Menstrual Bleeding as a Manifestation of Mini-Puberty of Infancy in Severe Prematurity

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We report 2 infants with severe prematurity who presented with uterine bleeding at age 6 months (approximately 2.5 months corrected for gestational age). Mini-puberty of infancy should be considered in the differential diagnosis of girls who present with uterine bleeding during the first 6 months of life. *(J Pediatr 2016;178:292-5).*

Uterine bleeding in the neonatal period typically occurs shortly after birth. The result of exposure of the infantile endometrium to maternal estrogens during fetal life and a withdrawal effect of placental hormones shortly after delivery, it is considered of no clinical significance.[1] It occurs in approximately 3%-5% of newborns; rates of microscopic hemorrhage are even higher, in the range of 25%-60%.[1] Vaginal bleeding later in life can be caused by various factors, including trauma, local lesions of the genital track, foreign bodies, and sexual precocity.[2] Physical examination, laboratory evaluation, and imaging can help establish the correct diagnosis.

Here we report uterine bleeding at age 6 months (approximately 2.5 months corrected for gestational age) in 2 girls with a history of severe prematurity. The timing of bleeding was later than anticipated for benign uterine bleeding caused by maternal estrogen withdrawal after birth. Laboratory evaluation was significant for activation of the hypothalamic-pituitary-gonadal (HPG) axis and elevated serum estrogen concentrations suggestive of menstrual bleeding caused by central precocious puberty.[3] However, contrary to what is anticipated with central precocity,[3] clinical symptoms resolved spontaneously, and laboratory values returned gradually into the prepubertal range in a course that allowed us to establish retrospectively the diagnosis of metrorrhagia associated with exacerbated mini-puberty of infancy.[4]

Case 1

Infant 1 presented at age 6.0 months with vaginal bleeding that lasted 2 days. She was born at a gestational age of 25 weeks and had a prolonged inpatient stay of 5 months for respiratory problems and feeding difficulties. On presentation to endocrinology at 6 months (2.25 months corrected age), she had small glandular breast buds bilaterally (1.5 cm in diameter), stimulated nipples, minimal facial acne, and mild estrogen effects on the vaginal mucosa. There was no clitoromegaly or clinical signs of pubarche. Her sole medication was infant vitamins. Her laboratory evaluation on presentation was significant for elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH) values in the pubertal range and increased serum estrogen levels, indicating central activation of the HPG axis. Further evaluation revealed an unremarkable magnetic resonance imaging of the brain and pituitary and an enlarged right ovary with multiple follicles, including a $3.5 \times 3.3 \times 2.1$-cm cyst by ultrasonography (**Table**). The infant did not experience another episode of uterine bleeding, but her mother reported vaginal discharge for the next 2 months that resolved spontaneously. Laboratory surveillance at 4 months after presentation revealed decreasing levels of estradiol and gonadotropins that returned to the prepubertal range. The right ovarian cyst resolved spontaneously (**Table**).

Case 2

Infant 2 bears great similarities to infant 1. She was born at 24 weeks of gestation and had a complicated neonatal course that included severe respiratory problems, patent ductus arteriosus that was surgically closed, and feeding difficulties. At age 6 months (2.5 months corrected age), she presented to the endocrine division with a 3-day history of uterine bleeding. Her evaluation revealed LH and FSH values in the pubertal range, as well as increased levels of serum estrogen that decreased spontaneously over the course of 4 months (**Table**). Magnetic resonance imaging of the brain and pituitary was unremarkable, and pelvic ultrasound was significant for increased uterine length, enlarged ovaries with multiple follicles bilaterally, and a left dominant ovarian cyst. Follow-up showed resolution of the ovarian cyst coincident with the decline in estrogen levels (**Table**).

Methods

All assays were performed by the same commercial laboratory (Esoterix Laboratory Services, Austin, Texas). LH and FSH were measured by an electrochemiluminescent assay with the

FSH	Follicle-stimulating hormone
HPG	Hypothalamic-pituitary-gonadal
LH	Luteinizing hormone

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Table. Laboratory values and ultrasonography measurements of the 2 infants

Case 1

Age	6 mo (2.25 mo corrected)	7.5 mo (4 mo corrected)	8 mo (4.5 mo corrected)	9 mo (5.5 mo corrected)
Clinical symptoms	Vaginal bleeding, breast buds, facial acne	Vaginal discharge, breast buds	Breast buds	Breast buds decreased in size
LH, mIU/mL	2.0	0.5	0.1	0.07
FSH, mIU/mL	5.7	3.6	2.2	2.3
Estradiol, pg/mL	69	43	17	17
Uterine length, cm	2.2 × 1.9 × 1.2		4 × 1.6 × 1	4 × 1.6 × 1
Ovarian morphology	Multiple right ovarian follicles atypical for age, including a 3.5 × 3.3 × 2.1 cm cyst; left ovary not visualized		Multiple right ovarian follicles atypical for age with resolution of previous cyst; multiple left ovarian follicles, the largest measuring 1.9 × 1.4 × 1.9 cm	Small ovarian follicles bilaterally with no dominant cyst

Case 2

Age	6 mo (2.5 mo corrected)	7 mo (3.5 mo corrected)	8 mo (4.5 mo corrected)	9 mo (5.5 mo corrected)	10 mo (6.5 mo corrected)
Clinical symptoms	Vaginal bleeding, breast buds, facial acne	Breast buds	Breast buds	Breast buds	Small breast buds
LH, mIU/mL	11	5.1	2.0	0.4	0.1
FSH, mIU/mL	5.7	9.3	4.8	3.4	3.4
Estradiol, pg/mL	123	34	18	13	15
Uterine length, cm	4.1 × 1.7 × 1.3; active-appearing endometrium			3.4 × 1.8 × 1.1; no endometrial thickening	
Ovarian morphology	Multiple ovarian follicles bilaterally with a left dominant cyst measuring 0.8 × 0.8 × 0.8 cm			Multiple ovarian follicles bilaterally	

All assays were performed by the same commercial laboratory. Normative data are as follows:
Estradiol: During infancy, levels increase to 5.0-50 pg/mL between 30 and 60 days and then decline. Prepubertal children, <15 pg/mL. Mean (range) values according to Tanner stage: 16 (10-24) pg/mL for Tanner 2, 25 (7.0-60) pg/mL for Tanner 3, 47 (21-85) pg/mL for Tanner 4, and 110 (34-170) pg/mL for Tanner 5.
LH: During infancy, values increase at ~2 weeks after birth to a range of <0.02-7.0 mIU/mL within the first 3 months, then decline. Prepubertal children, mean (range), 0.07 (<0.02-0.3) mIU/mL. Mean values according to Tanner stage: 0.72 mIU/mL for Tanner 2, 2.3 mIU/mL for Tanner 3, and 3.3 mIU/mL for Tanner 4 and 5.
FSH: Infants, 0.24-14.2 mIU/mL; prepubertal children, 1.0- 4.2 mIU/mL. Mean values according to Tanner stage: 1.0-10.8 mIU/mL for Tanner 2, 1.5-12.8 mIU/mL for Tanner 3, 1.5-11.7 mIU/mL for Tanner 4, and 1.0-9.2 mIU/mL for Tanner 5.
Normative data during infancy specific for preterm infants are not provided for these assays.

Meso Scale Discovery assay platform (Meso Scale Diagnostics, Rockville, Maryland). The lower limits of detection for LH and FSH were 0.001 mIU/mL and 0.004 mIU/mL, respectively. Estradiol was measured by high-pressure liquid chromatography/tandem mass spectrometry. The lower limit of quantitation was 1 pg/mL. The interassay SD and precision (percent coefficient of variation) were 0.01 and 17.7%, respectively, for LH at 0.05 mIU/mL and 0.04 and 7.8%, respectively, for LH at 0.566 mIU/mL. For FSH, the interassay SD and precision (percent coefficient of variation) were 0.005 and 8.64% respectively, at 0.05 mIU/mL and 1.7 and 12.94%, respectively, at 13.2 mIU/mL.

Discussion

Mini-puberty of infancy refers to the transient activation of the HPG axis during the first few months of life. In males, testosterone levels are low at birth. As a result of HPG axis activation after birth, testosterone levels rise shortly after birth to peak at around age 1-3 months. Testosterone values decline gradually over the next few months while the HPG axis becomes quiescent.[4] This testosterone surge is followed by increases in penile and testicular size and prostatic activity.[4] In females, in contrast, the process is not so well described, with the original cross-sectional studies showing variable estradiol values during the first few months of life.[5] A better understanding of the hormonal changes during the first year of life was attained by the most recent longitudinal studies performed by Dunkel et al, which included both full-term and preterm male and female infants.[6-8] These studies documented a temporary activation of the HPG axis in both sexes. In females, hormonal changes during mini-puberty are associated with increases in mammary and uterine size and follicular development.[7,8]

The literature describing differences in postnatal HPG activation in preterm vs term infants is limited.[4,6-11] A small number of studies have documented an exaggerated gonadotropin surge in preterm infants compared with term infants.[6-11] Although there is considerable temporal and interindividual variation in LH and FSH values, preterm infants as a cohort have higher gonadotropin values than term infants.[6-11] Likewise, estradiol levels are greater in preterm females than in term females.[7]

Furthermore, longitudinal studies reported by Kuiri-Hänninen et al showed certain sex differences, with preterm females experiencing a more robust and prolonged HPG axis activation compared with preterm males.[4] Similar sex differences with prematurity were observed by Greaves et al, who reported lower LH/FSH ratios and FSH predominance in girls compared with boys.[11] Finally, a relationship between FSH surge and ovarian follicular development was demonstrated by