Original Report

The Use of Norethisterone for the Treatment of Severe Uterine Bleeding in Adolescents: An Audit of Our Experience

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A B S T R A C T

Study Objective: The purpose of this prospective study was to assess the effectiveness of norethisterone (NET) in the management of abnormal uterine bleeding (AUB) in adolescents in a tertiary care center.
Design: This was a prospective audit focused on administering high doses of NET in female adolescents with complaints of AUB.
Setting: We included female adolescents who presented to our Emergency Gynecological Department or Adolescent Gynecological Outpatient Department from October 2016 to January 2019.
Participants: The study included 29 female adolescents aged 11-17 (mean, 13.14) years.
Interventions: Patients were administered a daily dose of 10-30 mg, depending on the severity of the condition, bleeding duration, and patient weight.
Main Outcome Measures: Cessation of vaginal bleeding.
Results: Mean age at menarche of our patient sample was 11.4 years (range, 10.7-14 years). AUB presented at a mean time of 24.6 months after menarche (range, 0-79 months). Blood transfusion was deemed necessary in 9 patients. Bleeding stopped at a mean of 46.1 (range, 8-120) hours after onset of treatment with NET. No serious adverse events were reported with NET administration, with only 3 cases of minor side effects.
Conclusion: The use of NET is an effective and reliable treatment option among adolescents for whom control of AUB is desired in the acute setting.
Key Words: Abnormal uterine bleeding, Adolescents, Heavy menstrual bleeding, AUB, Norethisterone

Introduction

Adolescence in girls is characterized by a variety of physical and psychological changes that lead to reproductive maturity, including the beginning of menstruation.[1] Abnormal uterine bleeding (AUB) is considered one of the most commonly encountered medical problems in this transition period, generating concerns in adolescents and their families and leading to frequent visits to emergency departments and health care providers.[2] AUB in adolescence affects quality of life, through school absenteeism and limitations to sports or social activity participation.[3,4] Although common, this condition is likely underreported and population-derived prevalence rates are not well described for adolescents. Self-report surveys have shown that 30% of adolescents report irregular bleeding and 15%-40% perceive their bleeding as abnormally heavy.[5–7]

Medical management is generally considered first-line for acute AUB in adolescents. For decades, most textbooks advocate the use of conjugated equine estrogen orally or intravenously, a preparation that is no longer readily available in most hospital pharmacies, let alone emergency departments. As an alternative, current management protocols often propose the use of combined oral contraceptive tablets in multiples of the recommended dosage for contraception. Despite their widespread use, there exists very little information regarding the effectiveness, side effects, and patient satisfaction associated with these commonly used medical regimens. Norethisterone (NET), also known as norethindrone, is a synthetic progestogen that mimics the actions of progesterone, which also possesses weak estrogenic and androgenic properties. NET in a dosage of 5 mg, 3 times a day for 21 days is commonly used for the management of menorrhagia and is considered equally effective as the levonorgestrel intrauterine system.[8] On the basis of this knowledge, we have used NET for more than a decade in our department as standard management of acute or chronic AUB in adolescents.

With this audit, we aimed at recording the effectiveness of NET in an emergency setting where bleeding is acute and severe, usually leading to hospitalization of the adolescent girl due to hemodynamic instability or symptomatic anemia. Furthermore, our goal was to evaluate any side effects during and after NET treatment and to quantify dysmenorrhea symptoms in menstruation after NET cessation, because this has been commonly reported by our patients.

The authors indicate no conflicts of interest.

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Materials and Methods

This study was a prospective audit of the management of acute AUB in adolescent girls using NET. We collected data on all girls who presented to the Emergency Gynecological Department or Adolescent Gynecological Outpatient Department, from October 2016 to January 2019, with AUB and a significant decrease in their hemoglobin value. A dedicated proforma was used to facilitate data collection.

We included girls with a presenting hemoglobin value of less than 10 g/dL and/or bleeding more than 10 days. All experienced AUB for the first time. We excluded girls with a positive pregnancy test, history of genital trauma, or proven genital malignancy.

Information regarding demographic characteristics and menstrual history (onset of menarche, cycle length, duration of periods, number and type of sanitary products used) were recorded. Furthermore, information concerning sexual history and general medical history and comorbidities was assessed. A detailed family history with a focus on polycystic ovary syndrome, menstrual disorders, thyroid disorders, and bleeding diathesis was also recorded.

Subsequently, we recorded information concerning the AUB incident that led to the current visit, particularly with the aim at assessing the severity of blood loss, such as bleeding duration, hemoglobin decrease, number of pads required per day, and the necessity for blood transfusion.

Patients were usually hospitalized and treated with high doses of NET, ranging from 10 to 30 mg daily, taking into account their hemoglobin decrease, the severity of bleeding, and their body weight. For girls weighing less than 55 kg we administered 5 mg, 2-3 times a day, whereas for heavier adolescents, the starting dose was higher at 5-10 mg 3 times a day.

Thereafter, we evaluated the mean time of cessation of bleeding, resumption and duration of the next menstrual cycle, side effects, and dysmenorrhea symptoms after NET administration. This information was obtained during a follow-up visit, 4-5 weeks after the initial episode. For quantification of dysmenorrhea symptoms, we used the visual analogue scale. Patients were asked to rate the level of pain during the recent bleeding event, after NET cessation, from 0 to 10, where a rating of 0 indicated no pain and 10 indicated extreme pain. For comparative purposes, patients were also asked to rate pain during previous menstrual cycles.

Statistical analysis was conducted using the SPSS version 20 statistical package (IBM Corp) and the statistical significance level was set at P less than .05.

Ethical Approval

Approval for this study was obtained by the Ethics Committee and the Scientific Board of Alexandra University Hospital. Furthermore, a written consent was also acquired from all of our patients.

Results

We enrolled 29 consecutive female adolescent patients for evaluation. Their mean age was 13.14 years (range, 11-17 years) and the presenting episode had occurred at a mean of 23.9 months after menarche (range, 0-79 months). Of the 29 patients, 23/29 patients (79.3%) weighed less than 55 kg, whereas 6/29 patients (20.7%) weighed more than 55 kg. Patient characteristics and clinical manifestations of AUB in each group of patients are summarized in Table 1. Blood transfusion was deemed necessary, because of a hemoglobin level below 7 g/dL, in 9/29 patients (31%). In 5 patients there were comorbidities, namely chronic kidney failure in 1 case, diabetes mellitus type II in 1 case, heterozygous B thalassemia in 2 cases, and a uterus bicornis in 1 case.

Clinical effects of NET administrations in each group are summarized in Table 2. No serious adverse events were reported with NET administration. However, minor side effects were recorded in 3/29 cases (10%) and included mild headache, nausea, constipation, and drowsiness. Dysmenorrhea in menstruation after NET cessation reached a mean score of 5.7 (range, 0-10) on the visual analogue scale.

Analysis did not reveal a statistically significant correlation between body mass index and interval from menarche to AUB episode or interval from onset of NET treatment to bleeding cessation (Kendall tau). Similarly, there were no statistically significant differences in patient characteristics and response to treatment between the 2 weight groups (Mann-Whitney U test).

Discussion

The International Federation of Gynecology and Obstetrics proposed a new terminology and classification in 2011, with the aim to include and classify all causes of AUB, structural or functional.[9] Thus, AUB can be further classified

Table 1
Patient Characteristics and Clinical Manifestations of AUB in All Patients and Per each Weight Group

Characteristic	All Patients	Group of patients Weighting Less than 55 kg	Group of patients Weighting More than 55 kg
Patient n	29 (100%)	23 (79.3%)	6 (20.7%)
Age at AUB, years	13.2 (11-17)	13.17 (11-17)	13.3 (11.5-15)
Age menarche, years	11.4 (10.7-14)	11.4 (10.7-14)	11.5 (11-12)
Interval from menarche to episode of AUB, months	24.6 (0-79)	23.8 (0-79)	25.4 (0-72)
Hematocrit before AUB, %	37.9 (32-40.5)	37.78 (32-40.5)	38.25 (38-39)
Hematocrit after AUB, %	26.5 (15-33)	24.67 (15-33)	28.5 (22.9-32.6)
Duration of AUB, days	22.4 (5-60)	23.58 (5-60)	21.3 (9-50)

AUB, abnormal uterine bleeding.
Data are presented as mean (range) except where otherwise noted. Differences were not statistically significant between the 2 groups.

Table 2
Clinical Effects of NET Administration in All Patients and Per each Weight Group

Variable	All Patients	Group of patients Weighting Less than 55 kg	Group of patients Weighting More than 55 kg
Time from onset of NET administration to cessation of AUB, hours	46.1 (8-120)	49.1 (8-120)	43.1 (24-48)
Resumption of menses after NET treatment completion, hours	54.6 (36-72)	54 (36-72)	55.2 (36-72)
Duration of subsequent menstrual cycle, days	5.5 (3-8)	5.3 (3-8)	5.8 (5-7)

AUB, abnormal uterine bleeding; NET, norethisterone.
Data are presented as mean (range). There were no statistically significant differences between the 2 groups.

as AUB/heavy menstrual bleeding (HMB) (replacing the term "menorrhagia) and AUB/intermenstrual bleeding (replacing the term "metrorrhagia). HMB is defined as greater than 80 mL blood loss per period or periods lasting longer than 7 days.[10] Clinical features of HMB include the necessity of changing sanitary protection every 1-2 hours, poor iron status, passage of clots greater than a quarter in diameter, large number of products used during the period, and need to change protection overnight.[11]

Each of the descriptive terms (AUB/HMB and AUB/intermenstrual bleeding) is further classified into structural and nonstructural causes. In adolescents, nonstructural causes are the most common causes of AUB, due to immaturity of the hypothalamic-pituitary-ovarian axis and associated anovulatory cycles. On average, regular ovulatory cycles are achieved by 20 months after menarche. During anovulatory cycles, estrogen stimulates the endometrium, but because no ovulation occurs, there is no progesterone production from a corpus luteum. This lack of the stabilizing influence of progesterone on the endometrium can lead to unpredictable AUB.[12]

There appears to be wide variation in practice management of acute AUB in adolescents and decisions regarding therapy options can be complex among adolescents with coexisting medical conditions.[13,14] The ultimate goal of each treatment is to reduce morbidity, restore and maintain normal blood volumes, prevent life-threatening hemorrhage, re-establish regular menses, and improve quality of life.[1,2,15] There are many options effective in managing acute AUB such as conjugated equine estrogens, combined oral contraceptives, progesterone-only pills, depot medroxyprogesterone acetate, a levonorgestrel intrauterine device, gonadotropin-releasing hormone agonists such as leuprolide acetate, nonsteroidal anti-inflammatory drugs, and aminocaproic acid.[2] Surgical intervention is rarely necessary in adolescents because more than 90% of patients improve with medical management.[16] Each of the previously mentioned regimens has contraindications and side effects. The World Health Organization has issued specific guidelines regarding medical eligibility criteria for the use of any method of contraception.[13] For adolescents with relative or absolute contraindications to estrogen administration (cardiovascular disease, thrombophilic conditions, uncontrolled hypertension, migraine with aura, liver or renal disease, cancer), progestin-only options must be considered.[13,14]

At our institution, we tended to avoid the use of combined hormone therapy in an emergency setting, because it is often not possible to appropriately evaluate for contraindications. NET was shown to be effective and well tolerated in the management of acute bleeding in adolescents. In 12/29 patients (41.3%) bleeding stopped within 24 hours, whereas in all, no other measure was required to stop the bleeding, because there was a significant improvement of blood loss from onset of treatment. Bleeding cessation rates were similar with previous published studies using NET taper for AUB.[17–19] In these studies, the mean time to bleeding cessation was 3 days[18] and 4 days,[19] respectively.

Administration of NET was mainly on the basis of clinical judgement, taking into consideration the severity of bleeding at presentation, the value of hemoglobin, and the patient's weight and body mass index. Our Department has used NET for more than a decade as standard management of acute or chronic AUB in adolescents. Although girls in this instance were not managed on the basis of a strict protocol, we applied the algorithm proposed in Figure 1.

On the basis of our experience and proposed algorithm, adolescent patients, with AUB and a more prolonged bleeding period required a lower dose of NET, because by default the amount of daily blood loss was less profound. Girls who presented with an acute hemoglobin decrease soon after onset of bleeding required a more aggressive intervention with higher NET dosage.

NET administration was continued for 21 days, so as to allow for iron supplements to improve anemia before the next period. We were aware that girls complained of dysmenorrhea after administration, so opted to measure this as objectively as possible. None of the girls reported pain that could not be managed as an outpatient, however, most required usage of paracetamol or of a nonsteroidal anti-inflammatory drug.

Other potential advantages of the usage of NET is that it is not expected to promote epiphyseal closure, as might large doses of estrogen. This was particularly important in this cohort of patients, in which most were young and close to menarche. As such, it would have been important to

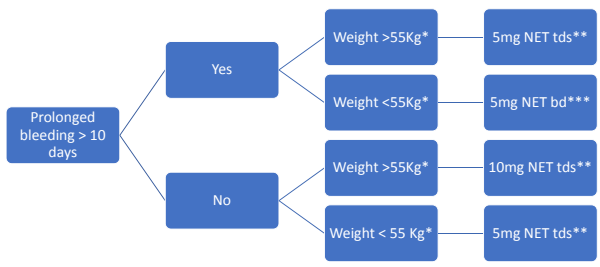

Fig. 1. The "Alexandra Hospital algorithm" for norethisterone (NET) administration in the management of adolescent abnormal uterine bleeding. bd, twice per day; tds, 3 times per day.

administer a medication that would not interfere with their final stature. For older patients, particularly those at an average of 2 years post menarche, NET might not have an advantage over the combined oral contraceptive.

Furthermore, NET was well tolerated in the acute phase for girls who were hospitalized, and for those in their immediate convalescence and after discharge at home. Although 1 girl complained of nausea, there were no incidences of severe nausea and vomiting, a common complaint when large dosages of estrogen are administered, including multiple pills of the combined oral contraceptive, per day. It should be noted however that NET is metabolized and converted to ethinylestradiol at a rate of 4-6 μg per 1 mg of orally administered NET. Thus, patients who receive an average dose of 15 mg of NET per day would be exposed to 60-90 μg of ethinylestradiol.[20]

It is not clear why in some girls NET was effective sooner, although our impression is that there is a dependence on severity of bleeding, weight, and NET dosage. Nevertheless, a larger number of patients would be required to obtain substantial conclusions.

Although most girls did not have any other comorbidities, there was 1 who was bleeding secondary to a bleeding diathesis and another who had chronic renal failure and was receiving hemodialysis. These girls did not react differently to the remaining cohort. Equally, some of the girls were no longer close to menarche, and were likely to have a secondary cause for their anovulation, such as polycystic ovarian syndrome. There was no difference in the effectiveness in older adolescents, thus allowing us to conclude that NET can be used in girls with an immature axis and those who might have a secondary cause for anovulation.

Conclusion

Our results indicate that the use of NET is an effective and reliable alternative among adolescents for whom quick control of AUB is required.

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