

CASE REPORTS

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MINIPUBERTY IN EXTREMELY PREMATURE FEMALE INFANTS – A REPORT OF TWO CASES

*MINIPUBERTET KOD EKSTREMNO PREVREMENO ROĐENIH ŽENSKIH ODOJČADI
– PRIKAZ DVA SLUČAJA*

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Summary

Introduction. Minipuberty occurs during the first months of life after the activation of the hypothalamic-pituitary-gonadal axis which causes an increase in gonadotropic and sex hormones. Usually, it does not induce clinically evident physical changes. Studies have shown that minipuberty in extremely premature infants is more pronounced and lasts longer, leading to higher levels of sex hormones induce clinically evident in physical changes. **Case Report.** We present two extremely premature female infants, born at 25 weeks of gestation, with clinically evident physical changes during minipuberty. The first infant presented with vaginal bleeding at the age of 4 months, corrected age of 2 weeks. The vaginal bleeding lasted for two days and stopped spontaneously. The infant also had small glandular breast buds of 1 cm bilaterally, swelling in the pubic region, swollen vulva and clitoris. The second infant presented with swelling in the genital region, suprapubic area and the anterior part of thighs, at the age of 4 months, corrected age of 2 weeks. Both infants had ovarian cysts. In both cases, laboratory tests were consistent with minipuberty. The described changes disappeared gradually and spontaneously. **Conclusion.** In order to avoid unnecessary testing, clinicians should be aware of possible physical changes during minipuberty in extremely premature infants. Clinical monitoring of these infants is recommended until regression of newly developed physical characteristics.

Key words: Hypothalamo-Hypophyseal System; Puberty; Infant, Extremely Premature; Ovarian Cysts; Uterine Hemorrhage; Genitalia, Female; Diagnosis; Signs and Symptoms

Introduction

Activation of the hypothalamic-pituitary-gonadal (HPG) axis, which causes gender-specific elevation in the gonadotropic hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and sex steroid hormones (testosterone in males and

Sažetak

Uvod. Minipubertet se odvija u prvim mesecima života nakon aktivacije hipotalamo-hipofizno-gonadalne osovine koja uzrokuje porast gonadotropina i polnih hormona. Uobičajeno, plima hormona minipuberteta ne dovodi do klinički evidentnih fizičkih promena. Studije su pokazale da je minipubertet kod ekstremno prevremeno rođene odojčadi izraženiji i traje duže, što dovodi do viših nivoa polnih hormona koji uzrokuju klinički evidentne fizičke promene. **Prikaz slučaja.** Prikazujemo dva odojčeta ženskog pola, koji su ekstremno prevremeno rođeni u 25. nedelji gestacije, kod kojih su evidentirane fizičke promene tokom minipuberteta. Prvo odojče je razvilo vaginalno krvarenje u uzrastu od četiri meseca, korigovani uzrast dve nedelje. Vaginalno krvarenje je trajalo dva dana i sponatno je prestalo. Odojče je imalo i pupoljke grudi promera 1 cm obostrano, otok u predelu pubične regije, vulvarni otok i otok klitorisa. Kod drugog odojčeta, u uzrastu od četiri meseca, korigovani uzrast dve nedelje, došlo je do pojave otoka genitalne regije, suprapubične regije i prednjeg dela butina. Oba odojčeta su imala ovarijalne ciste. Laboratorijski nalazi su ukazivali na minipubertet. Opisane promene su se spontano postepeno povukle. **Zaključak.** Kliničari bi trebalo da budu svesni mogućih fizičkih promena tokom minipuberteta kod ekstremno prevremeno rođenih novorođenčadi, što bi sprečilo nepotrebna ispitivanja. Savetovano je kliničko praćenje ove dece do povlačenja novonastalih fizičkih karakteristika.

Ključne reči: hipotalamo-hipofizealna osovina; pubertet; ekstremno prevremeno rođeno dete; ovarijalna cista; krvarenje iz materice; ženski genitalni organi; dijagnoza; znaci i simptomi

estradiol in females), occurs three times during lifetime. These three events can be described as “endocrine puberties”. The first endocrine puberty happens during intrauterine life. The second endocrine puberty, that occurs during the first months of life, is called minipuberty. The third puberty occurs in adolescence [1].

Abbreviations

HPG	– hypothalamic-pituitary-gonadal
LH	– luteinizing hormone
FSH	– follicle-stimulating hormone

Ordinarily, minipuberty does not induce clinically evident physical changes, but it is evident in serum hormone changes [2]. Data of minipuberty in extremely premature infants are scarce. Here, we report two cases of minipuberty in extremely premature female infants with elevated hormone levels that resulted in clinically evident physical manifestations of hormonal changes.

Case 1

At the age of 4 months, corrected age of 2 weeks, a female infant presented with vaginal bleeding that lasted for two days. She was born at 25 1/7 weeks of gestation and had a prolonged hospital stay due to bronchopulmonary dysplasia, patent ductus arteriosus and gastroesophageal reflux. The infant presented with small glandular breast buds of 1 cm bilaterally, swelling in the pubic region, swollen vulva and clitoris. The laboratory tests showed normal complete blood count, coagulation mechanism and albumin level. Elevated levels of LH, FSH and estradiol were detected and they were in the pubertal range (**Table 1**). Further laboratory tests showed normal levels of 17-OH progesterone, alpha-fetoprotein and beta-human chorionic gonadotropin, as well as normal female karyotype. Pelvic ultrasonography revealed a multiseptated 16 mm cyst on the right ovary. Vaginal bleeding spontaneously resolved. The infant did not experience another episode of uterine bleeding. Laboratory surveillance revealed decreasing levels of estradiol and gonadotropins that returned to the prepubertal range, and by that time, breast buds and genital swelling had regressed entirely. The ovarian cyst resolved spontaneously.

Case 2

At the age of 4 months, corrected age of 2 weeks, a female infant presented with swelling in the genital region, suprapubic area and the anterior part of thighs. She was born at 25 4/7 weeks of gestation and had a prolonged hospital stay due to bronchopulmonary dysplasia, intracerebral hemorrhage, patent foramen ovale and retinopathy of prematurity. Elevated levels of gonadotropins and estradiol were detected, also 17-OH progesterone was elevated - 7.34 ng/mL (reference levels < 3.1) (**Table 1**). Laboratory test results were in

reference range for blood glucose, sodium, potassium, albumin, testosterone, and she had a normal female karyotype. Pelvic ultrasonography revealed cysts on both ovaries, up to 37 mm. The swelling gradually subsided and the levels of estradiol, 17-OH progesterone and gonadotropins decreased. The cysts remained on both ovaries. This patient needs further monitoring.

Discussion

Minipuberty is the second transient activation of the HPG axis. It develops after birth as placental sex steroid hormones stop suppressing the HPG axis. A surge in gonadotropin secretion leads to sex-specific hormone changes. The FSH levels are higher in girls than in boys and remain high until the age of 3 - 4 years, compared to boys in whom they decline by the age of 6 months. According to FSH levels, estradiol levels are elevated in girls, with average levels that are same as those seen in Tanner stage 4 girls. Estradiol levels fluctuate with rises and falls of estradiol concentration [3, 4]. Serial urine estradiol measurements show vast inter-individual differences [4]. The LH levels are higher in boys than in girls, and they decline by the age of 4 - 6 months. It stimulates testosterone secretion and it peaks in the second and third months of life [5].

In general, the transient rise of sex hormones is not followed by clinically visible physical changes [2]. Its effects are visible through ultrasound evaluation of testicular size in boys and monitoring the speed of penile growth [6, 7]. In girls, a positive correlation of the mammary gland diameter and estradiol was described at the age of 3 months [8].

The onset of minipuberty in extremely premature infants is similar to that in full-term infants. Still, HPG axis activation in the extremely premature infants is increased and prolonged, resulting in higher sex steroid hormone concentrations in preterm babies [2]. Reference data based on serum measured in 82 preterm babies for LH and FSH showed higher levels of gonadotropins in preterm infants than in full-term infants [9]. This was confirmed in a study that showed that estradiol levels were significantly higher in preterm than in full-term girls. This study also proved the effect of estradiol level on target tissue, showing that mammary glandular diameter and uterine length were significantly larger in preterm than in full-term girls [4].

Vogiatzi et al. described two cases of menstrual bleeding as a manifestation of minipuberty, debat-

Table 1. Hormone levels

Tabela 1. Nivoi hormona

	Estradiol pg/mL/Estradiol pg/mL		LH IU/mL		FSH IU/mL	
	2 weeks 2 nedelje	7 months 7 meseci	2 weeks 2 nedelje	7 months 7 meseci	2 weeks 2 nedelje	7 months 7 meseci
Case 1 <i>Slučaj 1</i>	246	54	13	1.27	6.61	5.38
Case 2 <i>Slučaj 2</i>	276	7.43	21.13	3.72	7.2	6.35

Legend/Legenda: LH – Luteinizing hormone/Luteinizirajući hormon FSH – Follicle-stimulating hormone/Folikulostimulišući hormon

ing that estrogen level was high enough to cause uterine maturation and shedding. Their two cases were similar to our first case and showed two preterm babies born at 25 weeks of gestation with one episode of vaginal bleeding accompanied by breast buds. Vaginal bleeding spontaneously stopped and did not recur. Laboratory findings were consistent with minipuberty. The LH, FSH, and estradiol levels were higher than those seen in full-term girls and spontaneously returned to normal levels [10]. Another case report showed a preterm girl with vaginal bleeding that was primarily understood as precocious puberty and was treated as such. Later, the treatment was withheld; there were no signs of puberty, the former diagnosis was rejected and the vaginal bleeding was attributed to minipuberty [11].

The swelling in the genital area, described in both our cases, occurs due to the increase of estrogen level. Similar manifestations are described in preterm ovarian hyperstimulation syndrome [12]. It has also been established that high vascular endothelial factor levels contribute to genital swelling. Elevated vascular endothelial factor is predominantly the consequence of LH surge [13]. Clitoromegaly, which may be seen as part of swelling in the genital region, could lead to further unnecessary examinations.

Ovarian cysts form due to HPG axis activation and should gradually reduce in size and disappear

after HPG axis recovers. Therefore, it is essential to monitor ovarian cysts due to the possibility of surgical complications, i. e. ovarian torsion, rupture or hemorrhage, which is most common if the cysts are large ($> 4 - 5$ cm) [14].

Physical manifestations of minipuberty were also noted in extremely preterm male infants. A clinical study revealed higher testosterone levels in preterm boys than in full-term boys, resulting in significantly faster testicular and penile growth [15]. However, these physical manifestations have not been reported as the reason for inpatient visits, probably since these changes are less noticeable than those in girls.

Conclusion

Minipuberty in extremely preterm female infants may have physical manifestations ranging from mammary glandular tissue swelling, swelling in the genital area, to uterine bleeding. Since the neonatal care is constantly improving, the number of extremely preterm infants who survive increases. Clinicians should be aware of possible physical manifestations of minipuberty in premature infants in order to avoid further examinations and unnecessary treatment of this physiological condition. Instead, monitoring of these changes only through inpatient visits is advised to prove their transitory nature.

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