 17, 18].

The selective progesterone receptor modulators have both agonistic and antagonist activities depending upon the site of action. The above-mentioned compounds have been proposed for the management of the endometrial vascular development [19, 20].

2.1 Personal Data

Between the years 2004 to 2012, 82 adolescent patients visited the Division of Pediatric and Adolescent Gynecology of our Institution due to DUB (Table 2.1). Diagnosis was set after a thorough clinical and laboratory investigation. Conditions as hypothyroidism, disorders of the coagulation cascade, functional ovarian cysts, and other organic pathologies were excluded.

Thirteen patients (15.8 %) required hospital admission due to excessive bleeding and low Hct and Hb. In 52 of them (63.4 %), the (Polycystic Ovarian Syndrome (PCO) was diagnosed according to the Rotterdam criteria at some point during their follow-up.

2.2 Case Presentations

1. Adolescent: 12 years old. Severe menorrhagia during the first menstrual period. Hb: 7.6 gr%. US: endometrial hyperplasia, thyroid function: normal. *Diagnosis: DUB*. Treatment: low dose COCs.
2. Age: 10.5 years old. Height: 1.62 m, weight: 47 kg, BMI: 18 kg/m². AUB at menarche. free medical history and family history. HCT: 22 %, Hb: 7.3 gr%, coagulation factors: normal. Hormonal profile: normal. US: endometrial thickness 6 mm, ovarian volume normal. *Diagnosis: DUB due to immaturity of the hypothalamic–pituitary–ovarian axis*. Management: hospital admission, injection of hydroxyprogesterone caproate 0.5 × 2 Per Os, followed by E₂-COCs and iron supplement.

Table 2.1 Age and BMI of the patients

Patients	Mean	SD
Age	13.46 years	3.07
Menarche	12.04 years	1.63
BMI	20.65 kg/m ²	5.74 kg/m ²

3. Age: 16 years old. The patient presented with abnormal uterine bleeding. Height: 1.62 m, weight: 47 kg, BMI: 18 kg/m². Menarche 15.5 years old—oligomenorrhea. Medical and family history: free. Clinical examination: hirsutism. Hormonal evaluation: elevated luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio, elevated testosterone and D4-androstenedione. US: endometrial thickness 5 mm, ovarian volume 12.5 cc and 11.5 cc with a microfollicular ovarian morphology. *Diagnosis: AUB due to PCOS*. Treatment: COCs (ethinylestradiol/cyproterone acetate).
4. Age: 14 years old. Height: 1.49 m, weight: 54 kg, BMI: 24.3 kg/m². Main symptom: severe uterine bleeding. Menarche: 13 years old, normal menstrual pattern. Medical and family history: free. Blood pressure: 110/60 mmHg. Hb: 6.0 gr %. Elevated thyroid-stimulating hormone and anti-TPO: 5.06 and 2.37, respectively. US: ovarian volume 6 cc and 6.5 cc, respectively, microfollicular morphology. *Diagnosis: AUB due to hypothyroidism (Hashimoto thyroiditis)*. Management: admission to hospital, blood transfusion, COCs (2 tablets daily) until bleeding stops, then decrease dose within 4 days to 1 tablet daily for 60 days plus iron supplement.
5. Age: 9 years old. Height: 1.49 m (96th percentile), weight: 40 kg (95th percentile), BMI: 18 kg/m², medical history: free. One episode of severe uterine bleeding. Family history: Mother with Hashimoto thyroiditis. Hormonal profile: E2: 21 pg/mL, FSH: 3.5 mIU/mL, LH: 2 mIU/mL, normal androgen levels. US: endometrial thickness: 4.5 mm, ovarian volume: 8.5 cc and 15 cc, respectively. No presence of ovarian cyst(s). Bone age: 12.5 years. *Diagnosis: Idiopathic central precocious puberty*. Treatment: GnRH analogs (leuprolide acetate).
6. Thirteen-year-old adolescent. Height: 1.55 m, weight: 40 kg, BMI: 16.6 kg/m². Menarche 12.5 years old, normal MP except two DUB episodes. Severe abnormal uterine bleeding. Medical history: free. Family history: mother beta-thalassemia heterozygote and father with a history of hepatitis. Clinical examination: 6 cm³ palpable mass in the right adnexa. HCT: 33 %, Hb: 10.3 gr%, E2: 45.91 pg/mL, FSH: 0.1 mIU/mL, LH: 0.43 mIU/mL. Normal tumor markers—except elevated inhibin-β. Endometrial thickness: 6 mm, ovarian volume 4.41 cc and 199.96 cc, respectively. Solid mass with blood flow in the right ovary. *Diagnosis: Juvenile granulosa-theca cell tumor of the ovary*. Management: removal of the cyst.
7. Seventeen-year-old adolescent. Menorrhagia twice per month. First diagnosis: PCO, treated with COCs, due to heavy AUB. Further studies revealed Leiden mutation (heterozygosity). The patient also developed venous thromboembolism. Two weeks later, she was admitted to the hospital due to heavy menstrual

bleeding; Hb: 6.9 gr%. *Diagnosis: Severe DUB and anemia.* Management: blood transfusion and LHRH analogs.

References

1. Deligeoroglou E, Tsimaris P (2010) Menstrual disturbances in puberty. *Best Pract Res Clin Obstet Gynaecol* 24(2):157–171
2. Fraser IS, Sungurtekin U (2000) Defining menstrual disturbances. In: Maclean A, O'Brien PMS (eds) Study group on menstrual disorders. Royal College of Obstetricians and Gynecologist, London, pp 141–152
3. Deligeoroglou E, Karountzos V, Creatsas G (2013) Abnormal uterine bleeding and dysfunctional uterine bleeding in pediatric and adolescent gynecology. *Gynecol Endocrinol* 29(1):74–78
4. Ferenczy A (2003) Pathophysiology of endometrial bleeding. *Maturitas* 45(1):1–14
5. Talib HJ, Coupey SM (2012) Excessive uterine bleeding. *Adolesc Med State Art Rev* 23(1):53–72
6. Deligeoroglou E (1997) Dysfunctional uterine bleeding. *Ann N Y Acad Sci* 816:158–164
7. Deligeoroglou E, Tsimaris P, Deliveliotou A, Christopoulos P, Creatsas G (2006) Menstrual disorders during adolescence. *Pediatr Endocrinol Rev* 3(Suppl 1):150–159
8. Claessens EA, Cowell CA (1981) Acute adolescent menorrhagia. *Am J Obstet Gynecol* 139(3):277–280
9. Deligeoroglou E, Creatsas G (2012) Menstrual disorders. *Endocr Dev* 22:160–170
10. Reynolds LL, Birkimer JC (2002) Perceptions of child sexual abuse: victim and perpetrator characteristics, treatment efficacy, and lay vs. legal opinions of abuse. *J Child Sex Abus* 11(1):53–74
11. Mammen EF (2000) In: Beutler E (ed) *Williams hematology*, 6th edn. McGraw-Hill Professional, New York, NY, p 1673
12. Minjarez DA, Bradshaw KD (2000) Abnormal uterine bleeding in adolescents. *Obstet Gynecol Clin North Am* 27(1):63–78
13. Kouides PA (2001) Obstetric and gynaecological aspects of von Willebrand disease. *Best Pract Res Clin Haematol* 14(2):381–399
14. Bevan JA, Maloney KW, Hillern CA et al (2001) Bleeding disorders. A common cause of menorrhagia in adolescents. *J Pediatr* 138:856–861
15. Kadir RA, Aledort LM (2000) Obstetrical and gynaecological bleeding. A common presenting symptom. *Clin Lab Haematol* 22(Suppl 1):12–16
16. Creatsas G (1998) Tenoxicam versus Lyn-EE treatment of DUB during adolescence. *J Pediatr Adolesc Gynecol* 11(4):177–180
17. Edlund M, Andersson K, Rybo G (1995) Reduction of menstrual blood loss in women suffering from idiopathic menorrhagia with a novel antifibrinolytic drug (Kabi 2161). *Br J Obstet Gynaecol* 102(11):913–917
18. Sokkary N, Dietrich JE (2012) Management of heavy menstrual bleeding in adolescents. *Curr Opin Obstet Gynecol* 24(5):275–280
19. Hickey M, Higham JM, Fraser I (2012) Progestogens with or without oestrogen for irregular uterine bleeding associated with anovulation. *Cochrane Database Syst Rev* 9, CD001895. pub3, doi: [10.1002/14651858](https://doi.org/10.1002/14651858)
20. Olive DL (2002) Role of progesterone antagonists and new selective progesterone receptor modulators in reproductive health. *Obstet Gynecol Surv* 57(11 Suppl 4):S55–S63

Frontiers in Gynecological Endocrinology

Volume 1: From Symptoms to Therapies

Genazzani, A.R.; Brincat, M. (Eds.)

2014, XI, 263 p. 21 illus., 5 illus. in color., Hardcover

ISBN: 978-3-319-03493-5