

Use of Norethisterone for the treatment of Abnormal Uterine Bleeding in Adolescents

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Abstract

Introduction: Abnormal uterine bleeding (AUB) or Heavy menstrual bleeding (HMB) is one of the most commonly encountered medical problems in this transition from childhood to maturity and also a major Gynaecological problem responsible for frequent visits & hospitalization in Gynaecology OPD. AUB has significant effect on adolescent quality of life, daily school activity and peer relationship. Despite of being common, this problem is still under reported and population-derived prevalence rates are not well described for adolescents.

Aim: To estimate the effect of Norethisterone in managing AUB in adolescents and to observe the improvement in the health of adolescent girls due to reduction in blood loss with improved haemoglobin after treatment with Norethisterone.

Methods: This was a Prospective descriptive study conducted in the Department of Obstetrics and Gynaecology, JK Lon Hospital, Government Medical College, Kota, Rajasthan. Adolescent girls presenting

with AUB reported in gynae OPD are included in the study during the period of January 2020 to December 2020. The selected 100 adolescent girls with AUB were randomized into two groups. Out of them 50 girls were given tab Norethisterone 5mg TDS for 7 days which was followed by 5mg BD for next 14 days i.e., 21 days for each cycle for 3 months for 3 cycles along with iron supplementation. The other group was given only iron folic acid supplementation.

Results: The present study shows maximum girls, 60% presented at late adolescent 17-19 years of age. Most of the girls (44%) was found to have symptoms for more than one year, 82% girls have Hb 7-9 g% while 5% girls have Hb < 7g% before starting treatment. Significant change in Hb was observed after completion of treatment with norethisterone, mean Hb value in the study group was 7.87+/-0.85 became 10.3+/-6.92 after treatment, in control group there was improvement due to iron supplementation (7.75+/-0.71 to 8.75+/-0.87).

There is a significant change noted in PBAC score, it is shifted from 180+/-14.42 to 82+/-10.85 after treatment

with norethisterone in study group. Majority of patient's i.e 64% have stopped bleeding within 24-48 hrs duration of starting treatment. 40% girls have no side effects with norethisterone, 24% girls have nausea and 14% have bloating as side effect while only 10% have headache and constipation.

Conclusion: Reassurance in adolescent girls with HMB plays a very important role as most common cause is immaturity of HPO axis. First line of treatment is medical management which includes hormonal or non-hormonal.

Keywords: Norethisterone, Abnormal uterine bleeding, haemoglobin, headache, constipation.

Introduction

Adolescence in girls is marked by a host of physical and psychological changes, including those associated with menstruation. "WHO defines adolescence as the period in human growth and development that occurs from age 10-19 years". The complete maturation of the hypothalamic – Pituitary – Ovarian axis (HPO) may take up to 2 years. During this time, it is common for adolescents to present with complaints of menstrual irregularities. HMB is defined as > 80ml, blood loss per period or periods lasting > 7 days and passage of clots. International federation of obstetrics & Gynaecology (FIGO) defines the etiology of Abnormal Uterine Bleeding using the PALM – COEIN Classification: Structural causes- Polyp, Adenomyosis, Leiomyoma, Malignancy and Non-structural causes – Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, Not yet classified. In adolescents, non-structural causes are mostly responsible for Abnormal Uterine Bleeding, due to immaturity of HPO axis. Management is largely based on severity of bleeding and anaemia. Treatment options include iron supplementation, combined oral

contraceptives, high dose estrogens (iv Premarin) and Progesterone's (Med Roxy progesterone acetate, Norethisterone), non-steroidal anti-inflammatory drugs (NSAIDS), anti - fibrinolytics (Tranexamic acid), desmopressin, GnRH analogue etc.

Progesterone's has antiestrogenic, antimetabolic and growth limiting effect on endometrium. Norethisterone (NET) also known as Norethindrone, is a synthetic first-generation progestogen, which also possess weak estrogenic and androgenic properties. Norethisterone causes suppression of endometrial proliferation hence causes endometrial atrophy.

During anovulatory cycles, estrogen stimulates the endometrium, as no ovulation occurs there is no progesterone production from corpus luteum, this lack of stabilizing influence of progesterone on endometrium causes unpredictable AUB. Along with AUB, Norethisterone is also used in endometriosis, postponement of menstruation, HRT, premenstrual symptoms.

Methodology

This Prospective descriptive study was carried out in Department of Obstetrics and Gynaecology, JK Lon Hospital, Government Medical College, Kota, Rajasthan for a period of one year from January 2020 to December 2020. Adolescent girls reported in gynae OPD with complaints of AUB were screened for following inclusion and exclusion criteria.

Inclusion criteria

- Girls of 11 to 19 yrs of age presenting with Abnormal uterine bleeding.
- Girls with bleeding >80ml per menses and / or associated with passage of clots.
- Girls with cycle duration >7 days.

Exclusion criteria

- Girls < 11yrs and above age 19yrs
- Girls with UPT positive
- Girls with associated Coagulopathies
- Girls with associated thyroid disorder
- Girls with associated prolactin disorder
- AUB with other structural causes.

Amongst the screened adolescent girls who fulfilled the above criteria were recruited for the present study. These recruited girls were explained about the purpose of the present study and an informed written consent taken from these girls and their parents.

The selected 100 adolescent girls with AUB were randomized into two groups. Randomization was done by sealed envelope technique. Out of them 50 girls were given tab Norethisterone 5mg TDS for 7 days which was followed by 5mg BD for next 14 days i.e., 21 days for each cycle for 3 months for 3 cycles along with iron supplementation. The other group was given only iron folic acid supplementation.

A detailed history regarding menstruation, age, socioeconomic status, milestones of growth and onset of puberty were taken. The baseline investigations done in all the cases were Urine for pregnancy test, haemoglobin (HB), complete blood count, peripheral blood smear for red and white blood cell (RBC & WBC) morphology, platelet count, coagulation profile, blood grouping and Rh typing, LFT, RFT, Serum, RBS, Thyroid profile (T3, T4, TSH), Serum Prolactin and USG pelvis. Patients were called for follow up every month on day 1 of menses for three months.

On each visit girls were requested to fill the PBAC score card of her previous menstrual cycle. CBC done at each visit to look for the change in Hb levels.

Results from both the case and control group were collected to analyse the data statistically. The approval of the institutional ethical committee was obtained prior to the commencement of the study.

Results

The present study shows maximum girls, 60% presented at late adolescent 17-19 years of age and maximum number of girls i.e., 33% belonged to lower middle class. The mean age of menarche was 13.07+/-0.76 yrs in this study. Most of the girls (44%) was found to have symptoms for more than one year, 82% girls have Hb 7-9 g% while 5% girls have Hb < 7g% before starting treatment. Significant change in Hb was observed after completion of treatment with norethisterone, mean Hb value in study group was 7.87+/-0.85 became 10.3+/-6.92 after treatment, in control group there was improvement due to iron supplementation (7.75+/-0.71 to 8.75+/-0.87). Majority of patients i.e., 64% had stopped bleeding between 24 -48 hours duration, 12% i.e., 6 girls stopped bleeding within 24 hours.

For all patients cessation of bleeding seen within 7 days. This study shows, mean days of menses in study group before treatment was 11.42+/-2.34 days which became 4.90+/-0.83 days after norethisterone cyclical treatment while for case group it had no significant change.

34% girls had dysmenorrhea, 18% had itching as associated symptoms, few of them have dysuria (4%), white discharge (15%).

There is a significant change noted in PBAC score, it is shifted from 180+/- 14.42 to 82+/-10.85 after treatment with norethisterone in study group. 40% girls have no side effects with norethisterone, 24% girls have nausea and 14% have bloating as side effect while only 10% have headache and constipation.

Table 1: Severity of anaemia before treatment.

HB (g/dl)	Case group [n=50]	Control group [n=50]	Total (n =100)	%
<7	3	2	5	5%
7-9	40	42	82	82%
9-11	7	6	13	13%
>11	nil	Nil	nil	
$\chi^2=0.325$; d.f.=2; $p=0.849$				

Table 2: Severity of anemia after completion of treatment.

Hb (g/dl)	Case group [n=50]	Control group [n=50]	total	%
<7	nil	Nil	nil	Nil
7-9	6	30	36	36%
9-11	42	20	62	62%
>11	2		2	2%
$\chi^2=6.77$; d.f.=2; $p=0.033$				

Table 3: Days of menses before and after treatment in both groups populations.

Days of menses	Treatment	Study group [n=50]	Control group [n=50]
Mean days	Before	11.42±2.34	11.08±2.13
	After	4.90±0.83	11.16±2.10
P value		<0.0001	0.209

Table 4: Pictorial blood loss assessment in both groups.

PBAC Score	Treatment	Study group [n=50]	Control group [n=50]
Mean loss	Before	180.62±14.42	174.98±17.44
	After	82.00±10.85	175.70±17.87
P value		<0.0001	0.081

Table 5: Associated symptoms in both groups.

Associated symptoms	Case group [n=50]	Control group [n=50]	Total	%
Itching	7	11	18	18%
White discharge	7	8	15	15%
Dysmenorrhea	19	15	34	34%
Dysuria	3	1	4	4%
NAD	14	15	29	29%

Table 6: side effects of Norethisterone in study group.

Side effects	No. of patients (n)	Percentage (%)
Spotting	1	2%
Bloating	7	14%
Nausea	12	24%
Constipation	5	10%
Headache	5	10%
NAD	20	40%

Discussion

AUB accounts for half of Gynaecological problems among adolescent girls. The underlying cause that is responsible for AUB, itself may have potential for long term consequences on health of adolescents which affects life quality and also responsible for poor school performance. Approach for diagnosis and management of AUB in adolescents is a challenging process. The etiology of abnormal uterine bleeding in adolescents is most often related to an immature hypothalamic-pituitary axis which results in anovulatory cycles. Treatment is directed towards stabilizing the endometrium and treating the hormonal alterations.

In present study majority of adolescent girls were of age group 17-19 yrs i.e., late adolescent group. Only 11% girls were of 11-13 yrs age i.e., early adolescent age group. Similar results were obtained in studies of Vijay Shree et al (17-19yrs) and Rattan Chandra et al (16-

19yrs). In present study, 71% of girls had complaints of AUB for more than 8 months. In studies Prameela et al and Vijay Shree et al duration of symptoms was 6 months to 1 year i.e. similar to present study. Longer duration of symptoms indicates ignorance, unawareness toward health or it could be due to the fact that even in middle and lower socio-economic groups, women still hesitate to talk about menstruation with their daughters. Girls with longer duration complaints have low haemoglobin status, more decompensated health.

In present study mean Hb value for study group before treatment was 7.87 ± 0.85 and after treatment it was found to be 10.31 ± 6.92 . Whereas in control group mean Hb value was 7.97 ± 0.75 before treatment and after oral iron supplementation it was 8.75 ± 0.87 . Although there is improvement in both groups (p value < 0.001) but significant improvement was noted in case group. In study Sayantan Sen et al, they compared two drugs Norethisterone and COC. Out of 100, 50 patients received Norethisterone where pretreatment mean Hb was 7.64 ± 0.58 which was improved to 10.44 ± 0.78 after completion of treatment. They observed that maintaining a sustained level of progesterone helps in regaining near normal level of menstrual bleeding. The study supports the efficacy of Norethisterone as treatment mode in AUB. In study by Chitragada et al, mean Hb increased by 23% for Ormeloxifene while for Norethisterone group this increase was 12.26%.

In present study, mean days of menses before treatment were 11.42 ± 34 and after treatment it was found to be 4.9 ± 0.83 in case group. While in control group pre and post supplement mean days of menses were 11.08 ± 2.13 and 11.16 ± 2.10 respectively which was significant for case group (p value < 0.0001).

NET was started from day 5 of menses at doses as per severity of symptoms and given for 3 cycles. Results showed NET as a good medication for adolescent girls with better safety profile. A comparative study conducted by Yaaqoub et al, between NET and Dydrogesterone in treatment of AUB. Out of 200 patients, 100 were treated with norethisterone which was study group and 100 patients were treated with dydrogesterone. In this study, in NET group 75% patients had regular cycle while in other group i.e., Dydrogesterone group only 46% patients had regular cycle. Hence results showed NET as more effective regimen than Dydrogesterone. In study I.K. Papapanagiotou et al, duration of subsequent menstrual cycle after treatment with norethisterone was found to be 5.5 days. In study Irvine et al, they compared two drugs Levonorgestrel IUS and Norethisterone. NET reduced menstrual blood loss by 87% (median reduction 95ml, range 56 to 212ml). While LNG-IUS showed 94% reduction in blood loss (median reduction 103ml, range 70 to 733). In this study they used NET in dosage of 5mg TDS for 21 days for 3 months. Study showed that although NET is effective drug in AUB but better results were seen with LNG-IUS. However, oral NET has better acceptance as compare to LNG-IUS in adolescent girls.

PBAC score is a simple tool for assessment of menstrual blood loss. It is quite cost effective as it requires no special equipments or setup and is less time consuming also. With this score, we can easily differentiate girls having normal blood flow during menses from those having heavy menstrual bleeding. In present study mean PBAC score for NET group was 180 ± 14.42 which had shifted to 82.00 ± 10.85 after 3 cycles of norethisterone treatment (P value < 0.001).

Similar results were obtained in study Sayantan Sen et al, where 50 patients were treated with Norethisterone

and 50 were treated with COCs. Pretreatment PBAC score in NET group was 176+/-5.75 which was found to be 77.80 after treatment. For COCs group pretreatment PBAC score was 175.58 which was after treatment 78.88. Similarly, Comparative study between COCs and NET done by Priyanka et al showed fall in PBAC score from 212.85 to 134.7 (for NET treatment group) and from 217 to 136.85 for COCs group.

In present study mean time for cessation of bleeding after administration of norethisterone was 48.6hrs. Also mean time of resumption of menses after Norethisterone treatment completion 52.6 hours (36-72 hours). In study I.K. Papapanagiotou et al, for 12 patients out of 29(41.3%) bleeding stopped within 24 hours. Mean time of cessation of bleeding after start of treatment was 49.1hours (8- 120 hours) for patients weighting 55kgs it was 43.1hrs (2448hours). Mean time of resumption of menses after norethisterone treatment was 54hours and 55.2 hours for patients weighting 55kgs respectively. In study Deborah Hendry et al mean time for cessation of bleeding for 78% patients was 2.7 +/- 2.3 days. All patients achieved complete cessation of bleeding within maximum 7days of duration.

In present study, out of 50 girls who were treated with NET, 12 girls (24%) complaint of nausea while 5 girls (10%) had constipation and headache. 7 Girls (14%) had bloating and only one girl was reported with spotting per vaginum. No severe episode of nausea or bleeding was reported. In comparative study between NET and Ormeloxifene done by Sanchita et al, none of girl presented with complaint of amenorrhea in NET group while in Ormeloxifene group 14 girls reported with same complaint. Only 6 girls had complaint of spotting and one had breakthrough bleeding episode with NET treatment. In another study by Satyajeet al 13(26%)

patients had no side effect with NET while 12(24%) patients had nausea and 7(14%) patients had complaint of breakthrough bleeding.

As per ACOG recommendations when selecting a combined OC, monophasic pills that contain 30–50 micrograms of ethinylloestradiol with second-generation progesterone should be chosen as first-line therapy because they are more likely to stabilize the endometrium than lower dose formulations. Progestin therapy is another option for adolescents and women who cannot tolerate estrogen containing therapy or in whom estrogen is contraindicated.

However, NET is metabolized and converted to ethinylestradiol (EE) at a rate of 4-6mcg per 1mg of orally administered NET. Thus, patients receiving an average dose of 15mg of NET per day, would be exposed to 40mcg of EE. Other potential advantages of the usage of NET over COCs is that it is not expected to promote epiphyseal closure, as large doses of estrogen might cause when given COCs. This was particularly important in cohort of patients, where the majority are young and close to menarche.

In present study to determine the efficacy of NET primary outcome measures were reduction in days of menses, reduction in amount of blood loss which was assessed by fall in PBAC score. Along with these measures cessation of bleeding occurred within 48-72hrs after start of treatment and resumption of menses after treatment completion was 36-72hrs. The study showed NET has a good impact on physical, psychological and social health of girls and also a well-tolerated drug. Although some girls complained of nausea, vomiting and headache but no significant side effects observed that might require the cessation of treatment.

Conclusion

Abnormal uterine bleeding is a commonly encountered Gynaecological problem amongst adolescent girls which affect their quality of life, daily school activities and peer relationships. Definitely, reassurance counselling of these girls along with correction of their nutritional status and anaemia is the key management.

The results obtained from our study prove the efficacy of Norethisterone in treating abnormal uterine bleeding in adolescence. A decrease in duration and severity of menstrual bleeding along with the improved haemoglobin levels reflecting the good response of the drug. Thus we can conclude that NET is easily available, effective and well tolerated drug that can be used in treating Abnormal uterine bleeding in adolescents.

References

1. <https://www.who.int/southeastasia/health-topics/adolescent-health>
2. Munro, Malcolm G.; Critchley, Hilary O.D.; Fraser, Ian S. (2018). The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. *International Journal of Gynecology & Obstetrics*, (), -. doi: 10. 1002/ijgo.1266
3. Comparison of the efficacy and safety of norethisterone vs. combined oral contraceptive pills for the management of puberty menorrhagia Nita K. Patela,
4. A comparative study of norethisterone and combined oral contraceptive pill in the treatment of dysfunctional uterine bleeding Sayantan Sen
5. Levonorgestrel Intrauterine System And Norethisterone For The Treatment of Chronic Abnormal Uterine Bleeding: A Randomized Clinical Comparison MN Ashra
6. Munro MG, Critchley HO, Broder MS, Fraser IS FIGO Working Group on Menstrual Disorders. FIGO classification system (PALMCOEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. *Int J Gynaecol Obstet*. 2011; 113:3–13.
7. Naqaish T, Rizvi F, Khan A, Afzal M. Patient satisfaction for levonorgestrel intrauterine system and norethisterone for treatment of dysfunctional uterine bleeding. *J Ayub Med Col Abbottabad*. 2012; 24:23-6.
33. Studd J TS, Chervenak FA. *Progress in Obstetrics and Gynaecology*. illustrated ed: Elsevier, 2006.
8. Coulter A, Peto V, Jenkinson C. Quality of life and patient satisfaction following treatment for menorrhagia. *Fam Pract*. 1994; 11:394-401.
38. Tariq N, Ayub R, Jaffery T, Rahim F, Naseem F, Kamal M. Efficacy of levonorgestrel intrauterine system (LNG-IUS) for abnormal uterine bleeding and contraception. *J Coll Physicians Surg Pak*. 2011; 21:210-3.
9. ACOG Practice Bulletin No. 206: Use of hormonal contraception in women with coexisting medical conditions. *Obstet Gynecol* 2019 Feb; 133(2): e128-e150.
10. Patel NK, Patel S, Damor R, Pandya MR. Comparison of the efficacy and safety of norethisterone vs. combined oral contraceptive pills for the management of puberty menorrhagia. *Int J Basic Clin Pharmacol* 2012; 1:191-5.
11. Chauhan M, Gupta N, Dwivedi S, Agarwal S. A study to compare the efficacy of ormeloxifene with norethisterone and conventional oral contraceptive pills. *Int J Reprod Contracept Obstet Gynecol* 2017; 6:4469-72.
12. A Comparative Study of Norethisterone and Combined Oral Contraceptive Pill in the Treatment of Dysfunctional Uterine Bleeding Original Article

Sayantana Sen, Tappan Kumar Mandal, Arijit Dutta, Himel Mondal¹, Tufan Khalua.

13. A Clinical Study of Adolescent AUB in a Tertiary Care Centre Vijayasree M* Department of Obstetrics and Gynaecology, Mamata Medical College, India.

14. Cyclical progestogens for heavy menstrual bleeding Monitoring Editor: Magdalena Bo fill Rodriguez, corresponding author Anne Letha by, Cindy Low, Iain T Cameron, and Cochrane Gynaecology and Fertility Group.

15. Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia J T Preston 1, I T Cameron, E J Adams, S K Smith DOI: 10.1111 /j. 1471- 0528. 1995.tb11293.x

16. Comparison between Ormeloxifene and Norethisterone in reducing menorrhagia in dysfunctional uterine bleeding Swati Gett, Shruti Singh.

17. Clinical efficacy of levonorgestrel and norethisterone for the treatment of chronic abnormal uterine bleeding Muhammad Nadeem Ashraf, Agha Habib – Ur - Rehman 2, Zahid Shehzad 3, Shakir Dakheel Allah AlSharari 4, Ghulam Murtaza 5.

18. Ormeloxifene- A new treatment modality in Dysfunctional Uterine Bleeding: efficacy and safety Sanchita Karmakar¹, *, Hemant Deshpande² ¹Assistant Professor, IQ City Medical College, Durgapur, Burdwan, ²Professor & HOD, Padma Shree Dr. D.Y. Patil Medical College, Pune.

19. Comparison of the efficacy and safety of norethisterone vs combined oral contraceptive pills for the management of puberty menorrhagia June 2012 International Journal of Basic & Clinical Pharmacology 1 (3):191 DOI: 10 .5455/ 2319- 2003. Ijbcpc 003512 Authors: Nita K. Patel Shalin Patel, Rohit Damar, Manish R Pandya.

20. A Comparative Study between Norethisterone Progestogens and Dydrogesterone in the Treatment of Dysfunctional Uterine Bleeding Nabila K. Yaaqoub Department of Gynaecology and Obstetrics, Faculty of Medicine, University of Tikrit, P.O. Box 42, Tikrit Salahuddin, Iraq.

21. A double blinded randomized controlled trial to compare Ormeloxifene and Norethisterone in the treatment of Dysfunctional Uterine Bleeding Dr. Chitrangada MS, Dr. Satyajeet Kumar Singh MSDr Prof Subrata Nag.