ABNORMAL UTERINE BLEEDING AND DYSFUNCTIONAL UTERINE BLEEDING IN ADOLESCENCE: DIAGNOSIS, MANAGEMENT AND TREATMENT

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ABSTRACT
Abnormal Uterine Bleeding (AUB) is a common cause for concern among adolescents and their families, as well as a frequent cause of visits to the Emergency Department and/or health care provider. While there are many etiologies of AUB, the one most likely among otherwise healthy adolescents is Dysfunctional Uterine Bleeding (DUB). This is due to the immaturity of the Hypothalamic-Pituitary-Ovarian (HPO) axis, which results in anovulatory cycles & unpredictable bleeding. Dysfunctional Uterine Bleeding describes the spectrum of abnormal menstrual bleeding patterns that may occur in adolescent girls who have no medical illness or pelvic pathology. DUB is characterized by any abnormal uterine bleeding when all possible underlying pathologic causes have been previously excluded.

Key words: abnormal uterine bleeding; dysfunctional uterine bleeding; adolescence; menstrual disorders

INTRODUCTION
Abnormal Uterine Bleeding (AUB) is a common cause for concern among adolescents and their families, as well as a frequent cause of visits to the Emergency Department and/or health care provider. While there are many etiologies of AUB, the one most likely among otherwise healthy adolescents is Dysfunctional Uterine Bleeding (DUB). This is due to the immaturity of the Hypothalamic-Pituitary-Ovarian (HPO) axis, which results in anovulatory cycles & unpredictable bleeding. Dysfunctional Uterine Bleeding describes the spectrum of abnormal menstrual bleeding patterns that may occur in adolescent girls who have no medical illness or pelvic pathology. DUB is characterized by any abnormal uterine bleeding when all possible underlying pathologic causes have been previously excluded.

NORMAL MENSTRUAL CYCLE & ABNORMAL BLEEDING
In the vast majority of females, menarche occurs two or three years after thelarche. The mean age of menarche varies with ethnicity: 12.7 years for non-Hispanic white girls, 12.3 years for black girls, & 12.5 years for Mexican American girls. Many adolescents may report “irregular” periods for 2 to 3 years after menarche due to anovulatory cycles and an immature Hypothalamic-Pituitary-Ovarian axis. Once a “regular” menstruating pattern is established, the cycle is characterized by periodicity and ranges between 21 and 40 days, with bleeding usually lasting 2 to 7 days and an average blood loss of 20 to 80 mL.

Abnormal bleeding may present as:
1. Menorrhagia, defined as bleeding that lasts more than 7 consecutive days or by more than 80 mL of blood loss but still occurring at regular intervals.
2. Metrorrhagia defined as bleeding that occurs at irregular intervals.
3. Menometrorrhagia characterized by heavy irregular bleeding.

If the interval of menstrual cycle is between 41 days and 3 months, this is considered to be oligomenorrhea.

As mentioned before, DUB is defined as abnormal apoptosis of the endometrium in the absence of a structural or medical abnormality and is most often due to anovulation. Although underlying pathology is recognized in less than 10% of abnor-
mal bleeding, DUB is a diagnosis of exclusion, and other causes must be ruled out (7). In the United States of America (USA) the definition of DUB refers to anovulatory bleeding. (9) On the other hand, 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 caused by demonstrable pelvic disease, complication of pregnancy or systemic disease. According to this definition by ESHRE, DUB can be either ovulatory or unovulatory. (10)

**PATHOPHYSIOLOGY & DIFFERENTIAL DIAGNOSIS OF DUB**

The pathophysiology of DUB is not well established. In anovulatory DUB, the positive “feedback” of estradiol (E2) to luteinizing hormone (LH) is not working properly, making menstrual cycles monophasic and anovulatory. (11) Due to the absence of midcycle LH surge, (12) follicle atresia occurs and become cystic, producing only estrogens but not progesterone. (13) During these anovulatory cycles, unopposed estrogens, which are products of ovarian follicles and of the extragonadal aromatization of androstendione, induce endometrial proliferation. The lack of progestagenic stabilization effect, results in abnormal shedding of the endometrium. (14) Furthermore, the imbalance of prostaglandins (PGs), seems to play a role in ovulatory DUB. During menstruation there is a balance between the vasoconstriction effect of PGF2a and vasodilation of PGE2 and PGI2 (Prostacyclin). Circulating steroid levels have a great influence in endometrial PG release. An increase in total PG release and disproportional rise in PGE2 have been demonstrated in ovulatory DUB (15,16).

The list of diagnoses to be considered in approaching the problem of abnormal vaginal bleeding in adolescents is long but necessitates the careful consideration and examination of each patient. The differential diagnosis is shown in table 1. Some causes require immediate exclusion because failure to do so may result in significant morbidity and mortality (17). Pregnancy-related complications for example, can present with any pattern of abnormal bleeding and among them ectopic pregnancy is one of the more serious conditions to be considered. Adolescents with pelvic inflammatory disease (PID) and endometritis caused by Neisseria gonorrhoeae or Chlamydia trachomatis frequently present with heavy or irregular bleeding. PID may present with vaginal bleeding in addition to lower abdominal pain. (17) The possibility of coagulopathy should be kept in mind, particularly in the adolescent whose menstrual history is short and not yet well defined. Although, the most common cause of AUB in adolescents is anovulation, more than a third may have a coagulation defect. (18,19) Bleeding disorders are usually associated with cyclic heavy or prolonged bleeding (menorrhagia). The same pattern may be observed in women receiving treatment with anticoagulants. (20) In addition, severe thrombocytopenia can be assessed quickly with a complete blood cell count. The possibility of an underlying abnormality is high, if an adolescent has to be hospitalized and her hemoglobin is less than 10 g/dL. (19) Although adult women are commonly presented with an underlying pathology such as

<table>
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<tr>
<th>TABLE 1. Differential diagnosis of AUB</th>
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<tr>
<td><strong>Hematologic</strong></td>
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<tr>
<td>von Willebrand disease</td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>Platelet dysfunction</td>
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<tr>
<td>Coagulation defects</td>
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<td>Factor deficiencies</td>
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<td>Endocrine</td>
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<td>Hyperprolactinemia</td>
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<td>Thyroid disorders</td>
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<tr>
<td>Adrenal disorders</td>
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<tr>
<td>Polycystic ovarian syndrome</td>
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<td>Ovarian failure</td>
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Adapted from Speroff, Leon; Fritz, Marc A. Title: Clinical Gynecologic Endocrinology & Infertility, 7th Edition. Copyright ©2005
fibroids, dysplasia, or cancer, adolescents rarely present with such conditions. These conditions however, are sometimes seen in young women and should be considered during the differential diagnosis of abnormal bleeding. (17) Furthermore, a variety of different medications can predispose to abnormal bleeding, including glucocorticoids, tamoxifen, and anticoagulants.

**MENSTRUAL HISTORY, PHYSICAL EXAMINATION & LABORATORY INVESTIGATIONS**

According to Vihko and Apter (21) the role of age at menarche is crucial. Specifically, the patient who is older at menarche is more likely to have a longer time of anovulatory, “irregular” cycles. The length of cycles and the length of bleeding in days, as determined by recording data on a calendar, should always be considered. It is also of great importance the number of pads or tampons used over a 24-hour period, as well as how many days they are used. According to Brown (22) more than three soaked pads or six full regular-absorbency tampons per day for 3 or more days likely equates to greater than 80 mL of blood loss. The number, if any, of “regular” periods experienced by the patient and the history of heavy bleeding, clots or leaking, especially overnight (because this may be associated with a clotting disorder) should always be mentioned. (22) In addition questions should be made about the characteristics of the patient’s very first period, because a “heavy” first period may conceal a bleeding disorder, most commonly von Willebrand disease. (19,22) Finally, patient’s past medical history and family history should always be taken into consideration. Clinical examination is always very helpful and in a patient with prolonged or heavy bleeding the evaluation should always begin with vital signs. The physician should assess the patient hemodynamically and look for signs of tachycardia, hypotension or orthostatic changes. Then the physical examination should proceed to the genitourinary system and the physician should search for signs of anemia, as well as clues of other possible underlying causes, such as lacerations, vaginal discharge/inflammation or trauma. Furthermore, it is of great importance the verification that the bleeding is in fact from the vagina/cervical origin (in sexually active women), the absence of a foreign body (e.g., a retained tampon) and that the appearance of the cervix is normal. Finally, pain during bimanual palpation of the cervix, the adnexa or the uterus is indicative of possible PID. In sexually active adolescents who cannot tolerate a speculum or b-

**MANAGEMENT**

Management of AUB is based on the underlying etiology and the severity of the bleeding. Primary goals are prevention of complications, such as anemia and reestablishment of regular cyclical bleeding. In case of an underlying systemic, endocrine or bleeding disorder, patients may require referral to the appropriate specialists (endocrinologist, hematologist etc.) for further evaluation and management. The management of DUB can in part be directed by the amount of flow, the degree of associated anemia, as well as patient and family comfort with different treatment modalities. (2,5,7) Patients’ management falls into four (4) major categories (Table 2). (23)
In case estrogens are contraindicated, progestosterone only pills (10 mg) once or twice daily for 5 to 10 days may prove effective for light to moderate flow. Patients also may be cycled monthly on a progestosterone-only regimen. Depot medroxyprogestrone acetate, 150 mg intramuscularly every 3 months, or Levonorgestrel intrauterine device (which lasts for 5 years) can also be used. However the above methods are often associated with irregular bleeding and spotting. (23)

**TREATMENT OF DUB**

Treatment options for DUB are: Compounded Oral Contraceptives (COCs), Progestogens, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Tranexamic Acid (anti-fibrinolytic), GnRH analogues, Danazol and Levonorgestrel releasing Intra Uterine System (LNG IUS).

COCs reduce endometrial development, reestablish predictable bleeding patterns and decrease menstrual flow. The prolonged estrogenic exposure and buildup of the endometrial lining may lead to acute episodes of heavy bleeding. An interval of 24 hours is usually needed for bleeding to be controlled, as the overgrown endometrium becomes pseudodecidualized. An alternate diagnosis should be sought after, if flow fails to abate in 24 hours. (26) On the other hand, estrogens alone in high dosages, are indicated in certain clinical situations. Prolonged uterine bleeding suggests that the epithelial lining is almost absent. A progestin is unlikely to control this kind of bleeding, while estrogen alone will rapidly help the endometrium to grow and control the hemorrhage. If bleeding is not controlled within 12-24 hours, a Dilatation and Curettage is indicated.

Progestin therapy should begin soon after initiating estrogen therapy, in order to prevent a subsequent bleeding episode, due to the prolonged treatment with unopposed estrogen. Progestin therapy is indicated for patients who suffer from chronic DUB. This is best accomplished with an Oral Contraceptive, if it is not contraindicated, taking into account its additional benefits including decreased dysmenorrhea, decreased blood loss, ovarian cancer prophylaxis, and decreased androgens. Whenever the pill is contraindicated, cyclic progestin administration for 12 days per month using medroxyprogestrone acetate (10 mg/d) or norethindrone acetate (2.5-5 mg/d) leads to uterine withdrawal bleeding. However, this method does not provide contraception. Cyclic natural progestosterone(200 mg/d) may be used in women susceptible to pregnancy, but may cause drowsiness and does not decrease blood loss as much as a progestin.

NSAIDs block formation of prostacyclin, an antagonist of thromboxane TXA₂, which is a substance that accelerates platelet aggregation and initiates coagulation. Prostacyclin is produced in large quantities in menorrhagic endometrium. Due to inhibition of blood-prostacyclin formation, NSAIDs might effectively decrease uterine blood flow. Despite NSAIDs’ capability to treat menorrhagia in ovulatory cycles, they are not generally effective for the management of DUB. Lethaby et al.25 mentioned that the levels of prostaglandin are higher in women with Heavy Menstrual Bleeding (HMB) and are reduced by NSAIDs. Danazol, tranexamic acid and LNG IUS are more effective in reducing HMB compared to NSAIDs and that was shown in the review of several trials. (25) Despite Danazol caused a shorter duration of bleeding and more side effects than NSAIDs this did not discouraged women from using them. These results are based on a small number of underpowered trials. (25)

Tranexamic acid is a synthetic lysine derivative with an antifibrinolytic effect based on the reversible

<table>
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<th>TABLE 2. Major categories of management for patients with DUB</th>
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<tr>
<td><strong>Light to Moderate Flow; Hemoglobin &gt; 12 g/dL</strong></td>
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<tr>
<td><strong>Moderate Flow; Hemoglobin 10-12 g/dL</strong></td>
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<tr>
<td><strong>Heavy Flow; Hemoglobin 8-10 g/dL; Hemodynamically Stable</strong></td>
</tr>
<tr>
<td><strong>Heavy Flow; Hemoglobin &lt; 7 g/dL or if Hemodynamically Unstable</strong></td>
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blockage of lysine binding sites on plasminogen and thus preventing fibrin degradation. Tranexamic acid can be used as a first-line treatment for the initial management of idiopathic menorrhagia, especially for patients in whom hormonal treatment is either not recommended or not wanted (24). According to Lethaby et al. (25) antifibrinolytic therapy causes a greater reduction in the amount of heavy menstrual bleeding when compared to placebo or other medical therapies (NSAIDS, oral luteal phase progestagens and ethamsylate). This treatment is not associated with an increase in side effects compared to placebo, NSAIDS, progestagens or ethamsylate. As significantly improvement in flooding, leakage and sexual life was found after tranexamic acid therapy when compared with oral luteal progestogens but no other parameters of quality of life were assessed. Therapy cost as an outcome measure, was not used in any study, and no data are available from randomized controlled trials recording the frequency of thromboembolic events.

GnRH agonists work by reducing the concentration of GnRH receptors in the pituitary via receptor down regulation and induction of post-receptor effects, which suppress gonadotropin release. After an initial gonadotropin release associated with rising estradiol levels, gonadotropin levels fall to castrate levels with resultant hypogonadism. This leads to amenorrhea, thus stops abnormal bleeding in many anovulatory patients. (29) However, the usage of GnRH agonists especially during adolescence for more than 6 months is related with menopausal-like symptoms (such as hot flushes, increased sweating, vaginal dryness) and in some cases with reversible osteoporosis. The administration of GnRH agonists is not often used for more than 6 months and add-back therapy of low-dose hormonal replacement is usually given. These drugs can be used to achieve short-term relief from a bleeding problem, particularly in patients with renal failure or blood dyscrasia, but should not be used as a first-line treatment. (29) Increased costs of these drugs make their use cost-effective only in refractory cases.

During the past years treatment options with certain androgenic substances have been used in order to treat mild to moderate bleeding, particularly in ovulatory patients with abnormal uterine bleeding. Androgens might cause signs of masculinization in the patient and might stimulate erythropoiesis and affect clotting efficiency. Androgens alter endometrial tissue, which is becoming inactive and atrophic. Danazol (Danatrol® Sanofi Aventis) is a synthetic steroid with anti-estrogenic and anti-progestogenic activity, and weak androgenic properties. Danazol acts by suppressing estrogen and progesterone receptors in the endometrium, leading to endometrial atrophy and reduced menstrual loss, while some women may present with amenorrhea after Danazol usage. (29) According to Beaumont et al. (30) Danazol appears to be an effective treatment for heavy menstrual bleeding compared to other medical treatments. The use of Danazol may be limited by its side effects profile, its acceptability by women and the need for continued treatment. The small number of trials and the small sample sizes of these trials limit the recommendations for clinical use.

In some women, rarely in adolescents, including those who are unable to tolerate systemic progestins, control of endometrium shedding may be achieved by a progestin secreting IUS via a local release of levonorgestrel. (27) Lethaby et al. (25) mentioned that progestagens may offer some help in reducing heavy menstrual bleeding but are not as effective as danazol and tranexamic acid. Progestogens are taken per os either during days 15 or 16 to day 26 of the menstrual cycle (short course) or from day 5 to day 26 (long course). According to Hickey et al. (28) there is no randomized controlled trial in which progestogens with estrogens are compared with progestogens or with placebo in the management of irregular bleeding associated with anovulation. Progestogens can be used alone, or with estrogen, to try and control DUB where cycles are anovulatory.

Lethaby et al. (25) noticed that the LNG IUS is more effective than oral norethisterone taken over 21 days of the cycle and women are more satisfied and willing to continue this treatment. However short term adverse effects are more frequent. No differences, regarding women’s rates of satisfaction or quality of life were noticed, even though the LNG IUS results in a smaller reduction in menstrual blood loss than does endometrial ablation and women encounter more short term side effects. There are no randomized comparisons of the LNG IUS with other medical or surgical treatments. LNG IUS is rarely used in adolescence.

The young patient with AUB might also have a bleeding disorder. Desmopressin, a synthetic analog of arginine-vasopressin, has been used as a last resort to treat uterine bleeding in patients with documented coagulation disorders. Treatment is followed by a rapid increase in von Willebrand factor and factor VIII, which lasts about 6 hours. (29) Arginine-vasopressin derivatives are indicated in patients with thromboembolic disorders, while Desmopressin Acetate (DDAVP) has been used to treat uterine bleeding in patients with coagulation defects. (31)

Etamsylate is believed to reduce bleeding from capillaries by correcting anomalies of platelet
adhesion. Etamsylate does not seem to play a role in the fibrin cascade. The therapeutic regimen is 500 mg four times daily from, but not before, the onset of bleeding. Etamsylate appears to be more effective in reducing menstrual blood loss (MBL) when compared to NSAIDs. However, evidence on the effectiveness of etamsylate to control MBL is insufficient, with figures from one review reporting that etamsylate reduces MBL by an average of 13.1%, less than other pharmaceutical treatments. (32)

CONCLUSIONS

DUB is a common cause for concern among adolescents and their families, as well as a frequent cause of visits to the Emergency Department and/or health care provider. In about 95% of cases it is caused by the late maturation of the HPO axis, leading to anovulatory cycles. These adolescents lack the E2 (estradiol) positive feedback on LH.

Thus, the continuous production of estrogen with consequent endometrial proliferation is the basic cause of DUB. The diagnosis of DUB is made primarily by exclusion and the list of diagnoses to be considered in approaching the problem of abnormal vaginal bleeding in the adolescent is long. A thorough medical history followed by complete physical examination and the appropriate laboratory investigations is of great importance. The management of DUB in patients with no other etiology will in part be directed by the amount of flow, the degree of associated anemia, as well as patient and family comfort with different treatment modalities, while the options for medical care of DUB generally include: COCs, Progestins, NSAIDs, anti-fibrinolytic tranexamic acid, GnRH analogues, Danazol and LNG IUS. The pediatric-adolescent gynecologist should be comfortable with its evaluation, management and treatment.

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