Abstract: Preterm ovarian hyperstimulation syndrome (POHS) is an uncommon disorder characterized by prematurity, hypogastric and upper leg swelling of various intensities, high serum estradiol and gonadotropin levels, and ovarian follicular cyst/cysts. In this paper, we present the first case of POHS presenting with vaginal bleeding. A female infant was born via spontaneous vaginal delivery at 25 weeks of gestation with a birth weight of 610 g. At 36 weeks of post-conception age, she developed breast enlargement, swelling of the clitoral hood, labia major and minor, hypogastrium and upper legs. Several weeks later, vaginal bleeding started and lasted 3 days. The vaginal bleeding continued to occur at monthly intervals. The elevated levels of gonadotropins and estrogens, vulvar swelling and cysts in both ovaries confirmed the diagnosis of preterm ovarian hyperstimulation syndrome.

Keywords: ovarian hyperstimulation syndrome; preterm infants; vulvar swelling.

Case report

A premature female infant was born via spontaneous vaginal delivery at 25 weeks of gestation with a birth weight of 610 g. The preterm birth was as a result of cervical insufficiency. Her birth weight was suitable for gestational age. Apgar scores were 5 and 8, at 1 and 5 min, respectively. She was followed up at the Neonatal Intensive Care Unit because of prematurity respiratory distress syndrome, sepsis, necrotizing enterocolitis, bronchopulmonary dysplasia, cystic periventricular leukomalacia, and hypothyroxinemia. At 36 weeks of post-conception age (WPCA), she developed breast enlargement (Tanner II), swelling of the clitoral hood, labia major and minor, hypogastrium and upper legs (Figure 1). Several weeks later (at 39 WPCA), vaginal bleeding started and lasted 3 days. The vaginal bleeding continued to occur at monthly intervals. The ultrasound and computed tomography imaging of the abdomen and minor pelvis were normal. The differential diagnoses including estrogen producing tumor, exogenous estrogen display and McCune-Albright syndrome (MAS) were excluded. MAS is suspected when two of the three following features are present: (i) polyostotic fibrous dysplasia (PFD); (ii) café-au-lait skin pigmentation; and (iii) autonomous endocrine hyperfunction (e.g., gonadotropin-independent precocious puberty and hyperthyroidism). Laboratory evaluation of the baby showed high concentrations of E₂ [316 pg/mL (reference range <56 pg/mL)], follicle stimulating hormone (FSH) [8.34 IU/L (reference range=0.2–6.6 IU/L)], and luteinizing

Introduction

Preterm ovarian hyper stimulation syndrome (POHS) is a very rare entity characterized by vulvar, hypogastric and upper leg swelling, elevated serum estradiol (E₂) and gonadotropin levels, and ovarian follicular cysts (1–3). The main etiopathology is the immaturity of the gonadal axis and the lack of the negative feedback of the placental steroids.
hormone (LH) [13.18 IU/L (reference range = 0.1–6 IU/L)]. Her bone age was compatible with her chronological age. The cranial magnetic resonance imaging revealed hypoplasia of the right cerebellar hemisphere and asymmetric appearance of the frontal horn of left lateral ventricle. The pituitary size was normal. L-tiroksin treatment (5 μg/kg/day) was started due to transient hypothroxinemia [TSH level; 4.25 μIU/mL (reference range = 1.0–4.80 μIU/mL) and free T4 level; 0.4 ng/dL (reference range = 0.7–1.48 ng/dL)] at postnatal second week and continued for 6 months.

The pelvic and abdominal ultrasonography examinations revealed enlarged uterus (2.2×1.4×2.7 cm) with an endometrial stripe of 4.5 mm and multiple small cysts in the left ovary with a maximum diameter of 1.5×0.9 cm. A cyst with a diameter of 3.1×1.7 cm was also present in the right ovary (Figure 2). The elevated levels of gonadotropins and estrogens, vulvar swelling and cysts in both ovaries confirmed the diagnosis of preterm ovarian hyperstimulation syndrome.

Laboratory examinations were performed to monitor changes in the hormonal levels, and at PGA of 52 weeks, serum levels of the concentrations of estrogens and gonadotropins returned to normal infant range. Consecutive pelvic ultrasonography revealed the regression of the ovarian cysts. Breast enlargement regressed to Tanner I and vaginal bleeding ceased in 2 months (at 44 WPCA), and swellings improved in 3 months (at 48 WPCA). Clinical and laboratory findings were normal at 52 WPCA. She is currently 18 months old and both her clinical and laboratory values are completely normal.

**Discussion**

Preterm ovarian hyperstimulation syndrome was first described in 1985 (1). It has been rarely reported in medical literature until this time (1, 2, 4). The characteristic features include prematurity (24–31 WPCA), swelling of vulva, hypogastric region and upper leg, elevation of E2 and gonadotrophin, and multiple cysts in both ovaries (2, 5). The only pathognomonic sign of POHS is the swelling of the vulva occurring as a result of high levels of vascular endothelial growth factors secreted by theca and granulose cells (2).
Ovarian cysts are not specific for POHS. Single or multiple follicular cysts are relatively common (30%–34%) in healthy fetuses and newborn infants (1–3). Fifty percent of these cysts regress spontaneously in the first month of life with another 25% disappearing by the end of the second month (6). The origin of ovarian cysts is still a controversial topic. Meizner et al. showed excessive stimulation of fetal ovaries by placental or maternal hormones (7). Fetal ovarian cysts are frequently associated with a large placenta with a consequent increase in hCG production (8–11). Infrequently, a postnatal surge of gonadotropins possibly due to the infantile ovarian dysfunction can produce overstimulation of the ovaries with cyst formation and estrogen production in healthy neonates and preterm infants.

High level E2 and gonadotropin are not specific for POHS, either. Fetal gonadotropins decrease during the last trimester of pregnancy, but increase after birth. This transient increase of gonadotropin levels after birth is known as the mini-puberty (12). FSH and LH levels in the newborn peak at 3 to 4 months of age and then subsequently decrease, reaching prepubertal levels at 2–3 years of age (13, 14). This may be as a result of an immaturity of the hypothalamic-pituitary-gonadal (HPG) axis, the lack of negative feedback on axis and rapid withdrawal of placental sex steroids (15). Changes of gonadotropin surge is more marked and prolonged in preterm infants (16). However, our knowledge about postnatal developmental changes in the HPG axis and gonadotropin levels is limited, especially in older preterm infants. Our patient had high gonadotropin levels but high free FSH and LH levels are not sufficient to discriminate between the diagnoses of POHS and mini-puberty.

We made the diagnoses of POHS in our patient as she had swelling of vulva and hypogastrium and upper leg that is not seen healthy newborns and preterm infants in mini-puberty.

Although they have high E2 concentrations, estrogenization signs varies in POHS cases. In the present case, we did not observe any high E2 concentration-dependent accelerated growth and bone maturation. This condition has been explained by decreased peripheral E2 receptor sensitivity that is a result of immature gonadal axis (12, 17). In contrast to this hypothesis, the initial signs were the breast enlargement (Tanner II) and vaginal bleeding in addition to swellings in our case. To our knowledge, our patient is the first case presenting with vaginal bleeding and the third case presenting with breast enlargements in the literature (2, 5).

Autonomous ovarian cysts may cause vaginal bleeding. However, it is difficult to attribute the vaginal bleeding in our patient to the presence of the autonomous cyst alone as vaginal bleeding continued to occur during cyst regression.

The first line approach for treatment of neonatal and infantile ovarian cysts in POHS patients is to follow-up patients without any treatment unless there is a risk of torsion, rupture and hemorrhage of the cyst. Surgical removal of the ovarian cyst should be performed in the presence of these complications. Ultrasound-guided aspiration of large neonatal ovarian cysts may be attempted prior to surgical exploration (18, 19).

Our case was followed up regularly to assess growth and regression of ovarian cysts. The size and the number of the cysts regressed on follow-up ultrasound imaging over time. Both laboratory and clinical findings returned to normal at 52 WPCA (in 16 weeks).

In conclusion, POHS has a widespread hyperostrogenization symptom spectrum. Vaginal bleeding has never been reported before and breast enlargement in only two newborn cases with POHS. These major signs in addition to common findings of POHS in our patient improved without treatment. This case may illustrate that POHS might appear with different presentations and POHS does not require any therapy in the absence of cyst torsion.

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References