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Research Article

PROGESTIN-ONLY USE FOR PATIENTS WITH ABNORMAL UTERINE BLEEDING (AUB) WITH THE RISK OF VENOUS THROMBOEMBOLISM (VTE): CASE SERIES AND LITERATURE REVIEW

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ABSTRACT

Background: Risk of venous thromboembolism (VTE) has been the main concern for all the hormonal contraceptives used for AUB. Hormone treatment with estrogen and progesterone has shown risk of developing VTE among the patients. Progestin only is being used by various clinicians to avoid the complication of VTE. The present case series and the literature review have focused on progestin-only use (oral, IUD, injectable, implant) to manage abnormal uterine bleeding specially among high risk patients group.
Material and methods: It was a case series study in which 4 cases of AUB with risk of VTE were treated with progestin only hormone and were followed up for venous thromboembolism .A literature review on the tretment of abnormal uterine bleeding patients with risk of VTE by progestin only hormone was done.The outcome of the progetin only hormone treatment on the case series was compared by the literature review.
Results: Among the four cases with Abnormal Uterine Bleeding (AUB),the first and the fourth cases were treated with oral Primolut N (Norethisterone) and the patient ended up with massive right lower limb DVT in the third case and pulmonary embolism and deep vein thrombosis in the leg in the fourth case. The second case in her young age (29 years) admitted for AUB with h/o SLE and positive anti-phospholipid antibodies was treated with Mirena IUD and the patient improved without any sign of DVT. The third post-menopausal obese case with hypertension, Type 2 DM and endometrial hyperplasia with atypical cells was teated with Megestrol acetate at a dose of 160mg/orally /day and the patient improved after 2 weeks of treatment without any thromboembolic event.
Conclusion: A progestin-only oral formulation used in therapeutic doses in the women with abnormal uterine bleeding was not found free from risk of developing VTE. However the literature reviews suggest that its use in contraception dose did not appear to increase the risk of venous thromboembolic disease. Mirena IUD appeared to be better option for women suffering from abnormal uterine bleeding with risk factors of venous thromboembolism. This case series and the review demonstrated the complex situation for the clinician for treating women with progestin for abnormal uterine bleeding. Each case need to be assessed on its own merit and the health care professional must develop the suitable treatment plan for the women at high risk of VTE

INTRODUCTION

Abnormal Uterine Bleeding (AUB), defined as a menstrual cycle abnormality outside of normal volume, duration, regularity, or frequency (less than 21 days) is a frequent condition in gynecology. But the diagnosis of AUB is always a diagnosis of exclusion which means bleeding from the uterus not caused by pelvic diseases, uterine fibrosis, ovarian cysts, endometrial polyps, coagulation disorders, malignancy inflammation, medical illness or pregnancy.[1]

According to one estimate, Abnormal Uterine Bleeding (AUB) affects 11-13 percent of the general population among reproductive age women at any given time. However this prevalence increases with age, reaching 24 percent in those ages 36 to 40 years.[2]

One third of outpatient visits to the gynecologist are for AUB and it accounts for more than 70% of all gynecologic consults in the premenopausal and postmenopausal years. [3] Management of AUB can be either medical or surgical management. The medical treatment which consists of estrogen, progestogens, combination (estrogen and progestogen) hormonal formulations, non-steroidal anti-inflammatory drugs, anti fibrinolytic, or gonadotropin releasing hormones is considered as the first line of treatment. Surgical intervention is usually reserved for women with persistent bleeding that does not respond to medical therapy or for women who have finished childbearing and do not wish to indefinitely continue medical therapy. [4]

The choice of appropriate initial line management of AUB depends on many factors, including (patient age, menopausal status, acute or chronic presentation, stability of the patient, possible cause of AUB, medical comorbidities such as chronic medical conditions and history of VTE) and the treatment is individualized accordingly. Studies suggest that parenteral estrogen, a multi dose combined oral contraceptive regimen, a multi dose progestin-only regimen, and tranexamic acid are all viable options for patients with acute abnormal uterine bleeding with a normal uterus. Levonorgestrel-releasing intrauterine system, combined oral contraceptives, continuous oral progestin, and tranexamic acid have shown high efficacy

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among patients with heavy menstrual bleeding. Progestin-only methods as well as a gonadotropin-releasing hormone agonist have been found very effective among women on anticoagulation therapy. [5]

\Risk of venous thromboembolism (VTE) has been the main concern for all the hormonal contraceptives used for AUB. Studies have shown 3-5 fold increase in the incidence of VTE among child bearing women who are taking oral estrogen than those who are not taking any treatment. The possible mechanism of estrogen induced VTE is the increase of plasma concentration of clotting factor II,VII,X,XII, Factor VIII and .nitrogen due to estrogen action.[6]

Estrogens are hence risky especially for women with medical conditions associated with increased risk for thrombosis. To counter the problem of VTE with the use of estrogen contraceptive, many practitioners prefer to use progestin only pills containing norethindrone or progestin-releasing intrauterine device containing levonorgestrel(LNG) or depot medroxyprogesterone acetate (DMPA) injection.[7]

Progestin, a synthetic form of progesterone is being used not only for regulation of the menstrual cycle prevention of endometrial cancer and hyperplastic precursor lesions, and contraception (especially among women with contraindication to estrogen), but also for treatment of dysfunctional uterine bleeding. Though the use of progestin in abnormal uterine bleeding (AUB) and menstrual disorders is well established but still its use to manage abnormal uterine bleeding among special high risk patients group (VTE, SLE, migraine with aura, Active malignancy . [8,9]

Use of progestin-only hormone was assessed by various studies with respect to venous thromboembolism risk. In one meta-analysis study, Mantha and colleagues reported that the use of progestin-only hormone by oral or intra-uterine delivery is relative safe but that injectable progestin formulation was associated with an increased risk of venous thromboembolism (VTE) compared with non-users of hormone treatment. [10]

Similarly a systematic review from PubMed database (2016) did not suggest an increase in odds for venous or arterial events with use of most Progestin-only hormone. However limited evidence suggested increased odds of VTE with use of injectable progestin-only hormone. [11]

Abnormal Uterine bleeding among the women of child bearing is common occurrence in Saudi Arabia. According tone study the researchers have found a prevalence of AUB among child bearing age Saudi women as high as 65%. [12] Various treatment modules are used to treat AUB with different results. However hormone treatment with estrogen and progesterone has shown risk of developing VTE among the patients. Progestin only is being used by various clinicians to avoid the complication of VTE.

The present case series and the literature review have focused on progestin-only use (oral, IUD, injectable, implant) to manage abnormal uterine bleeding; in special high risk patients group (VTE, SLE, migraine with aura, Active malignancy).

Material and Methods:

It was a case series studies in which 4 cases of Abnormal uterine bleeding with risk of Venous thromboebembolism treated with progestin only hormone were followed up for venous thromboembolism in Obstertric and gynecology department of King fahad University Hospital during the year 2020.. All the patients diagnosed with abnormal uterine bleeding with risk of venous thromboembolism and on progestin only treatment was the study population. Four cases who reported the Obstetrics and gynecology clinics with abnormal uterine bleeding and on different form of progestin only treatment were the study sample. The approval was taken from the ethical committee of the King fahad University Hospital,Al Khobar before starting the research. Written consent of the casesselected for this syudy was also takeen.

Details of the Case series of Abnormal uterine bleeding on progestin only treatment

For the convenience of comparison of the cases the details of the case studies have been presented in the table No. 1

Table 1 Showing the details of the high risk VTE cases of abnormal uterine bleeding with Progestin only treatment

	Clinical features ,Investigation and management
Case1	
Age	44y old ,Single
Clinical Presentation	Continues heavy vaginal bleeding for 2 weeks, Admitted to the hospital. with low hemoglobin (5.6g/dl) , and symptomatic anemia due to menorrhagia ,
History	The patient had a Regular menstrual cycle; lasting for 5 days duration, average flow, patient reported that her cycle started to be prolonged and heavy for 3 months. She was diagnosed earlier with Uterine fibroid (intramural 7*8cm) which was causing her anemia requiring blood transfusion ,
Management	Initially at the first presentation patient bleeding was managed medically by Primolut N (Norethisterone) one tablet three times a day. After 2 month of treatment Patient was admitted to the hospital with massive right lower limb DVT, and discharged on tropic dose of Rivaroxaban (factor X inhibitor).
Case 2	
Age	29-year-old
Clinical presentation	Heavy menstrual periods for the past 6 month, lasting for 7days with low Hemoglobin (9.6 mg/dL). Other investigations and ultrasound were within normal
Medical History	Systemic lupus erythematous (SLE) and positive anti-phospholipid antibodies with history of dysmenorrhea. She had no personal or family history of VTE.
Management	She did not want more oral medications to be added to her lupus medications. So the patient was inserted Mirena (20 micrograms evonorgestrel-releasing) IUD .The recommendation of Mirena was based on Medical Eligibility Criteria (CDC-MEC) 1 guidelines which characterizes the LNGIUD as category 3 (risks generally outweigh benefits) in patients with SLE and positive antiphospholipid antibodies but recommendation are based on a theoretical risk of VTE.
Follow up	Patient was on continuous follow up after she was indicated about warning signs and symptoms of VTE. After 3month patient's menorrhagia improved. After 6 month during the clinic visit patient reported less dysmenorrhea, fewer days bleeding in each month and no period in the last month. Patient continued follow up for safely for total of 2 years and 8 months. After this period IUD was removed on patient's request for pregnancy.
Case 3	
Age	70 year-old
Clinical Presentation	Came to clinic complaining of post-menopausal heavy bleeding for the past 3months palpitation and shortness of breathing with hemoglobin 8.6g/dl.
Medical history	Obese with BMI 35, Post menopause, hypertensive controlled with medications, Type 2 diabetics on insulin with Hx of obstructive sleep apnea.
Investigations	TVS done showed endometrial thickness of 11 mm .in-office endometrial biopsy demonstrated endometrial hyperplasia with Atypical cells, malignancy.
Management	Due to multiple co morbid conditions and after anesthesia consultation patient labeled as high risk for surgical intervention. Patient was started with Megestrol acetate at a dose of 160mg/orally /day with the prognosis explained that it might cause VTE due to active malignancy
Follow up	Patient's bleeding improved over the few days of medication initiation and medication stopped by the 2 weeks of administration. Patient had no thromboembolic event during the first 3 months of treatment. After

	3 months patient reviewed again in the clinic and in-office endometrial biopsy was done, it showed regression of atypical cells.
Case 4	
Age	39 years
Presentation	Attended ER with history of chest pain (left side) of 1 day duration associated with shortness of breathlessness with hemoglobin level 5.6 mg/dl. CT pulmonary angiography showed pulmonary embolism
	Abnormal Uterine bleeding since 1 year.
Gynecological	
Past history	Diabetes Mellitus on insulin, Hypothyroidism on thyroxin 150 microgram daily, dyslipidemia, Stroke (2 times) without any
Medical history	neurological deficit, pulmonary embolism (4 years back) and deep vein thrombosis (3 years) on warfarin.
	Patient had pelvic MRI 2 months ago showing bulky uterus with diffuse endometrial thickness .Patient refused endometrial biopsy.
Investigation:	Patient was informed that, due to multiple co-morbidity, she was not fit for surgical intervention.
Management	On tablet Primolut N (Norethisterone) one tablet (5mg) two times a day

RESULTS

We present four cases of Abnormal Uterine Bleeding (AUB) who attended the emergency room of the Obstetrics and gynecology department for treatment. One was young while the second in her middle age, the third in the menopausal age and the fourth one unmarried with high risks of VTE. All of these cases were having the signs and symptoms of severe anemia with their serum hemoglobin ranging from 5.6-9.6 gm/dl. The first and the fourth cases were treated with oral Primolut N (Norethisterone) and the patient ended up with massive right lower limb DVT in the third case and pulmonary embolism and deep vein thrombosis in the leg in the fourth case. The second case in her young age (29years) admitted for AUB with h/o Systemic lupus erythematous (SLE) and positive anti-phospholipid antibodies was treated with Mirena (20 micrograms evonorgestrel-releasing) IUD and the patient improved without any sign of DVT. The third post-menopausal obese case was with co morbidity of hypertension, Type 2 Diabetes Mellitus and diagnosed with endometrial hyperplasia with atypical cells, malignancy. Megestrol acetate at a dose of 160mg/orally /day was given and patient improved after 2 weeks of treatment without any thromboembolic event.

DISCUSSION

Management of AUB with the high risk patients for VTE by contraceptive hormone is challenging. Expert opinions and recommendations from various studies had been divergent and differed on most points from clinical practice. Progesterone only and combined contraceptives containing estrogen and progesterone have been associated with changes in the hemostatic balance and contribute to increased risk of thromboembolic events. Study shows that combined oral contraceptives is associated with a 2-4 fold increased risk of venous thrombosis.[12,13]Four generations of the combined hormonal contraceptive have been in use since decades. The first generation consists of 50 mg of ethinyl estradiol (EE) while second generation consists of lower doses of estradiol (20, 30, or 35 mg) and the progestin norethindron and its derivatives, including levonorgestrel). The third and fourth generations of the combined oral contraceptives contained progestins desogestrel and gestodene and combination containing Drospirenone (fourth generation progestin) respectively. Studies show that all these combinations have different risk of deep vein thrombosis with the highest risk associated with the third-generation progestogen desogestrel and the more recently introduced progestogens cyproterone acetate and drospirenone.[6] Norethisterone also known as norethindrone**,** was discovered in 1951 and was one of the first progestin to be developed. It is a "first-generation" progestin. Therapeutic indications for Norethisterone Includes; [14] low dose: Abnormal uterine bleeding, Menorrhagia ,Pre-menstrual syndrome, Endometriosis and at high dose: Disseminated carcinoma of the breast. Norethisterone progestogenic effects on the endometrium is the base of the treatment of abnormal uterine bleeding, A Complete transformation of the endometrium from a proliferative to a secretory state can be achieved in estrogen-primed women with orally administered doses of 100 - 150 mg Norethisterone per cycle.[14] Gonadotropin secretion inhibition and anovulation can be achieved with a daily intake of 0.5 mg of Norethisterone. Norethisterone is primarily metabolized in the liver. The metabolites are eliminated slowly from plasma, with half-lives of about 67 hours. Therefore, during long-term treatment with daily oral administration of Norethisterone, some of these metabolites accumulate in the plasma. Norethisterone is partly metabolized to ethinylestradiol after oral administration of Norethisterone or Norethisterone acetate in humans. This conversion results in an equivalent dose of about 4-6 µg ethinylestradiol per 1 mg orally administered Norethisterone / Norethisterone acetate. [15]

Progestin only hormone have been recommended as safe alternative for patients with risk of VTE. But our first case with 2 months of treatment with Primolut N (Norethisterone) a synthetic form of progestin (15mg/day) developed massive right lower limb DVT. Many case reports are published which show the complications of venous thrombosis due to depot-Norethisterone enanthate injection. Ramya *et al* and Rajput *et al* have reported in their case reports that Norethisterone depot injection and norethindrone acetate pills caused Cerebral Venous Sinus Thrombosis in patients with risk factor associated with VTE.[15,16.]

In a literature review, Diana Mansour did not find any change in the overall positive benefit/risk balance for prescribing therapeutic doses of Norethisterone to the women of low risk of VTE. However he cautioned the use of Norethisterone in women with high risk of VTE. Based on one small study this literature review suggested that medroxyprogesterone acetate, administered three times a day, is as effective in reducing heavy menstrual bleeding in women with risk of VTE as giving daily dose of 15 mg Norethisterone taken from Day 12 to Day 25. [17]

The middle aged women with risk of VTE (Systemic lupus erythematous (SLE) and positive anti-phospholipid antibodies) was treated with Mirena (20 micrograms evonorgestrel-releasing) IUD in our study. The patient did not complain of any sign and symptoms of VTE during 3 months of therapy and abnormal uterine bleeding also subsided. Mirena, a levonorgestrel releasing intrauterine system with daily average release of 20 mcg has been a popular choice because of its favorable bleeding patterns and many non-contraceptive benefits. The release of daily lower dose of LNG compared with systemic hormonal contraceptives is thought to be associated with lower risk of venous thrombosis.In a major clinical review based on published data from the last 5 years the researchers have come to the conclusion that LNG-IUS was not associated with an increased risk of either venous or arterial thrombotic events rather its use was associated with a

significantly decreased risk of venous thromboembolism compared with non-hormonal method users. [18]

The efficacy of LNG-IUS use for women at risk of thromboembolism has also been established in a study byGiordana C. Braga *et al* who did not find any significant change in the risk of VTE after 12 months of **LNG-IUS use.**[19] The use of a levonorgestrel intrauterine device was not associated with an increased risk of VTE (odds ratio, 0.3; 95% CI, 0.1 to 1.1) in a case control study.[20] Similarly the LNG IUD was not found to be associated with an increased risk of venous thrombosis in a recently reported large follow-up study (relative risk, 0.9; 95% CI, 0.6 to 1.3). This study also revealed that increased sensitivity to activated protein C was reported 3 months after the insertion of an LNG IUD which indicates that this contraceptive does not have a prothrombotic effect. [21]

One alternative to medroxyprogesterone acetate include megestrol acetate, 40 to 80 mg twice daily for up to 7 days followed by reduced dosing, and norethindrone acetate , 5 mg orally 3 times per day for up to 7 days followed by reduced dosing (eg, 5 mg/day) for up to 3 weeks . The dose of megestrol acetate up to 320 mg/day have been suggested by some clinicians in obese individual and continuing the dosing for a duration of at least 4 weeks depending on the clinical situation. This management plan was suggested for abnormal uterine bleeding irrespective of risk factor of venous thromboembolism.[22] Megestrol acetate is also supposed to block estrogen and suppress the effects of estrogen and androgens. It is effectively used as non-surgical treatment of endometrial intraepithelial neoplasia. Our third case of endometrial hyperplasia with atypia and the fact that cancer couldn't be excluded and the patient was not operable due to poor surgical candidacy and multiple Co morbidities; medical management was the safest option for the patient. And so, this menopausal case was treated with Megestrol acetate at a dose of 160mg/orally /day for 2 weeks. The patient not only improved for AUB but also no thromboembolic event occurred during the first 3 months of treatment and biopsy of endometrial tissue after 3 months showed regression of atypical cells However, a high incidence of deep vein thrombosis has been reported among nursing home residents in a study where megestrol acetate was prescribed. The megestrol acetate caused deep vein thrombosis even among ambulatory individuals without other known risk factors.[23]That study suggested that the risk of deep vein thrombosis must be considered when prescribing megestrol acetate.

The treatment option for abnormal uterine bleeding is dependent on multiple factors. The cause, fertility, medical comorbidities, adverse effect and relative effectiveness must be considered before starting the treatment. And the real dilemma occurs with the treating clinicians when patient refuse to go for surgical intervention to keep her fertility intact. The fourth case in our cases series had multiple comorbidities with high risk for DVT and with associate endometrial pathology was treated with Primolut N (Norethisterone) one tablet two times a day for months and ended up with VTE with pulmonary embolism. This was the second patient our case series who had complication of VTE.

The study suggests and recommends contraceptive dose of 0.35 mg of Primolut N in this situation where there is active deep vein thrombosis and pulmonary embolism . Low dose of Primolut N was not associated with increased risk of VTE in this situation. However FDA lists Primolut N in its therapeutic dose to be used in women with abnormal uterine bleeding with active deep vein thrombosis and pulmonary embolism as a contraindication for use.[10,24,25]

CONCLUSION

A progestin-only oral formulation used in therapeutic doses in the women with abnormal uterine bleeding was not found free from risk of developing VTE. However the literature reviews suggest that its use in contraception dose did not appear to increase the risk of venous thromboembolic disease.Mirena (20 micrograms evonorgestrel-releasing) IUD appeared to be better option for women suffering from abnormal uterine bleeding with risk factors of venous thromboembolism. This case series and the review demonstrated the complex situation for the clinician for treating women with progestin for abnormal uterine bleeding. The available data, clinical practice and expert opinion are often contradictory. Each case need to be assessed on its own merit and the health care professional must develop the suitable treatment plan for the women at high risk of VTE. However more researches are needed to get additional information on VTE risk of progestin used for the management of abnormal uterine bleeding.

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