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Management in Abnormal Uterine Bleeding

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Abstract

AUB (Abnormal Uterine Bleeding) is any change in common menstruation cycle such as change in uniformity, recurrence of blood loss, prolongation of blood flow, or in amount of blood loss among adolescents' girls in gynecologic department. Around 25%to 30% adolescents' girls having abnormal uterine bleeding (AUB). AUB is due to hormonal problem such as thyroid, high concentration of prolactin in blood and polycystic ovarian disease and PALM-COEIN classifications. The most frequent clinical presentation of Abnormal Uterine Blood Loss (AUBL) is Heavy Menstrual Bleeding (HMB). Anemia assessments from blood loss for adolescents' girls who present with (HMB) include. AUB divided into two groups, Acute (AUB) and Chronic (AUB). Acute (AUB) treated with the use of high dose of Estrogen. The Chronic AUB is difficult to manage. This article evaluates new terms in (AUB), medical history, examination and laboratory evaluation of (HMB) and describe the management of AUB, HMB depend upon the severity of bleeding and Anemia.

Keywords: - Abnormal Uterine Bleeding (AUB), Abnormal Uterine Blood Loss (AUBL), Heavy Menstrual Bleeding (HMB), Adolescent Girls, Anemia

INTRODUCTION:

At reproductive age menstrual problem is most common in adolescents' girls. Various medical issues and other health problems have been seen in adolescents' girls who unaware about the bleeding pattern and therefore less anxiety are seen in those adolescent girls who know about the menstruation (1). Therefore, now a day's Abnormal uterine blood loss (AUBL) is common problem among the young girls in gynecologic department. Abnormal Uterine blood loss is any change in common menstruation cycle such as change in uniformity, recurrence of blood loss, prolongation of blood flow, or in amount of blood loss (2). Around 25%to 30% adolescents' girls having Abnormal Uterine Bleeding (AUB). AUB having remarkable impact on adolescents' girls in terms of quality of life (social, sexual and occupational activities). Abnormal uterine blood loss affects the quality of life in adolescent girls in comparison to the other girls. (3). The term Abnormal uterine bleeding (AUB) is recommended by FIGO (International Federation of Gynecology and Obstetrics) to describe short form of menstruation intensity, control, time and/or repetition in non-pregnant woman or adolescents' girls (4). AUB is due to hormonal problem such as thyroid, high concentration of prolactin in blood and polycystic ovarian disease and classification of PALM-COEIN (5). Some definitions discarded by the International Federation of Gynecology and Obstetrics (FIGO) like "menorrhagia", "**,** metrorrhagia", "hyper/hypomenorrhea", "polymenorrhagia" as well as "dysfunctional uterine bleeding" because all of them complicated as well as imperfectly explain. Abnormal uterine bleeding- some terminology recommended by FIGO (6,7). AUB divided into Acute AUB and Chronic AUB. In acute AUB instant treatment is require to stop extra blood loss due to excessive bleeding. Three stages to evaluate Acute AUB is (patient acuity, bleeding cause, appropriate treatment) (8). Irregular menstrual bleeding in terms of quantity, frequency, duration, from previous 6 month is known as Chronic AUB (9). Structural damage of uterus not cause AUB which formerly known as Dysfunctional uterine bleeding (DUB) and the common clinical presentation of Abnormal Uterine Blood Loss (AUBL) is Heavy Menstrual Bleeding (HMB) (10). According to ACOG, if menses is more than 7 days, time taken by pad to soak blood is 1 to 2 hours, clot size is larger than 1 inch in diameter, and blood loss is more than 80 ml it is known as heavy menstrual bleeding (HMB) (11). Imperfection of neuroendocrinology is the main cause of HMB and it led to anovulatory cycle (12). Heavy menstrual bleeding (HMB) cause iron deficiency anemia and it affect the women life as work, expenses, medical resources (13). HMB develop anemia (fewer red blood cells than normal) in some girls due to acute or chronic blood loss and shortness of breath and heart problems is caused by severe anemia (14). Incidence of anemia in adolescents' girls is high during blood loss in menstruation (15).

Normal Menstrual Cycle

Menarche is the first menstruation that occurs in adolescent girl at the age of 12 to 13 years in developed countries (16, 17). Time and progression of puberty is influenced by environmental factor (18). 98% young girls have menarche by the age of 15 year (19). Normal menstrual cycle in adolescent girls with bleeding occurs in 21 to 45 days for 2 to 7 days (20, 21, 22). In normal menstrual cycle blood loss is 30 to 40 ml (23). 50% endometrial transudate is total menstrual loss and

contain 30-50% entire blood constituent (24). Persistent blood loss is f ≥80 mL, related to anemia (25).

In mid reproductive age normal range of menstrual parameters (26)

Scientific Specification	Illustrative Terms	Common Limitations
Recurrence of menstruation cycle	Persistent	Less than 24 days
	Usual	24 days to 38 days
	In Frequent	More than 38 days
Uniformity in menstrual cycle	Missing	No blood loss
	Uniform	Changes + 2 days -20 days
	Non-Uniform	More than 20 days
Prolongation of blood flow	Extend	More than 8.0 days
	Standard	4.5 days to 8.0 days
	Precise	Less than 4.5 days
Amount of blood loss on monthly bases	Massive	More than 80 days
	Standard	5 days to 80 days
	Light	Less than 5 days

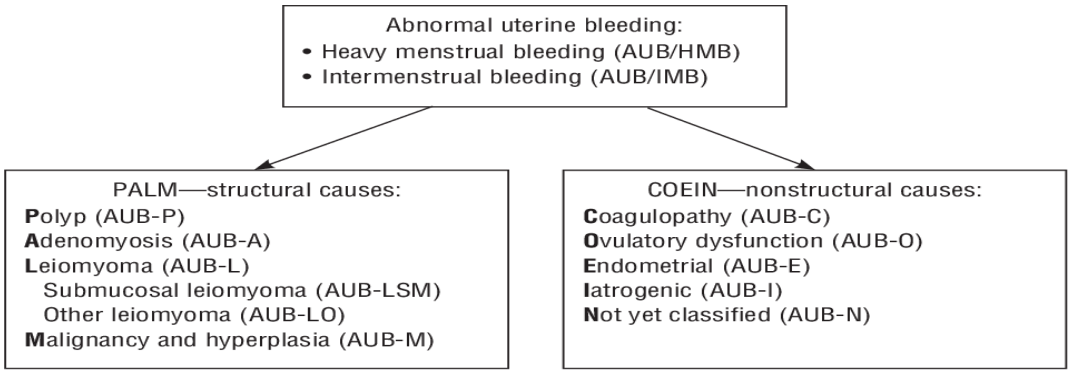
Epidemiology:
Internationally 3% to 30% prevalence of abnormal uterine blood loss is seen among adolescent girls. HMB (Heavy Menstrual Bleeding) studies are limited. In case of improper menstruation and metrorrhagia the prevalence is 35% or more than 35% (27%).

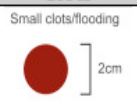
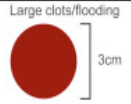
Etiology:
Cause of AUB is stated by American College of Obstetricians and Gynecologist (ACOG) such as ovulation problem, fibroids and polyps, growth of endometrium in uterus wall, disorder in bleeding pattern, miscarriage, uterus cancer, birth con troll pills (28). For acute and chronic AUB etiology is multifactorial. FIGO (International Federation of Gynecology and Obstetrics) and ACOG (American College of Obstetricians and Gynecologist) classified etiology of Abnormal uterine Bleeding (AUB) as PALM-COEIN (29,30). 1.3% – 1.7% Abnormal uterine bleeding (AUB) is hardly related to changes in uterus structure in adolescents' girls (31,32). The problem of abnormal uterine blood loss (AUBL) among adolescents' girls in anovulatory cycle is due to HMB (Heavy Menstrual Bleeding) and imperfection of neuroendocrinology (33). Among hospitalized girls 5% - 28% another leading etiology is coagulopathy prevalence with HMB in different studies (34, 35, 36, 37, 38). Due to blood clotting elements coagulopathy occur (39, 40, 41, 42).

Sign and Symptom:
Half of adolescents' girls have menarche (HMB) heavy menstrual bleeding and other adolescents' girls not have (HMB) in menarche until the menstruation turn out ovulatory (43). Around 75 – 80 % adolescent girls and women having inherited heavy menstrual bleeding with clinical manifestation of their disorder (44). Bleeding disorders with regular heavy menses in adolescent girls due to anovulation or prolonged heavy menses, 70% of adolescents' girls report the presence of blood clots on clothes, sanitary pads, bed sheets (45). Headache and fatigue symptom are associated with anemia that result from bleeding. In heavy menstrual bleeding, low iron (anemia) is seen in adolescent girls which is due to low ferritin level, in the absence of anemia fatigue, learning and memory is affected by decreased cognition in adolescents' girls (46,47,48). Adolescents girls with heavy menstrual bleeding (HMB) having symptoms of depression, mood swings or anxiety (49).

Assessment and Detection:
For assessment and detection of abnormal uterine bleeding in adolescents' girls needs

- Past medical history
- Present medical history
- Physical examination
- Laboratory parameters
- Imaging testing



Day 1 of Menstruation		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	7	8	9	10	Total Tallies	Row Total
Score	**Towels**												
1													
5													
20													
	Tampons												
1													
5													
10													
	Clots												
1													
5													
5	Menstrual Accidents or Flooding												
											Total Score (Sum of Rows)		

Pictorial Blood Assessment Chart (52)

1. Medical history

In bleeding disorders, identification of risk factor as well as medical conditions is important. Girls with heavy menstrual bleeding (HMB) disorder go for screening tool to evaluate the underlying bleeding. Pictorial blood assessment chart help to asses treatment, in known bleeding disorder among adolescent girls. If a menstrual cycle app is used by patient, then that data also helpful (50). Medical history must include patient history such as menstrual history, sexual history, past medical history and family history (51).

2. **Physical Examination**

Physical, dermatological, abdominal, vaginal examination is necessary for a patient with bleeding disorder. In physical examination hemodynamic stability, pulse measurement, orthostatic blood pressure assessment is necessary for patient with HMB. Pallor, bruises and petechiae examination is done for sign of anemia and bleeding disorder. Hepatosplenomegaly, distention is assessed for abdominal examination. In vaginal examination, the vaginal bleeding is in accordance with sexual maturity level. Speculum examination is not necessary for adolescent girl with HMB (53).

Different diagnostic parameter for heavy menstrual bleeding in adolescents

Endocrine causes	**Infections**
Anovulatory bleeding	Cervicitis
PCOS	Adenomyosis
Thyroid disease	**Disorders of the uterus**
Other	Myoma
Bleeding disorders	Intrauterine device
von Willebrand disease	Polyps
Platelet dysfunction	Cancer
Thrombocytopenia	**Medications**
Clotting factor deficiency	Depot medroxyprogesterone
Pregnancy	Anticoagulants
Abortion	**Trauma**
Ectopic pregnancy	**Foreign body**
Gestational trophoblastic disease	**Hemorrhagic ovarian cysts**

PCOS: polycystic ovary syndrome

(53).

3. **Laboratory Test**

For severity of bleeding laboratory test are performed and to identify the potential etiologies of AUB/HMB. For anemia assessment from blood loss, it includes serum ferritin, anovulation, bleeding disorder in adolescent girl with HMB. Hemodynamically unstable patient with acute HMB, involve a blood type and cross

match. In adolescent girl with HMB serum ferritin level is routinely monitored (54, 55). Low iron store shows low level of serum ferritin while normal or high level of serum ferritin does not show Iron Deficiency Anemia, and inflammatory stress elevate the level of serum ferritin (56). Von Willebrand Factor (VWF) test is for adolescent girl who is having bleeding disorder, it includes Plasma Von Willebrand Factor (VWF), antigen and functional tests for (VWF) and factor VIII activity (57, 58). Lower levels of Von Willebrand Factor (VWF) have blood type O and those having blood type A or B contain normal level of Von Willebrand Factor (VWF). For each patient's blood type reference value of (VWF) is used (59).

Imaging Recommendations

In adolescents' girls structural cause of AUB is rare therefore use of imaging may not be helpful in diagnosis in this age group (60). On the bases of clinical judgement of the obstetrician imaging examination is performed - in adolescent patient's transabdominal ultrasonography is more suitable than transvaginal ultrasonography (61, 62).

Treatment

The management of heavy menstrual bleeding needs to maintain hemodynamic parameters, improvement of anemia and care of regular menstrual cycles in terms of bleeding. Management of heavy menstrual bleeding is depends upon the brutality of anovulatory bleeding and anemia and management includes Iron supplements, combined oral contraceptives, progesterone, NSAIDs, anti-fibrinolytic agents, gonadotropin-releasing hormone analogues and desmopressin (63).

Severity of Bleeding:

1. Mild Anovulatory Uterine Bleeding

- In mild anovulatory uterine bleeding, menstruation is longer than 7 days or menstrual cycle is shorter than 3 weeks for two months by slight or moderate increase in bleeding.
- Hemoglobin standard value is > 12 g/dl or decreased is 10 – 12g/dl.
- In mild anovulatory uterine bleeding, hemoglobin level is normal.
- Medicines like NSAID (ibuprofen and naproxen sodium) decrease the menstrual flow.
- On hemoglobin range 10-12 g/dL needs iron supplementation (elemental iron 60 mg) per day.
- Re-evaluation is done in 3 months if bleeding persists.

2. Moderate Anovulatory Uterine Bleeding

- In moderate anovulatory uterine bleeding, menstruation is sustained or frequents for every 1 to 3 weeks by moderate to heavy blood loss and it cause hemoglobin range equal or greater than 10 g/dl.
- For stabilization and shedding of endometrial proliferation, iron supplementation, hormonal therapy is used (64).
- Adolescent girls with bleeding and moderate anemia are treated with combined oral contraceptive (COCs) and estrogen as it improves hemostasis (65).
- For the prevention of breakthrough bleeding Ethinyl estradiol 30mcg is used, 1tablet until the bleeding stops for 8-12 hours, and then continue 1 tablet per day for 21 days.
- On reoccurrence of bleeding dose should be increased twice a day for 21 days. If high doses of Ethinyl estradiol cause nausea, then use Ondansetron 4 to 8 mg (66).
- Placebo should be given for 7 days during the end of 21 days. Combined oral contraceptives should continue for 3 to 6 months till hemoglobin range is equal or greater than 12 g/dL (67,68,69).
- In moderate anemia adolescent girl with Combined oral contraceptives, Progestin is the only hormonal therapy that is used as an alternate for those are not currently bleeding (70, 71).
- Oral micronized progesterone, medroxy-progesterone, norethindrone acetate, DMPA (depot medroxyprogesterone acetate) all are progestin options. No sufficient data is available to state that Progesterone is safer than synthetic progestin (72).

3. **Severe Anovulatory Uterine Bleeding:**

- Severe anovulatory uterine bleeding cause heavy blood loss and increase hemoglobin level up to 10 g/dl.
- Adolescent girls with heavy bleeding and hemodynamically unstable should be hospitalized and blood transfusion is required (73).
- In severe anemia patient, 60 to 120 mg elemental iron is essential for patient till patient get capable of taking oral tablet.
- Hormone therapy is required on hemoglobin range 8 to 10 g/dl. Ethinyl estradiol (30-50mcg) is used for 2 to 4 days for 6 hours. Same dose is used for 3 days in every 8 hours and then 12 hours for the next 14 days.
- If hemoglobin range gets less than 7 g/dl or 10 g/dl with dense blood loss then combined oral contraceptives must be administered in every 4 hours till bleeding gets reduce, 1tablet for 2-3 days for 6 hours, then administered every 12 hours for 2 weeks and last till a hemoglobin range reach to equal or greater than 10 g/dl.

- On hemoglobin range exceeds to the 10 g/dl, then cyclic pattern of combined oral contraceptives is used for 3 to 6 months till the hemoglobin range reach to the equal or greater than 12 g/dl (74).
- On continuation of dense bleeding after 24 hours intake of combined oral contraceptives, administered Intravenous conjugated estrogen (25 mg) for each 4 to 6 hours (2 to 3 times) till bleeding less. Later the management is continued with oral combined oral contraceptives (75).
- High dose combined oral contraceptives should be given if bleeding exceeds to 24 hours then aminocaproic acid, desmopressin and hemostatic agents like tranexamic acid should be prescribed.
- In heavy menstrual bleeding (HMB) Tranexamic acid dose of 3.9 g to 4 g/day is prescribed for 4 to 5 days and it is more active than placebo (76).
- On failure of hormonal therapy and hemostatic agent to discontinue the bleeding in 24 to 36 hours then anesthesia and endometrial sampling should be used (77, 78).

CONCLUSION

In Gynecology department AUB is the most common problem among adolescent girls and the most frequent clinical presentation of Abnormal Uterine Blood loss (AUB) and it is also known as heavy menstrual bleeding (HMB). In adolescent girl having heavy menstrual bleeding issues must be asked for rigorousness of bleeding disorder. It is necessary to evaluate the patient be for rigorousness of bleeding, anemic issues, and after attaining the hemodynamic stability. Management of heavy menstrual bleeding is depending on the iron supplements, combined oral contraceptives, progestin, IV estrogen and / or hemostatic agents, tranexamic acid. For all women in their reproductive-aged iron replacement therapy should provide for anemia due to bleeding. Those girls suffering from heavy menstrual bleeding problem are requiring combined therapy with hemostatic agents. Patient follow up is must once the treatment is finished.

REFERENCES:

1. Frank, D., Williams, T., Journal School nursing. 1999, 15, 25-31.
2. Fraser, M.D., Hilary, O.D., Critchley, M.D., Michael Broder, M.D., The FIGO Recommendation on Terminologies and Definition for Normal and Abnormal Uterine Bleeding: Semin Repord Med. 2011,29, 383-390.
3. Aruna Rastogi, Abnormal Uterine Bleeding, National Health Portal India. 2017.
4. Fraser, I.S., Critchley, H.O., Broder, M., Munro, M.G., Semin Reprod Med. 2011, 29(5), 383-90.
5. Munro, M.G., Critchley, H.O., Broder, M.S., Fraser, I.S., Int J Gynaecol Obstet.2011, 113(1), 3-13.
6. Fraser, I.S., Critchley, H.O., Broder, M., Munro, M.G., Semin Reprod Med. 2011, 29(5), 383-90.
7. Fraser, I.S., Critchley, H.O., Munro, M.G., Broder Hum Reprod. 2007, 22(3), 635-43.
8. Munro, M.G., Critchley, H.O., Broder, M.S., Fraser, I.S., Int. J. Gynaecol Obstet. 2011, 113, 3-13.
9. American College of Obstetricians and Gynecologists. ACOG committee opinion no. 557. Obstet Gynecol. 2013, 121(4), 891-6.
10. Khrouf, M., Terras, K.J., Obstet Gynaecol India. 2014, 64(6), 388-93.
11. Committee on Practice Bulletins—Gynecology Practice bulletin no. 128. Obstet Gynecol. 2012, 120(1), 197-206.
12. Jayasinghe, Y., Moore, P., Donath, S., Campbell, J., Monagle, P., Grover, S., Aust N Z J Obstet Gynaecol. 2005, 45, 439-443.
13. Liu, Z., Doan, Q.V., Blumenthal, P., Dubois, R.W., Value Health. 2007, 10, 183-94.
14. American College of Obstetricians and gynecologists 409. 20024 – 2188.
15. Alina, V., Solovyova, Viola Gace, Kristina, S., Ermolenko, Vadim, A., Khorolskiy, 2017.
16. Chumlea, W.C., Schubert, C.M., Roche, A.F., Kulin, H.E., Lee, P.A., Himes, J.H., Pediatrics. 2003, 111, 110-113.
17. Finer, L.B., Philbin, J.M., Women Health Issues. 2014, 24, e271-279.
18. Apter, D., Hermanson, E., Current Opinion Obstet Gynaecol, 2002, 14, 475-481.
19. Chumlea, W.C., Schubert, C.M., Roche, A.F., Kulin, H.E., Lee, P.A., Himes, J.H., Pediatrics. 2003, 111, 110-113.
20. World Health Organization Task Force on Adolescent Reproductive Health, J Adolescent Health Care. 1986, 7(4), 236-44.
21. Flug, D., Largo, R.H., Prader, A., Ann Hum Biol. 1984, 11(6), 495-508.
22. Widholm, O., Kantero, R.L., Acta Obstet Gynecol Scand Suppl. 1971, 14, 1-36.
23. Bennett, A.R., Gray, S.H., Current Opinion Pediatric. 2014, 26(4), 413-419.
24. Fraser, I.S., Warner, P., Marantos, P.A., Obstetrics Gynecology. 2001, 98, 806-814.
25. ACOG Committee Opinion No. 651, Obstetric Gynecology. 2015,126(6), e143-146.
26. Adapted from Fraser et al. It is recommended that these parameters be defined on the basis of published population data, using medians and confidence intervals. Anything outside these limits should be regarded as AUB.
27. Munro, M.G., Critchley, H.O., Fraser, I.S., Int J. Gynaecol Obstet. 2018, 143(3), 393-408.
28. American College of Obstetricians and Gynecologists 409, 20024 - 2188.
29. Munro, M.G., Critchley, H.O., Fraser, I.S., Broder, M.S., Int J. Gynaecol Obstet. 2011, 113, 3-13.
30. American College of Obstetricians and Gynecologists, Obstet Gynaecol. 2012, 120, 197-206.
31. Pecchioli, Y., Oyewumi, L., Allen, L.M., Kives, S.J., Pediatric Adolescent Gynecol. 2017, 30(2), 239-242.
32. Claessens, E.A., Cowell, C.A., American J. Obstet Gynecol. 1981, 139(3), 277-280.
33. Lemarchand-Béraud, T., Zufferey, M.M., Reymond, M., Rey, I., J. Clin Endocrinol Metab. 1982, 54(2), 241-246.
34. Claessens, E.A., Cowell, C.A., American J. Obstet Gynecol. 1981, 139(3), 277-280.
35. Smith, Y.R., Quint, E.H., Hertzberg, R.B., J. Pediatric Adolescent Gynecol. 1998, 11(1), 13-15.
36. Başaran, H.O., Akgül, S., Kanbur, N.O., Gümrük, F., Cetin, M., J. Pediatric. 2013, 55(2), 186-189.
37. Oral, E., Cağdaş, A., Gezer, A., Kaleli, S., Aydin, Y., Oçer, F., Arch Gynecol Obstet. 2002, 266(2), 72-74.
38. Falcone, T., Desjardins, C., Bourque, J., Granger, L., Hemmings, R., Quiros, E., J. Reprod Med. 1994, 39(10), 761-764.
39. Claessens, E.A., Cowell, C.A., Am J. Obstet Gynecol. 1981, 139(3), 277-280.
40. Falcone, T., Desjardins, C., Bourque, J., Granger, L., Hemmings, R., Quiros, E., J. Reprod Med. 1994, 39(10), 761-764.

41. Kanbur, N.O., Derman, O., Kutluk, T., Gürgey, A., Int J. Adolesc Med Health. 2004, 16(2), 183-185.
42. Díaz, R., Dietrich, J.E., Mahoney, D., Srivaths, L.V., J. Pediatric Adolescent Gynecol. 2014, 27(6), 3249.
43. Dowlut-McElroy, T., Williams, K.B., Carpenter, S.L., Strickland, J.L., J. Pediatric Adolescen Gynecol. 2015, 28, 499-501.
44. Mikhail, S., Kouides, P., J. Pediatric Adolescent Gynecol. 2010, 23, S3- S10.
45. Diaz, R., Dietrich, J.E., Mahoney, D., Srivaths, L.V., J. Pediatric Adolescent Gynecol. 2014, 27, 324- 329.
46. Bruner, A.B., Joffe, A., Duggan, A.K., Casella, J.F., Brandt, J., Lancet 1996, 348, 992–996. 47. Falkingham, M., Abdelhamid, A., Curtis, P., Fairweather, S., Dye, L., Hooper, L.,Nutr J. 2010, 9, 4.
48. Johnson, S., Lang, A., Sturm, M., J. Pediatric Adolescent Gynecology. 2016, 29, 628–631.
49. Haamid, F., Sass, A.E., Dietrich, J.E., J. Pediatr Adolesc Gynecol. 2017, 30, 335–340.
50. Nashar, S.A., Shazly, S.A., Gynecol surg. 2015, 12, 157-163.
51. American College of Obstetricians and Gynecologists. ACOG committee opinion no. 557, Obstet Gynecol 2013, 121(4), 891-6.
52. Hald, K., Lieng, M., J. Minim Invasive Gynecol 2014, 21,662-8.
53. Haamid, F., Sass, A.E., Dietrich, J.E., J. Pediatr Adolesc Gynecol 2017, 30,335–40.
54. Johnson, S., Lang, A., Sturm, M., O'Brien, S.H., J. Pediatr Adolesc Gynecol 2016,29, 628–31.
55. Sekhar, D.L., Murray-Kolb, L.E., Kunselman, A,R., Paul, I.M., Clin Nutr ESPEN 2015,10, e118–23.
56. Powers, J.M., Buchanan, G.R., Hematol, Clin North Am 2014, 28,729–45.
57. American College of Obstetricians and Gynecologists, ACOG committee opinion no. 557 Obstet Gynecol 2013, 121(4), 891-6.
58. Demers, C., Derzko, C., David, M., Douglas, J., Int J Gynaecol Obstet 2006 ,95 (1), 75-87.
59. Klarmann, D., Eggert, C., Geisen, C., Becker, S., Seifried, E., Klingebiel, T., Kreuz, W., 2010, 50 (7),1571-80.
60. Pecchioli, Y., Oyewumi, L., Allen, L.M., Kives, S., J. Pediatr Adolesc Gynecol 2017, 30, 239–42.
61. American College of Obstetricians and Gynecologists, Committee Opinion No. 557, Obstet Gynecol 2013, 121, 891–6.
62. American College of Obstetricians and Gynecologists, Practice Bulletin No. 128, Obstet Gynecol 2012,120,197–206.
63. Gray, S.H., Pediatr Rev. 2013, 34 (1), 6-17, 17-8.
64. Hickey, M., Higham, J.M., Fraser, I., Cochrane Database Syst Rev. 2012,12, (9), CD001895.
65. Gray, S.H., Pediatr Rev. 2013, 34 (1), 6-17,17-8.
66. . Deligeoroglou, E., Karountzos, V., Creatsas, G., Gynecol Endocrinol,2013, 29 (1),74-8.
67. American College of Obstetricians and Gynecologists, ACOG committee opinion no. 557, Obstet Gynecol. 2013, 121 (4), 891-6.
68. Bradley, L.D., Gueye, N.A., Am J Obstet Gynecol, 2016, 214 (1), 31-44.
69. Rimsza, M.E., Pediatr Rev. 2002, 23 (7), 227-33.
70. Santos, M., Hendry, D., Sangi-Haghpeykar, H., Dietrich, J.E., J. Pediatr Adolesc Gynecol, 2014, 27 (1), 41-4.
71. Cowan, B.D., Morrison, J., Engl J Med. 1991, 13, 324 (24),1710-5.
72. Files, J.A., Ko, M.G., Pruthi, S., Mayo Clin Proc, 2011, 86 (7), 673-80,680.
73. Gray, S.H., Emans, Laufer, Goldstein's, Emans, S.J., Lippincott Williams & Wilkins, Philadelphia, 2012,159.
74. Gray, S.H., Emans, Laufer, Goldstein's, Emans, S.J., Lippincott Williams & Wilkins, Philadelphia, 2012,159.
75. Zreik, T.G., Odunsi, K., Cass, I., Olive, D.L., Sarrel PFertil Steril, 1999,71 (2), 373-5.
76. Leminen, H., Hurskainen, R., Int J. Womens Health, 2012, 4, 413-21.
77. Gray, S.H., Emans, Laufer, Goldstein's, Emans, S.J. Lippincott Williams & Wilkins, Philadelphia, 2012,159.
78. American College of Obstetricians and Gynecologists, Committee opinion no. 606, Obstet Gynecol. 2014, 124, 397-402.