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The relationship between estrogen and subsequent growth restriction among adolescents with heavy menstrual bleeding at menarche

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Abstract

Objectives: We sought to evaluate the impact of estrogen-containing treatment for heavy menstrual bleeding (HMB) on subsequent height compared to progesterone-only or non-hormonal treatment when initiated at menarche.

Methods: We performed a retrospective chart review of adolescent females aged 10–15 years who presented to an institution-affiliated outpatient, inpatient, or emergency setting for management of HMB within three months of menarche. Growth records over a 2 year period starting at menarche were recorded, and comparisons made among patients treated with 1) estrogen, 2) progesterone, and 3) non-hormonal methods (controls). Groups were compared using bivariate analysis with Chi-square or Fisher's exact test and linear regression.

Results: In an analysis of 80 patients at 24 months, the mean increase in height from menarche was 6.4 cm among controls (n=54), 7.2 cm among the progesterone-only group (n=10), and 3.8 cm among the estrogen group (n=16). The estrogen group's increase in height was significantly lower than the control group's, by a mean of 1.8 cm (p=0.04). Change in height did not differ significantly between the progesterone and control groups (p=0.87). Additionally, for every year younger at menarche, there was 1 fewer cm of growth (change in height) at 24 months after menarche (p<0.002).

Conclusions: Estrogen-containing treatment for HMB initiated within three months of menarche was associated with reduced growth at 24 months compared to progesterone-only or non-hormonal methods. The clinical applicability of the estrogen group's 1.8 cm absolute reduction in height may have considerable significance for those who are shorter at baseline.

Keywords: adolescent gynecology; estrogen; growth; heavy menstrual bleeding; height; menarche.

Introduction

Heavy menstrual bleeding (HMB) is a common gynecological condition in adolescents, often resulting in presentation to healthcare providers for evaluation and management. Approximately 40% of healthy adolescent girls experience HMB, the majority of who present within the first year after menarche [1, 2]. For these adolescents, HMB can interfere with physical, social, emotional, or material quality of life [3]. The burden of HMB may manifest as missed school days and social events, limitations to physical activity, hospitalization, and excessive preoccupation and worry surrounding their menses [1].

In the adolescent population, the most common etiology of HMB is anovulatory cycles due to hypothalamic-pituitary-ovarian axis prematurity. Inherited coagulopathy is the second most prevalent subgroup, with studies reporting that 21–46% of adolescents presenting for HMB were found to have an underlying bleeding disorder [4–7]. Nearly half of girls with coagulopathies presented with HMB at time of menarche [8]. Given the potential for both short- and long-term complications in girls with and without bleeding disorders, acute management of HMB is often followed by a prolonged course of maintenance medical therapy.

Many therapeutic options exist for the management of HMB. While antifibrinolytic agents like tranexamic acid and aminocaproic acid can be used, most providers recommend hormonal treatment with progesterone and/or estrogen given their high efficacy, wide availability, and variety of delivery routes (oral, patch, ring, injection, implant, and intrauterine device). However, some providers choose to

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postpone the use of estrogen-containing therapies for adolescent girls until at least a year after menarche given the theoretical concern for potential height restriction secondary to early growth plate fusion [9].

Currently, there is insufficient evidence to support that estrogen-containing therapies used for HMB in adolescents at menarche result in clinically significant growth reduction, as few studies have specifically investigated this relationship. By comparing change in height between adolescents treated with estrogen-containing therapy, progesterone-only therapy, or non-hormonal therapy over 24 months, this study aims to address this gap in the current literature by elucidating if a true relationship exists between estrogen and curtailed growth.

Subjects and methods

A retrospective chart review was performed of female patients aged 10–15 years who presented to an institution-affiliated outpatient, inpatient, or emergency department setting for HMB between 2000 and 2021. A chart-filtering search engine was utilized to identify patients who had International Classification of Disease Codes 9 and 10 for both HMB and bleeding at menarche (see Supplementary Material, Appendix, for specific diagnosis codes). Individual charts were reviewed in the electronic medical record (EMR) to ensure data regarding height, age at menarche, and therapeutic management were available. Those without recorded heights at any of the intended study time points were excluded, whereas those who had record of some but not all three time points after menarche were excluded from the relevant statistical analysis for the respective time point variable. Those with all three time points available were included in the analytic sample. Additional exclusion criteria included presence of a congenital condition with the potential to impact normal projected growth or maturation (e.g., Turner syndrome and Marfan syndrome); pregnancy; history of or current malignancy; use of anticoagulant medications; use of exogenous hormones for reason other than HMB; use of hormone receptor modulators; paraplegia; or nutritional impairment due to an eating disorder or other medical condition.

Data was input into and managed using REDCap electronic data capture tools. Variables recorded included race/ethnicity; age at menarche; age at three post-menarche time points (6, 12, 24 months); height (cm) at menarche; height (cm) at three post-menarche time points (6, 12, 24 months); and primary treatment modality for HMB grouped by 1) estrogen-containing therapy, 2) progesterone-only treatment, or 3) non-hormonal management (control). Estrogen-containing therapy included daily doses of 20, 30, or 35 mcg of ethinyl estradiol as monotherapy or in a combined oral contraceptive pill. Progesterone-only treatments included isolated oral or injectable progestins. Non-hormonal methods included antifibrinolytics and expectant management. The primary treatment modality was determined to be the therapy used for the longest duration within one year after menarche and initiated within three months of menarche. Both height and age data points for each time point of interest were required to have been documented in the EMR within a 3 month window (±3 months) of the intended study timepoint to be included. The primary outcome was change in height between menarche and 24 months. Data entries were reviewed for accuracy by the senior author.

All analyses were performed in Stata version 16 (College Station, TX) using an α-level of 0.05. Bivariate analyses to investigate the relationships between the primary outcomes (change in height at 24 months) and explanators was conducted using Chi-square and Fisher's exact test where appropriate. Factors significant at the 0.1 level in bivariate analysis were assessed using linear regression, with the change in height at 24 months as the outcome variable. Further subanalysis was conducted using linear regression, with change in height at 24 months as the outcome variable separately for those age <12 at menarche and those age ≥12 at menarche. Additionally, standardization of the outcome of interest by near-final height was performed to further determine if a significant relationship existed. For each study participant, change in height from baseline to 24 months was divided by height at 24 months (near-final height). This standardized outcome variable was used in additional regression analyses.

The research related to human use was complied with all the relevant national regulations, institutional policies, and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board. Informed consent was waived, as this is a retrospective review of existing data included in the standard care of patients; the results will not negatively or positively affect the patients or their offspring.

Results

Of 403 patient charts reviewed, 80 were included in the study. The breakdown by primary treatment modality included: 54 patients in the non-hormonal treatment (control) group, 16 patients in the estrogen group, and 10 patients in the progesterone-only group. Most of the adolescents were White (76.3%) and the mean age at menarche was 11.8 years for the entire cohort (Table 1).

Table 1: Demographics of the study cohort.

Variable	Full sample (n=80)	Analytic sample (n=57)
Race/ethnicity		
White	61 (76.3)	47 (82.5)
African American	2 (2.5)	2 (3.5)
Asian	3 (3.8)	1 (1.8)
Latina/Hispanic	4 (5.0)	1 (1.8)
Other	4 (5.0)	1 (1.8)
Not listed	6 (7.5)	1 (1.8)
Age of menarche, years[a]	11.8 (1.3)	11.8 (1.2)
Treatment		
Non-hormonal (control)	54 (67.5)	39 (68.4)
Estrogen-containing	16 (20.0)	9 (15.8)
Progesterone-only	10 (12.5)	9 (15.8)
Height at study timepoints, cm[a]		
Menarche (n=80)	154.2 (6.4)	155.0 (6.5)
6 months (n=68)	156.4 (6.3)	156.6 (6.6)
12 months (n=79)	158.7 (6.3)	159.0 (6.7)
24 months (n=57)	161.1 (6.2)	161.1 (6.2)

Data presented as n (%) unless otherwise noted. [a]Mean (SD).

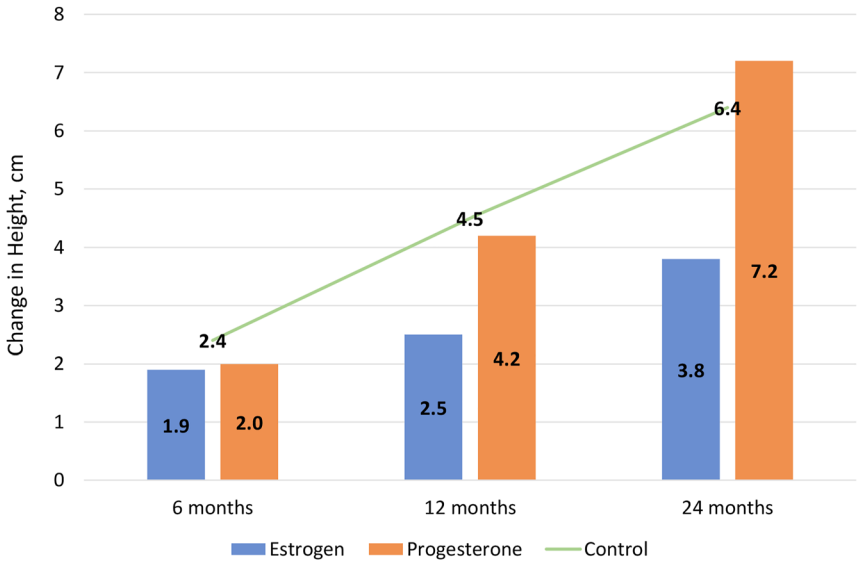

Figure 1: Change in height by treatment group.

Fifty-seven participants were included in the analytic sample, which was defined by patients who had recorded heights at baseline and 24 months. The mean change in height over the 24 month study period for those 57 participants (regardless of treatment group) was 4.7 cm. However, this growth differed by treatment group, with the estrogen group demonstrating the least overall growth. At 24 months, the mean increase in height from menarche was 6.4 cm among the control group, 3.8 cm among the estrogen group, and 7.2 cm among the progesterone-only group (Figure 1).

In the regression analysis, compared to the control group, the change in height for the estrogen group was 1.8 cm lower (p=0.04), while there was no significant difference for the progesterone-only group (p=0.87). Additionally, adolescents demonstrated 1 cm less increase in height for each year younger they were at menarche (p<0.002). In the subanalysis, girls age <12 at menarche who were treated with estrogen demonstrated significantly less growth (3.2 fewer centimeters, p=0.019) compared to girls age ≥12 at the time of menarche, who did not show that same significance (p=0.147) (Figure 2). Further, standardization of the change in height at 24 months divided by near-final height (height at 24 months) supported that, for girls age <12, the estrogen group had statistically significant less growth than the progesterone group (0.02 cm fewer; p=0.016). No significant growth differences existed between groups at the 6 month or 12 month timepoints (data not shown).

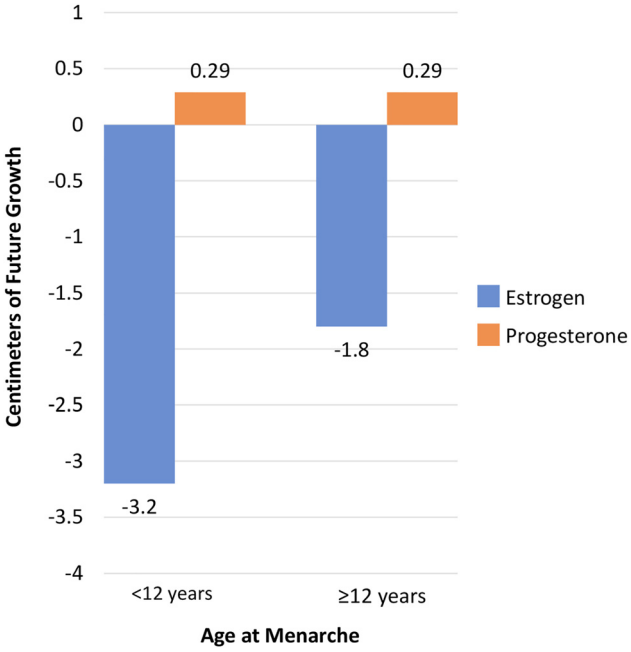

Figure 2: Bivariate analysis of change in height over 24 months in those who were under 12 years (n=31) and 12 years and older at menarche (n=26).

Discussion

For adolescents with HMB near menarche, progesterone-only or non-hormonal therapies are often favored over estrogen-containing treatments due to the theoretical concern that estrogen can cause early growth plate fusion and subsequent height restriction [9]. However, there is limited evidence available to evaluate if this effect is truly observed in the clinical setting. This study addresses this gap by comparing adolescents with HMB who received estrogen within three months of menarche to those who received progesterone-only or non-hormonal treatments. The adolescents who received estrogen ultimately grew less, on average, at 24 months after

menarche compared to the control group. The findings of this study thereby support the concern for estrogen's potential to cause premature cessation of growth. This concept was previously based on an understanding of estrogen's biological mechanisms within growth plate cartilage.

To describe in further detail, both *in vitro* and *in vivo* studies have demonstrated estrogen's function in modulating longitudinal bone growth [10–12]. Estrogen primarily exerts its effects through interaction with estrogen receptor-alpha (ERα) in growth plate cartilage, with low levels of estrogen promoting growth; however, states of high estrogen modulate chondrocytes of the growth plate cartilage to ultimately induce fusion and terminate further growth [13–15]. In addition to the role of ERα and changing estrogen levels, the expression of a specific estrogen receptor (GPR30) has been shown to decrease throughout pubertal progression, and its decline is thought to also contribute to the eventual termination of bone growth by growth plate fusion [16, 17]. In all, these studies established estrogen's importance in fundamental growth physiology.

In relation to normal adult physiology, early adolescence is a time of continued growth, whereas late puberty marks the stabilization of height – thereby corresponding to the progression of estrogen levels from low (growth) to high (cessation of growth) [18]. By utilizing these basic principles of estrogen and height, exogenous estrogens have been introduced into the medical practice to treat certain conditions related to excessive growth. For example, estrogens have been effectively used to manage constitutional tall stature and Marfan syndrome [19–21]. It can therefore be surmised that estrogen-containing therapies used for other medical applications might have unintended adverse effects on growth. However, in contrast to the high-dose estrogen therapies used for managing tall stature conditions, doses used for maintenance therapy of HMB tend to be lower [21, 22]. This poses the question of whether the popular theoretical concern was enough to impact medical practice protocols.

Current literature suggests that healthy adolescent girls are expected to grow an average of six additional centimeters after menarche, with most of the remaining growth potential occurring within one year after menarche [23, 24]. Similarly, this study demonstrated that by 24 months after menarche, the non-hormonal treatment (control) group displayed a mean of 6.4 cm of additional growth. Additionally, although the estrogen treatment group displayed less height increase, the mean growth of the progesterone-only group was not significantly different from the control group. This observation is consistent with current available literature, as unlike estrogen, progesterone has not previously been considered to be a major factor in growth plate fusion [25].

The average age of menarche demonstrated from previous studies is 12.07–12.25 years [26, 27], similar to the mean 11.8 (SD 1.3) years in this study cohort. Interestingly, though, our study's sub-analysis showed that adolescents under age 12 at menarche treated with estrogen demonstrated significantly less growth at 24 months compared to controls (3.2 fewer cm; p=0.019), unlike those who were 12 or older at the time of menarche (p=0.147). This age-dependent relationship was also observed in a study by Greenblatt et al., in which 24 girls aged 11–15 years were treated with exogenous estrogen. The study found that estrogen therapy initiated before 12.5 years of age resulted in less overall growth compared to the older cohort [28]. Additionally, this particular observation was further supported by our study's standardization of height difference at 24 months by near-final height, which helps to control for variability in heights and height potential between participants. This pattern may be attributed to the discrepancy in length of time prior to menarche, where older girls had more overall time to grow before onset of menarche. However, regardless of treatment modality, adolescents who achieved menarche at a younger age were overall shorter on average than girls whose menarche occurred later [29, 30]. In the Fels Longitudinal Study, it was observed that girls who started menstruating as early as age 10 grew up to 10 additional centimeters. In contrast, girls whose menarche was delayed until age 15 only grew an additional 5 cm after menarche [31].

While the results of this study support that when given to adolescent girls for HMB at menarche, estrogen has an observable negative impact on growth compared to progesterone-only and non-hormonal treatments, it is imperative to distinguish between statistical significance and clinical significance. On average, the estrogen group in this study grew 1.8 fewer centimeters compared to those who did not receive hormonal treatment. With the average height of a woman in the United States being 5 feet 4 inches (162.56 cm) [32], the mere 1.8 cm difference may be clinically negligible. However, girls who are shorter than average or who desire to achieve full height potential may consider 1.8 cm very impactful. Thus, appropriate shared decision-making must be established between provider and patient/parent. This study provides additional information to the overall discussion weighing the potential benefits and risks of estrogen-containing therapies over other modalities for use in management of HMB for adolescents at menarche.

This study is limited by its retrospective nature and relatively small sample size. Further, there was variability in therapy doses for individual patients during the study treatment period, and specific dose-dependent relationships were not studied. Similarly, treatment delivery mechanisms and type of treatments were subject to change within the study

window. Therefore, treatment group designations were determined by the type of treatment used for the longest consistent duration within a year after menarche. Additionally, growth points used for analysis were selected based on available chart data within an accepted 3 month window of the intended time point. Depending on when those points fell within this range, there is a potential for skewing of the results toward an earlier or later endpoint. While standardization of the outcome to near-final height was performed to help support the study claims, additional methods such as standardization to mid-parental height or bone age were unable to be performed due to the limited data available for these variables. Future prospective studies are warranted to better understand the relationship between estrogen used for HMB in adolescent girls at menarche and its effect on height. Multicenter studies may help to further expand the number of patients studied and provide a broader demographic pool.

Estrogen-containing treatment for HMB initiated within three months of menarche was associated with less growth (change in height from menarche) at 24 months compared to those treated with progesterone-only or non-hormonal (control) methods (p=0.04). The risks and benefits of implementing estrogen-containing therapies for management of HMB must be considered when discussing treatment options for adolescents near menarche given estrogen's potential to limit height up to two years after menarche.

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