Etiology of Abnormal Uterine Bleeding in Adolescents – Emphasis Upon Polycystic Ovarian Syndrome

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ABSTRACT

Introduction: Abnormal uterine bleeding is a frequent reason for physician visits by adolescents and this menstrual disorder has been shown to adversely affect quality of life. In Indian context, adolescents constitute 21.4% of the total population and this age group needs special attention as these are the formative years of an individual when major changes take place.

Objectives: To evaluate polycystic ovarian syndrome as common cause for abnormal uterine bleeding in adolescents.

Methods: We studied 200 patients aged 10 to 20 years admitted in our department with abnormal uterine bleeding having severe anemia or hemodynamic instability. On admission detailed history and clinical examination was taken. Hormonal testing for PCOS and other necessary investigations were done.

Results: Of the 200 patients, the mean age was 15.2±2.4 years. Mean hemoglobin was 6.0±1.5 g. 40% patients were overweight/obese. PCOS accounted for 30% of admissions. Hypothalamic pituitary ovarian axis immaturity 30% of admissions, endometritis (12%), bleeding disorders (14%). PCOS was more likely in overweight/obese females. Girls with HPOaxis immaturity had hemoglobin less than other etiologies.

Conclusion: PCOS is the common underlying etiology in adolescents hospitalized with abnormal uterine bleeding. Screening is important for early diagnosis to allow ongoing management and prevention of comorbidity.

Key Words: AUB, PCOS, Adolescents, Anemia

INTRODUCTION

Menstrual disorders and abnormal uterine bleeding (AUB) are among the most frequent gynecologic complaints of adolescents.1,2 Abnormal uterine bleeding (AUB) is a term coined to incorporate bleeding that is excessive or occurs outside of normal cyclic menstruation.3 Its importance lies in the fact that AUB has a major impact on women’s quality of life, productivity and utilization of healthcare services.4 AUB is defined as uterine bleeding lasting longer than 7 days, occurring more frequently than every 21 days and/or requiring tampon or pad changes every 1-2 hours4.

World health organization has defined adolescence as a period between 10-19 years. Abnormal uterine bleeding is a frequent reason for physician visits by adolescent girls and this menstrual disorder has been shown to adversely affect adolescents quality of life5,6. In India adolescents constitute over 21.4% of total population and this age group needs special attention when major physical, psychological and behavioral changes take place and additional roles and responsibilities are expected from them5,6. In India very little attention is paid to reproductive health of adolescent girls comprising 22% females Reason for neglect are ignorance, indifference, reluctance of parents and girls to consult a doctor. Mostly managed in OPDs but may develop severe symptomatic anemia and/or haemodynamic instability and require urgent hospitalization. ACOG divided causes of AUB into two groups PALM COEIN Structural and with non-structural.

Structural abnormalities include polyps, adenomyosis, leiomyoma and malignancy.
Non-structural abnormalities include bleeding disorders, ovulatory dysfunction, endometrial, iatrogenic and not classified causes of bleeding, most AUB episodes in adolescents are non structural. PCOS appears to underlie irregular menses in up to one third of girls (Venturoli et al). Menarche is not delayed but bleeding is then persistently irregular.

Over the past years, several small review studies of adolescents hospitalized for AUB with either severe anemia or haemodynamically unstable indicate that ovulatory dysfunction due to HPO immaturity as well as congenital or acquired bleeding disorders are the two most common causes of AUB requiring hospitalization.

In our study we hypothesized that ovulatory dysfunction related to PCOS would be a common underlying etiology as we frequently diagnose PCOS in adolescents in the outpatient settings.

**AIMS AND OBJECTIVES**

- Etiology of AUB in adolescents.
- To differentiate ovulatory dysfunction secondary to PCOS from other causes.
- Ovulatory dysfunction due to PCOS: a common underlying etiology.

**MATERIALS AND METHODS**

All females aged 10 to 20 years admitted between January 2017 to January 2018 for treatment of acute menorrhagia with severe anemia or orthostatic hypotension. After thorough history and examination, investigations including blood tests to assess for bleeding disorders and hormonal evaluations including PCOS were sent to laboratory prior to beginning any treatment with hormonal medication or blood transfusion. In this study, adolescent girls with dysfunction of PCOS were studied. Gynaecological age group was defined as chronologic age at the time of the hospitalization minus age at menarche. HPO axis immaturity as cause of AUB in adolescents if presenting just after puberty within two years and rest of the causes are absent. We classified PCOS if their gynaecological age was greater than 2 years and they met Rotterdam criteria. USG criteria was not used for PCOS as they are difficult to apply to adolescents. Endometritis as the cause of AUB in subjects with positive nucleic acid amplification test for chlamydia trachomatis or neisseria gonorrhea without identification of any other cause of AUB.

| Table 1: Various Characteristics of adolescents admitted to Lalla Ded Hospital (n=200) |
|---------------------------------|----------------|
| Age (years)                     | 15.2±2.4       |
| Age at menarche (years)         | 11.4±1.4       |
| Gynaecologic age                | 4.8±2.4        |
| Admission haemoglobin (g/dl)    | 6.0±1.5        |
| Urban Residence                 | 50%            |
| Weight status                   |               |
| Normal weight (BMI <85%)        | 48             |
| Overweight (BMI 85-95%)         | 18             |
| Obese (BMI > 95%)               | 34             |
| Gynaecological age ≤ 2 years    | 30%            |
| STI                             | 12%            |

- Mean age of 200 subjects was 15.2±2.4 years.
- Mean hemoglobin level at admission 6.0±1.5 g/dl.
- 40% of patients were overweight / obese.
- 30% of patients had a gynaecological age of 2 years or less.
- PCOS accounted for 30% of admissions

Comparing the 60 subjects diagnosed with PCOS with the 60 subjects diagnosed with HPO axis immaturity, we found a mean gynecological age of 62 months ± 29.6 versus 15 months ± 14.7 (p<0.001) respectively.

**RESULTS**

Ovulatory dysfunction related to PCOS accounted for 30% of admissions and ovulatory dysfunction related to HPO axis
immaturity accounted for next 30% of admissions, bleeding disorders (primarily thrombocytopenia and Von Willebrand disease) account for 14% of admissions. Endometritis 12% was the fourth cause. This is in contrast to the findings in most published studies of adolescents where bleeding disorders account for 20% or more of the cases. Our disparate finding is likely explained by the changing lifestyle, evolving childhood obesity epidemic and the fact that our protocol allowed for testing for hyperandro-genemia prior to treatment.

Table 2: Probability of etiology of AUB by initial hemoglobin level at the time of the index hospital admission (200)

| Etiology                  | Initial Hb level (g/dl) | P-value |
|---------------------------|-------------------------|---------|
| PCOS                      | 6.2±0.2                 | NS      |
| Other etiologies (60)     | 6.0±0.4                 |         |
| HPO axis immaturity       | 5.2±0.2                 | <0.05   |
| Other etiologies (60)     | 6.2±0.4                 |         |
| Endometritis (24)         | 6.4±0.2                 | NS      |
| Other etiologies          | 6.2±0.4                 |         |
| Bleeding disorders (28)   | 6.2±0.4                 | NS      |
| Other etiologies          | 6.0±0.6                 |         |
| Other endocrinopathies (16)| 6.0±0.6                | NS      |
| Other etiologies (60)     | 6.2±0.4                 |         |
| Structural abnormalities (12)| 8.2±0.2              | <0.001  |
| Other etiologies          | 6.4±0.4                 |         |

Comparisons of the etiologies of AUB by initial hemoglobin level at hospital admission found that hemoglobin level was significantly lower for adolescent subjects with HPO axis immaturity (5.2g/dl) versus all other etiologies (6.2g/dl), p <0.05.

Table 3: Probability of etiology of AUB by weight category (n=200)

| Etiology                  | Overweight/Obese BMl>85% | Normal weight BMI <85% | P-value |
|---------------------------|--------------------------|------------------------|---------|
| PCOS (n=60)               | 75                       | 25                     | <0.01   |
| All other                 | 45                       | 55                     |         |
| HPO axis immaturity (n=60)| 50                       | 50                     | NS      |
| All other                 | 63                       | 37                     |         |
| Bleeding disorder (n=28)  | 71                       | 29                     | NS      |
| All other                 | 54                       | 46                     |         |
| Endometritis (n=24)       | 50                       | 50                     | NS      |
| All other                 | 56                       | 44                     |         |

Comparison of six etiologies of AUB shown in above figure by weight category, overweight/obese versus normal weight, found that girls with PCOS were significantly more likely to be overweight/obese and those with Hypothalamic-Pituitary-Ovarian HPO axis immaturity were more likely to be normal weight than girls with all other etiologies of AUB. We found that nearly three quarters of our adolescent subjects with PCOS were overweight or obese, a significantly higher proportion than all other etiologies of AUB.

**DISCUSSION**

Polycystic ovary syndrome (PCOS) was among common etiology of AUB, accounting for 30% cases likely explained by the shifting food habits and sedentary habit of the adolescent population11, the evolving childhood obesity epidemic and the fact that we followed protocol for testing hyperandro-genemia prior to hormonal treatment of AUB12.

While bleeding disorders accounted for only 14% of cases. Our finding is in opposite to many other studies where PCOS is not reported as an etiology and bleeding disorders account for 20% or more of the cases4-7.

In our study subjects with PCOS had a mean gynecologic age of just over 5 years, well beyond the age associated with physiologic ovulatory dysfunction, whereas subjects diagnosed with HPO axis maturity were well within the 2-3 year accepted time frame with a mean gynecologic age of just over 1 year.

Fifty percent of our subjects were from urban areas and having high prevalence of PCOS and metabolic syndrome13, especially in conjunction with excess body weight. In a recent study of 48 South Asian adolescents admitted to hospital in India with AUB and severe anemia, 35% of the teens had a BMI greater than 25 kg/m2 and 10/48 (21%) were found to have PCOS14.

In our study nearly three-quarters of adolescent subjects with PCOS were overweight or obese, a significantly higher proportion than our subjects with all other etiologies of AUB. Because of the serious comorbidities of PCOS, including...
type 2 diabetes mellitus and cardiovascular disease\textsuperscript{15,16}, it is important to diagnose and treat this common endocrine disorder early. However, a barrier to early diagnosis of PCOS in adolescents is the absence of specific diagnostic criteria, as physiologic ovulatory dysfunction in the perimenarchal period and multifollicular ovaries are normal findings.

Recommendations in the 2010 Consensus Statement from the American Society for Reproductive Medicine/European Society of Human Reproduction and Embryology for diagnosis of PCOS in adolescents include using biochemical markers of hyperandro-genemia as we did in this study, instead of the non-specific clinical markers of hyperandrogenism such as acne, hirsutism and alopecia\textsuperscript{17,18}. However, there is a lack evidence for ultrasonographic criteria for PCOS diagnosis in adolescents.

A prompt diagnosis of PCOS provides adolescents and their parents with knowledge about the etiology of AUB, risk of recurrence of AUB if treatment is discontinued, and prevention of comorbidities. Thus making a diagnosis of PCOS as the etiology for AUB allows for intensive intervention to assist in improving the lifetime health of these adolescents.

We found that adolescent girls in our sample whose AUB with severe anemia was related to ovulatory dysfunction due to HPO axis immaturity had a significantly lower hemoglobin level on admission to hospital than girls admitted with all other etiologies of AUB. This is a surprising finding and suggests to us that for perimenarchal girls whose relative inexperience in judging normal quantities of menstrual blood loss coupled with embarrassment and reluctance to bring attention to their menstrual bleeding likely delays their presentation for needed health care and puts them at risk for lifethreatening anemia\textsuperscript{19}. We suggest that pediatricians and other clinicians caring for perimenarchal girls document detailed menstrual histories and monitor hemoglobin levels if prolonged or frequent uterine bleeding is uncovered so that treatment can be instituted prior to the development of severe anemia and the necessity for hospital admission.

Another finding of this study that is different from older published studies of adolescents admitted for AUB and severe anemia is that 12\% of the AUB episodes requiring hospitalization in our subjects were related to endometritis. Studies of adult women suggest that AUB secondary to infectious endometritis is frequently underestimated\textsuperscript{20}. In our sample of adolescents, more than 20\% were at risk for STIs because they were sexually active. Infectious endometritis is a known cause of AUB but unless a confidential sexual history, pelvic examination, and tests for STIs are obtained the diagnosis may be missed in adolescent girls and appropriate antibiotic treatment may not be given.

Many adolescents are ambivalent about taking “birth control pills”, the treatment used to prevent recurrences which is commonly seen. Cost utility analysis of screening for Von Willebrand disease in women with menorrhagia was found to be cost effective\textsuperscript{21}, and we propose that screening adolescent girls with AUB for PCOS as our protocol suggests may also be cost effective. Finally our findings reaffirm the importance of having a clinical protocol or guideline in order to standardize practice and insure that girls with AUB and severe anemia are tested for hyperandro-genemia before treatment with hormones is begun and that those who are sexually active are examined and tested for STIs\textsuperscript{22}. The findings of this study highlight the importance of considering gynecologic age, ethnicity, weight status, and sexual activity when determining the etiology of AUB with severe anemia in the adolescent population. For populations similar to ours, we recommend screening for biochemical markers of hyperandro-genemia to aid in the diagnosis of PCOS prior to beginning treatment with estrogens and/or progestins that suppress ovarian androgens and preclude making the diagnosis. In addition, all adolescents with AUB and significant anemia should have a confidential sexual history taken and STIs should be considered in the etiology of AUB in adolescents.

**CONCLUSION**

Abnormal Uterine Bleeding during adolescence is not always associated with an ovulatory cause, thorough investigation should be done and etiology ascertained. In our study we found PCOS was a frequent endocrine mechanism of menstrual disorder. Although most problems are explained by anovulation other causes must be considered and excluded in a cost effective manner. Hormonal evaluation of these patients is must and further management depends upon the cause.

**LIMITATIONS**

However a barrier to early diagnosis of PCOS in adolescents is the absence of specific diagnostic criteria for this age group, physiologic ovulatory dysfunction in the perimenarchal period and observation that many adolescents have multifollicular ovaries as a normal finding. A limitation of this study is that it was performed in a single centre and patients were not followed up. Despite these limitations, this study highlight the importance of considering gynecologic age, residence, weight status and sexual activity when determining the etiology of AUB with severe anemia in the adolescent population.

**RECOMMENDATIONS**

Pediatricians and other clinicians caring for perimenarchal girls document detailed menstrual histories and monitor hemoglobin levels if prolonged or frequent uterine bleeding. Finally our findings reaffirm the importance of having a protocol or guidelines in order to standardize practice and ensure that girls with AUB and severe anemia are tested.
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