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CASE REPORT

Menstruation in an infant: a case report of exacerbated mini-puberty

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Abstract

There are three periods throughout life in which an activation of the hypothalamus-pituitary-gonads axis takes place: prenatal, immediate postnatal period and puberty. The period that occurs after the first week of life and in which there are high levels of gonadotropins, is called mini-puberty. The possibility of premature girls presenting vaginal bleeding in the context of exacerbated mini puberty is poorly described. We report a case of a 5-month-old infant (2 months of corrected age), born premature (26 weeks), who presented spontaneous vaginal bleeding associated with premature thelarche and augmented clitoral hood. Laboratory analysis and pelvic ultrasound supported the diagnosis of precocious puberty of central origin. Clinical findings resolved spontaneously without any intervention due to gradual return of gonadotropins levels to the prepubertal range. This case highlights this benign and self-limited situation that can occur later in premature children and that should be recognized to avoid unnecessary investigations and therapeutics.

Keywords: Precocious puberty. Menstruation. Infant.

Menstruação em lactente: relato de caso de minipuberdade exacerbada

Resumo

Ao longo da vida existem três períodos em que se dá uma ativação do eixo hipotálamo-hipófise-gónadas (HHG): a fase pré-natal, a pós-natal imediata e a puberdade. Ao período que ocorre depois da primeira semana de vida e em que se verificam níveis elevados de gonadotrofinas, dá-se o nome de mini-puberdade. A possibilidade hemorragia vaginal em crianças do sexo feminino prematuras no contexto de mini puberdade exacerbada é pouco descrita na literatura. As autoras descrevem o caso clínico de uma lactente de 5 meses (2 meses de idade corrigida), com antecedentes de prematuridade de 26 semanas e 1 dia, que apresentou hemorragia vaginal com resolução espontânea associado a telarca e aumento clitoriano. A avaliação laboratorial e ecografia pélvica revelaram achados compatíveis com puberdade precoce de origem central. A sintomatologia resolveu espontaneamente com o retorno gradual dos nos níveis gonadotrofinas para valores pré-púberes sem necessidade de qualquer intervenção. Este caso destaca essa situação benigna e autolimitada que pode ocorrer mais tarde em crianças prematuras e que deve ser reconhecida para evitar investigações e terapêuticas desnecessárias.

Palavras chave: Puberdade precoce. Menstruação. Infantil.

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Keypoints

What is known

- Mini-puberty is a benign and self-limited situation.
- Vaginal bleeding in the immediate postnatal aperiod arises due to the deprivation of maternal hormones.
- After neonatal period, vaginal bleeding imposes a differential diagnosis with endocrine or traumatic causes namely sexual abuse.

What is added

- Exacerbated mini-puberty may manifest as vaginal bleeding in infants after the neonatal period, appearing even later in very premature infants.
- The improvement of neonatal care and extreme prematurity survivors probably will increase this phenomenon.
- Mini-puberty should be recognized to avoid family concern and unnecessary investigations and therapeutics.

Introduction

There are three periods in life during which there is an activation of the hypothalamus-pituitary-gonads (HPG) axis: the first is during fetal life, with a crucial role in sex determination; the second is during the first postnatal months of life; and the third is at the puberty onset. This axis is active during the intermediate phase of gestation but is silenced afterwards, until the gestation term by a negative feedback mechanism mediated by the placental hormones[1]. The period that occurs after the first week of life and in which there are high levels of gonadotropins, is called minipuberty[2,3]. At this time the levels of sexual steroids are comparable to those observed at puberty but are usually not associated with peripheral effects. This is the second transient activation of the HPG axis, with an increase of gonadotropins that reach the pubertal range between 1 and 3 months of life and then declines toward the age of 6 months. At this stage, in female infants, follicle-stimulating hormone (FSH) levels are higher than luteinizing hormone (LH), following a different trend than in males[1-3]. After this, the HPG axis remains quiescent until puberty. In girls, ovarian follicles maturation and rise of estradiol levels ensues[1,2]. The role of minipuberty in female newborns and the mechanisms that suppress the HPG axis activity are unknown[1].

There is little literature describing the differences in the activation of the HPG axis in premature infants and term newborns, but it is known that in premature newborns postnatal gonadotropin levels are higher and remain increased for longer than in term newborns[4]. However, the decrease in gonadotropin levels occurs approximately at the same postterm age in both fullterm and premature infants. It is readily understood that premature girls are not exposed to the high levels of estrogens that appear late in pregnancy and which will stimulate the fetal mammary glands and uterus.

Consequently, the effects of endogenous estrogens in the postnatal period are more visible, leading to the growth of the mammary gland and the uterus[1-3].

Regardless of HPG axis activation, benign neonatal uterine bleeding, also called neonatal menstruation, occurs in 5% of girls in the early postnatal period, a few days after birth[5]. It is considered a physiological phenomenon due to the sudden reduction of maternal progesterone levels. A study published in 1985 showed that neonatal menstruation is practically non-existent in premature newborns (0.8%) and is more frequent in the post-term (9.1%), suggesting a mechanism of progressive sensitization to progesterone[5]. In addition to nenatal menstruation, the development of sexual characteristics before one year of age is very rare, except for breast augmentation in girls, usually diagnosed as premature thelarche[3,4]. Vaginal bleeding can be caused by several factors, including trauma, foreign bodies and precocious puberty[6]. In premature prepubertal girls the possibility of vaginal bleeding in the context of exacerbated mini-puberty has been described[7,8]. Thus, it is important for health professionals to know the differential diagnosis of prepubertal vaginal bleeding, especially in girls with a history of prematurity, to better approach and evaluate these cases.

Case report

Female infant, with 5 months and 26 days of chronological age (2 months and 4 days of corrected age), with a history of spontaneous monitored trigemelar gestation, born by caesarean delivery at 26 weeks and 1 day. She was hospitalized until the 98th day of life in a neonatal intensive care unit, having been discharged with diagnoses of extreme prematurity, extreme lowbirth weight (773g), and moderate bronchopulmonary dysplasia, requiring supplemental oxygen in outpatient treatment.

Observed in the emergency room of a tertiary hospital because she started vaginal bleeding 3 days before. Her mother reported onset of a whitish vaginal discharge about 3 months earlier, in greater quantity since the previous week. No accelerated growth was reported. The observation showed bilateral thelarche with about 0.5 cm in diameter, augmented clitoral hood, and hypertrophy of outer and inner vaginal lips, without pubic hair and without apparent lesions of the genital region. The remaining examination was normal. The analytical evaluation showed increased FSH (5.6 IU/L), LH (8.12 IU/L) and estradiol (46 pmol/L) compatible with central

precocious puberty. Pelvic ultrasound showed enlarged uterus (32x9mm) and ovaries, with multiple small follicular structures, without a dominant cyst. The diagnosis of exacerbated mini-puberty in the context of extreme prematurity was considered and a spontaneous resolution of vaginal bleeding after 5 days was verified.

Breast buds regressed clinically, there was no recurrence of vaginal bleeding and she maintained follow-up in pediatric endocrinology ambulatory. Laboratory evaluation at the corrected age of 13 months showed a prepubertal value of LH < 0.79 IU/L, FSH 8.2 IU/L and estradiol < 6.7 pmol/L. At this age, pelvic ultrasound revealed a prepubertal uterus with a few microcystic follicles. She was last seen at the corrected age of 13 months, and there was no recurrence of pubertal development.

Discussion

Detailed history and physical examination should be performed on any pre-pubertal girl with vaginal bleeding. The history should include any other signs and symptoms of puberty, such as thelarche or adrearche, the onset and evolution of signs and symptoms, as well as personal history, including prematurity[6].

We present a rare case of an extreme preterm infant who presented self-limited vaginal bleeding at 5 months of age. During mini-puberty, menstruation has been described only in a few case reports in literature[7,8].

De Lange at al. reported a case of a 4-month-old infant with a history of prematurity of 25 weeks who presented uterine bleeding and high levels of serum gonadotropin and estradiol, compatible with central precocious puberty. She was treated with a luteinizing hormone-releasing hormone (LHRH) analogue for 15 months.

After treatment cessation, she remained prepubertal, suggesting an alternative diagnosis of exacerbated central mini-puberty instead of persistent central precocious puberty[7]. Recently, a case of a 3-month-old infant with a 23 week and 6 days prematurity with intermittent vaginal bleeding, bilateral breast buds and pubertal levels of gonadotropins, was published. At 8 months of age gonadotropins levels were normal, vaginal bleeding had resolved, and breast buds regressed clinically, without any treatment[8].

Postnatal HPG axis activation that occurs in preterm infants is even stronger and more prolonged than in term infants. It is possible that with improvement of neonatal care and more extreme prematurity survivors, we might increasingly face this phenomenon. However, until now, literature regarding mini-puberty manifestations in premature infants is scarce.

This case shows that the robust surge of gonadotropin in a premature infant can result in endometrial maturation and present as vaginal bleeding. Treatment with LHRH analogues is not necessary, and clinical resolution is expected with a gradual return of gonadotropin levels to the prepubertal range. We report this case to address this benign situation, that has a spontaneous resolution, in order to avoid unnecessary investigations and to highlight the importance of clinical surveillance and parents' reassurance.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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