

Vaginal Bleeding in Pre-pubertal Females

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ABSTRACT

Study Objective: Puberty is a normal process for adolescents, and the first signs may include change in body odor, breast development, or pubic hair growth. This is then followed by menarche approximately 2 years later. Vaginal bleeding in pre-pubertal female individuals is rare. The aim of this study was to investigate causes of pre-pubertal bleeding in a group of patients.

Design, Setting, Method, and Main Outcome Measures: Seventeen patients who presented with pre-pubertal recurrent vaginal bleeding with no other signs of precocious puberty were investigated, to determine the cause of this symptom.

Results: The mean age for the onset of vaginal bleeding was 7.4 years, ranging from 4 to 9.67 years. Gonadotrophin-releasing hormone (GnRH) stimulation tests showed a pre-pubertal response in all cases. Pelvic ultrasound scans showed a pre-pubertal uterus in all patients. Two patients were found to have foreign bodies identified during a genital examination under anesthetic, and in both cases removal of the foreign bodies terminated the vaginal bleeding.

Conclusion: In conclusion, recurrent vaginal bleeding was not associated with GnRH response, raised estradiol levels, or abnormal pelvic ultrasound findings. In cases of recurrent vaginal bleeding with normal hormonal investigations in pre-pubertal girls, it is recommended that a genital examination under anesthetic be undertaken to rule out undiagnosed causes of the presenting symptom.

Key Words: Isolated premature menarche, Pre-pubertal, Recurrent vaginal bleeding

Introduction

The first signs of puberty in girls include change in body odor, breast development, or pubic hair growth. Menarche usually commences a couple of years after this, at a mean age of 12.8 years in the United Kingdom.^{1,2} Early puberty, also known as precocious puberty, is defined as the presence of secondary sex characteristics in girls less than 8 years of age.³

Vaginal bleeding in pre-pubertal girls is rare, and patients require thorough investigation to ensure that they receive appropriate management. Causes of pre-pubertal vaginal bleeding include dermatologic conditions, foreign body, trauma, malignancy, hypothyroidism, and precocious puberty.^{1,4,5} Isolated premature menarche should be considered if the bleeding is isolated or cyclical and without evidence of other secondary sex characteristics and no other cause identified.^{1,2} The pathophysiology of isolated premature menarche remains unclear.² It is thought that it may be secondary to increased sensitivity of the endometrium to lower levels of estrogen.^{1,2,6}

The aim of this paper is to evaluate the presenting signs, symptoms, and hormonal investigations associated with

recurrent vaginal bleeding in the absence of other precocious puberty features.

Materials and Methods

Data were collected retrospectively from two pediatric centers between January 2007 and December 2018. Information was collected from 17 pre-pubertal girls who presented to the departments with recurrent vaginal bleeding, defined as vaginal bleeding on more than 1 separate episode, with no other signs of precocious puberty.

Information obtained included a detailed history of the patients' clinical presentations and the results of investigations, especially gonadotrophin (GnRH) stimulation tests, genital examination under anesthetic (EUA), and pelvic ultrasounds. The information was initially extracted from paper medical records and then transferred to an electronic database. Care was taken to ensure that this transfer was accurate, and the information was cross-checked by a second person throughout. The results were then analyzed and compared to determine whether any factors were associated with this condition. Consent obtained from all patients and data was anonymised.

Signs of puberty were examined by 1 of 2 pediatricians who trained in the same center. It was scored using the Tanner Staging system that grades breast (B) development, axillary (A) hair growth, and pubic (P) hair growth from 1 to 5, with 1 being pre-pubertal and 5 being adult-type.⁷ The height and body mass index for each patient were expressed as standard deviation scores (SDS) with reference to British standards.⁸ Bone age was estimated and reported by a consultant radiologist in the Department of Radiology

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Table 1
Demographic Findings and History of Pre-pubertal Bleeding

Patient No.	Age at Onset of Vaginal Bleeding (y)	History of Vaginal Bleeding	Time Between Bleeding Episodes	Family History
1	5	3 episodes	5–7 mo	Mother: menarche at 12 yrs
2	8.33	2 episodes	4 mo	Mother: menarche at 9–10 y
3	6.75	Intermittent bleeding over 24 h	<24 h	Maternal grandmother: menarche at 9 y
4	9	3 episodes	1 mo	Maternal cousin: menarche at 9 y
5	7	2 episodes with monthly pain	3 mo	Mother: menarche at 8 y
6	7.91	3 episodes	3 wk	No family history
7	7.9	4 episodes	4–6 wk	No family history
8	6	Multiple episodes for 6 mo	1–2 wk	No family history
9	9	Every 28 days for 10 mo	28 days	Father: precocious puberty
10	9	Intermittent bleeding over 24 h	<24 h	Great aunt: menarche at 9 y
11	5.08	4 episodes	Initially monthly for 3 mo and then 3-monthly	No family history
12	8.41	Sporadic over 18 mo	Sporadic	No family history
13	4	6–8-wk cycles over 12 mo	6–8 wk	No family history
14	9.66	6 episodes	1–2 mo	No family history
15	6.66	2 episodes	1 mo	Maternal grandmother: – menarche 9–11 y
16	8.83	Daily small bleed for 1 mo	Daily	No family history
17	7.16	4 episodes	Irregular	Mother: menarche at 8 y

using the radius, ulna, and short bones (RUS) Tanner Whitehouse 2nd edition (TW2) methodology.⁹ Each pelvic ultrasound was performed transabdominally using a Hitachi EUB 7500 scanner with a 6- to 14-MHz linear transducer.

GnRH stimulation tests are the gold standard for use in investigating for precocious puberty.¹⁰ Local guidance was used for this test and a stat dose of 100 µg of Gonadorelin, a gonadotropin-releasing hormone agonist, was given to each patient. Baseline luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol levels were taken initially, and the LH and FSH tests were repeated at 30 and 60 minutes after administration of Gonadorelin. The analytical sensitivities were 0.1 mIU/mL for LH, 0.3 mIU/mL for FSH, and 12 pg/mL for estradiol. Mean intra-assay coefficients of variation were 5.4% for LH, 5.0% for FSH, and 9.8% for estradiol. Mean interassay coefficients of variation were 6.8% for LH, 6.4% for FSH, and 10.0% for estradiol.

Table 2
Measurements and Physical Examination Findings for Each Patient on Presentation

Patient No.	Height SD	Weight SD	BMI SD	Pubertal Stage
1	1.55	0.68	−0.17	B1P1A1
2	1.55	3.08	3.2	B1P2A1
3	1.22	2.78	2.87	B1P1A1
4	−2.44	−2.34	−1.11	B1P2A1
5	1.25	2.6	2.69	B1P1A1
6	1.43	1.54	1.26	B2P1A1
7	0.98	0.73	0.34	B2P1A1
8	−0.05	0.84	1.19	B1P1A1
9	1.13	1.13	0.99	B2P1A1
10	−0.3	−0.34	−0.17	B2P1A1
11	−0.62	0.51	1.28	B1P1A1
12	1.45	2.43	2.2	B1P1A1
13	−0.16	0.03	0.43	B2P1A1
14	−1.33	−0.73	0.14	B1P1A1
15	−0.75	−0.04	0.53	B1P1A1
16	−0.64	−0.37	0.01	B1P1A1
17	0.21	1.81	2.01	B1P1A1

Tanner pubertal staging: breast development (B), pubic hair growth (P), and axillary hair growth (A). Tanner staging system grades breast (B) development, axillary hair growth (A), and pubic hair growth (P) from 1 to 5, with 1 being pre-pubertal and 5 being adult-type.

A decision to request an examination under anesthetic (EUA) was made at the discretion of the clinician and considered if the patient had had more than 2 episodes of vaginal bleeding with normal GnRH response and no other obvious cause. An EUA would include a vaginostomy in all cases described.

Results

In total, 17 pre-pubertal female patients presented with recurrent vaginal bleeding with no other signs of precocious puberty. All patients were of white ethnicity. The mean age was 7.4 years, ranging from 4 to 9.67 years. Table 1 shows the history and duration of the presenting complaint in all seventeen patients.

All patients reported recurrent vaginal bleeding. The duration for each bleeding episode ranged from 1 to 7 days, and the time between one bleed and the next ranged from 24 hours to 6 months. For 15 patients, the bleeding episodes persisted for between 6 and 18 months. There was no history of potential exposure to exogenous hormones. A family history was obtained for each patient; findings are summarized in Table 1.

The mean height SDS and weight SDS were 0.26 and 0.84, respectively. The height SDS ranged from −2.44 to 1.55 and weight SDS ranged from −2.34 to 3.08. The mean body mass index (BMI) SDS was 1.04 and ranged from −1.11 to 2.87 (Table 2). Each patient underwent a physical examination, and there were no dysmorphic features or skin manifestations such as café-au-lait spots identified. The results of the pubertal staging examination are found in Table 2.

GnRH stimulation tests were performed in 12 patients and all showed a pre-pubertal response. All estradiol levels were less than 12 pg/mL except for 1 level, which was 40 pg/mL (Table 3).

Wrist x-rays were performed for 15 of the patients to determine their bone age and were normal within 2 SDs (standard deviations) of chronological age in all cases. Pelvic

Table 3
Biochemistry Investigation Results for Each Patient

Patient No.	Estradiol (pg/mL)	Baseline LH (U/L)	Baseline FSH (U/L)	GnRH Stimulation
1	<12	0.3	3.1	Pre-pubertal
2	<12	0.1	1.1	Pre-pubertal
3	<12	0.1	1.9	Pre-pubertal
4	<12	0.1	2.2	Pre-pubertal
5	<12	0.1	0.7	Pre-pubertal
6	12.8	0	0.9	Pre-pubertal
7	<12	0.1	0.7	Pre-pubertal
8	<12	<0.1	1.1	Not done
9	<12	<0.1	1.7	Pre-pubertal
10	Not done	Not done	Not done	Not done
11	Not done	Not done	Not done	Not done
12	<12	0.2	1.6	Not done
13	23	<0.2	2.1	Pre-pubertal, but brisk FSH response
14	17	0	1.3	Pre-pubertal
15	<12	0.14	0.12	Pre-pubertal
16	13	<0.1	0.8	Not done
17	40	<0.1	0.8	Pre-pubertal

FSH, follicle-stimulating hormone.

imaging was performed on all patients, using a trans-abdominal ultrasound, and showed a pre-pubertal uterus with no identifiable endometrial echo. Each patient had a single ultrasound, and no evidence of ovarian cysts were reported. A genital vaginotomy by EUA was performed in 9 of the patients. The examination findings were normal in 7 cases. The 2 cases of abnormal examination findings were a foreign body in each patient. The foreign bodies identified were tissue and a ball of fibers. One patient had presented with vaginal spotting weekly for 6 months before the examination, and the other had multiple bleeds every 4 to 6 weeks. Removal of the foreign body terminated the bleeding in both cases (Table 4).

Discussion

Literature on vaginal bleeding in pre-pubertal girls is still limited, and the aim of this paper is to highlight the importance of thoroughly investigating these patients. The results showed that recurrent vaginal bleeding was not associated with identifiable endometrial echo on pelvic ultrasound, GnRH pubertal response, or elevated estradiol

levels. It is thought that the endometrial lining may respond to low levels of estradiol, which may result in vaginal bleeding. The causes of vaginal bleeding in pre-pubertal girls may include vulvovaginitis, urethral prolapse, genital injury, dermatoses, sexual abuse, precocious puberty, malignancy, and foreign body.^{4,5} As the differential diagnoses for pre-pubertal vaginal bleeding are varied, a thorough review and investigation are recommended.^{4,5}

Our study showed that a foreign body was found in 2 of the 9 patients who underwent a genital EUA. Therefore, it is recommended that a vaginotomy under anesthesia be considered if all other investigation findings are normal in a patient with a history of recurrent cyclical vaginal bleeding. The EUA will not only rule out a foreign body but will hopefully rule out several of the causes of recurrent cyclical vaginal bleeding. Our recommendation is supported by Smith et al, who investigated 41 pre-pubertal female patients with persistent or recurrent vaginal discharge in 2002.¹¹ Vaginoscopies under anesthesia were performed in 41% of these patients, and a foreign body was found in 18% of these.¹¹ All the patients with a foreign body identified presented with bloody or brown discharge. The results of

Table 4
Radiological Investigations for Each Patient

PatientNo.	Abdominal US Findings	EUA Findings	Bone Age (y)	Chronological Age (y)
1	Fluid between endometrium and cavity; prepubertal anteverted uterus	Not performed (parents refused)	7.83	7.41
2	Pre-pubertal anteverted uterus	No cause identified	11	9.5
3	Pre-pubertal anteverted uterus	No cause identified	6.83	7
4	Pre-pubertal	No cause identified	8.83	9.16
5	Pre-pubertal	No cause identified	8	7.83
6	Pre-pubertal anteverted uterus	No cause identified	7.91	8.16
7	Pre-pubertal	Foreign body (ball of fibers)	8.16	8.16
8	Pre-pubertal	Foreign body (tissue) 1.5 cm	Not done	Not done
9	Pre-pubertal	Not performed	11	9.83
10	Pre-pubertal	Not performed	8.18	9.12
11	Pre-pubertal	Not performed	5.25	5.81
12	Pre-pubertal	Not performed	8.83	8.83
13	Pre-pubertal	No cause identified	5.22	4.65
14	Pre-pubertal	Not performed	10.5	9.8
15	Pre-pubertal	Not performed	5.39	6.9
16	Pre-pubertal	Not performed	Not done	Not done
17	Pre-pubertal	No cause identified	5.75	7.5

EUA, examination under anaesthetic; US, ultrasound.

Smith et al's study showed that 10% of patients who presented with pre-pubertal vaginal bleeding were found to have a foreign body.¹¹

Merck et al investigated 9 female patients who presented with pre-pubertal vaginal bleeding. As with our results, there was no evidence of precocious puberty on physical examination, hormone analysis, or pelvic ultrasounds. Two of the 9 patients underwent a vaginotomy, the findings for which were normal in both cases.² McCune Albright syndrome was also discussed by the authors, as it must be considered in patients with pre-pubertal bleeding, especially if the bleeding commences before 2 years of age. It is important to complete a full examination to rule out café-au-lait spots and evidence of fibrous bone dysplasia.² These conditions were ruled out based on the absence of ovarian cysts on ultrasound.

In 2015, Soderstrom et al investigated 86 female patients 0 to 9 years of age with vaginal bleeding in Sweden.¹² Of those, 47 (54.7%) patients were diagnosed with a local lesion, commonly secondary to trauma, whereas in 23 (26.7%) patients, the etiology was unclear. Over 80% of patients in the study cohort underwent a genital examination.¹² Nine percent of patients went on to have a colposcopy, and 2 patients were diagnosed with tumors. The authors concluded that pre-pubertal vaginal bleeding is likely to be benign, but that full investigation is required to exclude possible threatening conditions.¹²

Broomfield et al reported an interesting case of a 5-year-old girl who presented with ongoing vaginal bleeding.¹³ The patient required blood transfusions because of the severity of the problem, and her case was reviewed by multiple teams. Initial investigations did not find a cause, and the patient underwent abdominal and pelvic magnetic resonance imaging, the results of which were also normal.¹³ Finally, an examination under anesthesia was performed, and an arteriovenous malformation was found and treated. After this, the patient had no further bleeding episodes.¹³ This is an extremely rare condition, but highlights the importance of completing all investigations if the cause remains unclear.

In contrast, Nella et al investigated more than 20 pre-pubertal patients with vaginal bleeding in the United States.¹⁴ After satisfactory laboratory studies and ultrasound imaging, the authors reported that the condition is generally self-limiting.¹⁴ It is noted that these patients did not undergo a genital examination, and it was difficult to conclude whether a cause could have been identified if so.

Blanco-Garcia et al reported 17 patients who experienced pre-pubertal vaginal bleeding. In contrast to our results, these authors reported elevated estradiol levels in their cohort of patients, and thought that the bleeding could be secondary to "ovarian activity" and "instability of the pituitary–gonadal axis."¹⁵

Our paper highlights the importance of thoroughly investigation of recurrent vaginal bleeding in pre-pubertal girls, including evaluation for a vaginal foreign body. Over time, improved ultrasound technology may produce increased confidence to support lack of hypothalamic–pituitary–ovarian stimulation and changes in genital anatomy with normal prepubertal clinical examination, such that a GnRH stimulation test may not be needed as a routine part of evaluating pre-pubertal vaginal bleeding.

In conclusion, in our patients pre-pubertal recurrent vaginal bleeding was not associated with GnRH response, raised estradiol levels, or abnormal pelvic ultrasound findings. In cases of recurrent vaginal bleeding with normal hormonal investigations in pre-pubertal girls, a vaginotomy under anesthesia is recommended to rule out undiagnosed explanations for the vaginal bleeding.

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