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

E. Deligeoroglou, MD, PhD; V. Karountzos, MD, G. Creatsas, MD
Division of Pediatric – Adolescent Gynecology and Reconstructive Surgery, 2nd Department of Obstetrics and Gynecology, University of Athens, Medical School, "Aretaieion" Hospital, Athens, Greece

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. (1) While there are many etiologies of AUB, the one most likely among otherwise healthy adolescents is Dysfunctional Uterine Bleeding (DUB).

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. (1) 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. (2) DUB is characterizing 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. (3) 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 (4). Many adolescents may report "irregular" periods for 2 to 3 years after menarche due to anovulatory cycles and an immature Hypothalamic-Pituitary-Ovarian axis. (5,6) 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. (7)

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 occuring 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. (8)

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. (5,7) Although underlying pathology is recognized in less than 10% of abnor-

Adresa de corespondență:
E. Deligeoroglou, MD, PhD., Medical School, "Aretaieion" Hospital, Athens, Greece
e-mail: deligeoroglou@yahoo.gr

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 gonorrheae 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 1. *Differential diagnosis of AUB*

Hematologic	Pathology of the reproductive tract	Pregnancy	Other
von Willebrand disease	Fibroid	Ectopic pregnancy	Excessive exercise
Thrombocytopenia	Myoma	Implantation	Eating disorders
Platelet dysfunction	Polyp	Placenta accreta	Stress
Coagulation defects	Endometriosis	Retained products of conception	Systemic disease
Factor deficiencies	Cervical dysplasia	Threatened, spontaneous or missed abortion	Intrauterine Device
	Infectious	Hormonal contraceptives	
	Cervicitis (especially Chlamydial)		
Endocrine	Trauma	Medication	
Hyperprolactinemia	Sexual abuse	Antipsychotics	
Thyroid disorders	Laceration	Platelet inhibitors	
Adrenal disorders	Foreign body	Anticoagulants	
Polycystic ovarian syndrome	Related to abortion or other surgical procedure		
Ovarian failure			

Adapted from Speroff, Leon; Fritz, Marc A. Title: Clinical Gynecologic Endocrinology & Infertility, 7th Edition.
Copyright B©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 for 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 conceals a bleeding disorder, most commonly von Willebrand disease. (19,22) Finally, patient's past medical his_tory 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 bimanual examination, a pelvic examination under anesthesia may need to be done. In non-sexual active adolescents recto-abdominal palpation should be carefully considered.

Initial laboratory investigations should include the following:

1. urine pregnancy test and/or quantitative serum β-HCG;
2. complete blood cell count;
3. pelvic ultrasound may prove helpful to the diagnosis.

According to Brown (22), in case of severe bleeding or when an underlying bleeding disorder is suspected, the following lab tests should be added:

1. prothrombin time;
2. partial thromboplastin time;
3. bleeding time and platelet aggregation;
4. von Willebrand panel, must be done prior to initiating hormonal therapy and coagulation factor levels/activity (depending on family history and ethnicity). On the other hand, if an endocrine disorder is suspected laboratory investigations should include:

- Thyroid Stimulating Hormone (TSH), for thyroid disorders;
- Prolactin (PRL) levels >100 ng/mL suggest a possible pituitary adenoma;
- Total and free Testosterone (Testo, FTesto), usually elevated in polycystic ovarian syndrome;
- Dehydroepiandrosterone Sulfate (DHEA-S) to assess for adrenal tumors;
- LH and FSH, may aid in the evaluation of pituitary or ovarian function. Finally for patients in whom an infectious etiology is suspected a swab culture of the discharge and a urethral meatus swab for gonorrhea and chlamydia testing should be taken.

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, progesterone 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 progesterone-only regimen. Depot medroxyprogesterone 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: Compined 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 medroxyprogesterone 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 progesterone (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 TXA_2, 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 2. *Major categories of management for patients with DUB*

Light to Moderate Flow; Hemoglobin > 12 g/dL	The physician should reassure these patients. Iron supplementation may be given, while a non steroidal anti-inflammatory drug (NSAIDs) may help to decrease flow. It is important to re-evaluate the patient in 3 months or sooner if bleeding persists or becomes more severe.
Moderate Flow; Hemoglobin 10-12 g/dL	Oral Contraceptive Pills (OCPs) should be used (e.g., monophasic with 30 to 35 μg of ethinyl estradiol). One pill twice daily for 1 to 5 days until the bleeding stops. Once the bleeding stops, OCP therapy should be continued with one pill daily, for 3 to 6 months. Iron supplementation for 6 months should be given, in order to replenish iron stores, while NSAIDs may also be helpful.
Heavy Flow; Hemoglobin 8-10 g/dL; Hemodynamically Stable	Physician may be able to manage the patient as under "Moderate Flow" if the family can assist with the management plan and follow-up. If bleeding persists, OCPs should be increased to 3 or 4 times a day for a few days until the bleeding stops, then two per day (for 4 days) and then one pill daily for 3 to 6 months. Adolescent patient may additionally require an antiemetic medication to help prevent nausea/vomit, due to the high dose of estrogens. The patient should be followed closely. Iron supplementation should also be given.
Heavy Flow; Hemoglobin < 7 g/dL or if Hemodynamically Unstable	The patient should be admitted to the hospital. The possibility of blood transfusion should be considered, depending on the degree and persistence of bleeding, as well as the severity of hemodynamic instability. Monophasic OCPs should be administered every 6 hours until bleeding limitation. The physician should taper administration of pills to one pill a day over the next 7 days (e.g., one pill every 6 hours for 2 days, then every 8 hours for 2 days, every 12 hours for 2 days, then once daily). Anti-emetic agents may need. If bleeding still persists despite the measures implemented, Dilation & Curettage should be considered.

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. A 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.

REFERENCE

1. **Benjamins L.J.** – Practice guideline evaluation and management of abnormal vaginal bleeding in adolescents. *J Pediatr Health Care.* 2009 May-Jun; 23(3): 189-93. Review.
2. **Speroff, Leon; Fritz, Marc A.** – Clinical Gynecologic Endocrinology & Infertility, 7th Edition. Copyright B©2005 Lippincott Williams & Wilkins
3. **Carswell J., Stafford D.** – Normal Physical Growth and Development. Adolescent Health Care: A Practical Guide, ed. Neinstein L., Gordon C., Katzman D., Rosen D., Woods E. 2008; 3-26.
4. **Wu T., Mendola P., Buck G.M.** – Ethnic differences in the presence of secondary sex characteristics and menarche among US girls: the Third National Health and Nutrition Examination Survey, 1988-1994. *Pediatrics.* 2002 Oct;110(4):752-7.
5. **Gray S.H., Emans S.J.** – Abnormal vaginal bleeding in adolescents. *Pediatr Rev.* 2007 May; 28(5):175-82.
6. **Lavin C.** – Dysfunctional uterine bleeding in adolescents. *Curr Opin Pediatr.* 1996 Aug; 8(4):328-32.
7. **Mitan L.A., Slap G.B.** – Dysfunctional uterine bleeding. In: Neinstein LS. (Ed.) Handbook of Adolescent Health Care. Lippincott Williams & Wilkins, *Philadelphia,* 2009, pp. 467-469.
8. **Deligeoroglou E., Tsimaris P., Deliveliotou A., Christopoulos P., Creatsas G.** – Menstrual disorders during adolescence. *Pediatr Endocrinol Rev.* 2006 Jan; 3 Suppl 1:150-9.
9. **American College of Obstetricians and Gynecologists.**
10. **Fraser I.S., Sungurtekin U.** – Defining menstrual disturbances. In: Maclean A and O'Brien, P.M.S. (eds) Study Group on Menstrual Disorders. *Royal College of Obstetricians and Gynecologist,* 2000; 141-152.
11. **Deligeoroglou E., Stergioti E., Tsimaris P., Bacopoulou F., Creatsas G.** – Gynecological problems during childhood and adolescence. Proceedings of 5th Panhellenic Congress on Paediatric subspecialties. March 8-9 2008, Athens, Greece
12. **Creatsas G.** – Vaginal and Uterine Bleedings in: Obstetrics and Gynecology of young age. G. K. Creatsas. Published by P. X Paschalidis, Athens 2001, Pages 273-276.
13. **Kalogeropoulos A.** – Menstrual disorders and abnormal genital tract bleeding. Gynecology. Achilleas Kalogeropoulos. University Studio Press, 2nd Edition, Thessaloniki 2004, Pages 419-450.
14. **Deligeoroglou E.** – Dysfunctional uterine bleeding. *Ann N Y Acad Sci.* 1997; 816:158-64.
15. **Baird D.T., Cameron S.T., Critchley H.O., Drudy T.A., Howe A., Jones R.L., Lea R.G., Kelly R.W.** – Prostaglandins and menstruation. *Eur J Obstet Gynecol Reprod Biol.* 1996 Dec;70(1):15-7.
16. **Smith S.K., Abel M.H., Kelly R.W., Baird D.T.** – Prostaglandin synthesis in the endometrium of women with ovular dysfunctional uterine bleeding. *Br J Obstet Gynaecol.* 1981 Apr; 88(4):434-42.
17. **Emans S. Jean Herriot; Laufer, Marc R.; Goldstein, Donald P.** – Pediatric & Adolescent Gynecology, 5th Edition Copyright B©2005 Lippincott Williams & Wilkins.
18. **Smith Y.R., Quint E.H., Hertzberg R.B.** – Menorrhagia in adolescents requiring hospitalization, *J Pediatr Adolesc Gynecol* 11:13, 1998.
19. **Claessens E.A., Cowell C.L.** – Acute adolescent menorrhagia, *Am J Obstet Gynecol* 139:377, 1981.
20. **van Eijkeren M.A., Christiaens G.C.M.L., Haspels A.A., Sixma J.J.** – Measured menstrual blood loss in women with a bleeding disorder or using oral anticoagulant therapy, *Am J Obstet Gynecol* 162:1261, 1990.
21. **Vihko R., Apter D.** – Endocrine characteristics of adolescent menstrual cycles: impact of early menarche. *J Steroid Biochem.* 1984 Jan; 20(1):231-6.
22. **Brown D.L.** – Congenital bleeding disorders. *Curr Probl Pediatr Adolesc Health Care*. 2005 Feb; 35(2):38-62.
23. **Deligeoroglou E., Tsimaris P.** – Menstrual disturbances in puberty. *Best Pract Res Clin Obstet Gynaecol.* 2010 Apr; 24(2):157-71.
24. **Wellington K., Wagstaff A.J.** – Drugs. 2003; 63(13):1417-33.
25. **Lethaby A., Farquhar C., Cooke I.** – Antifibrinolytics for heavy menstrual bleeding. Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD000249.
26. **Jick S.S., Hernandez R.K.** – Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. *BMJ*. Apr 21 2011; 342:d2151.
27. **Teichmann A., Apter D., Emerich J., Greven K., Klasa-Mazurkiewicz D., Melis G.B., et al.** – Continuous, daily levonorgestrel/ethinyl estradiol vs. 21-day, cyclic levonorgestrel/ethinyl estradiol: efficacy, safety and bleeding in a randomized, open-label trial. *Contraception.* Dec 2009; 80(6):504-11.
28. **Hickey M., Higham J.M., Fraser I.** – Progestogens versus oestrogens & progestogens for irregular uterine bleeding associated with anovulation. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD001895.
29. **Speroff L., Glass R.H., Kase N.G., eds.** – Dysfunctional uterine bleeding. In: Clinical gynecologic endocrinology and infertility. 5th ed. Baltimore: Williams & Wilkins, 1994:575-93.
30. **Beaumont H.H., Augood C., Duckitt K., Lethaby A.** – Danazol for heavy menstrual bleeding. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD001017.
31. **Rose E.H., Aledort L.M.** – Nasal spray desmopressin (DDAVP) for mild hemophilia A and von Willebrand disease. *Ann Intern Med* 1991 Apr 1; drug effects(7): 563-8.
32. **Heavy Menstrual Bleeding** – NICE Clinical Guidelines, No. 44. National Collaborating Centre for Women's and Children's Health (UK). London: RCOG Press; 2007 Jan.