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Premature pubarche during minipuberty – literature review and two case reports

Owłosienie łonowe w okresie niemowlęcym – przegląd literatury i prezentacja dwóch przypadków

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Abstract

Introduction: Isolated premature pubarche (PP) in infancy may be the reason for many diagnostic difficulties. This is due to the low incidence and, therefore, the limited number of studies on this subject and the lack of strict laboratory standards because of the physiological variability of gonadotropic hormone and androgen concentrations during minipuberty.

Material and methods: We aimed to present current knowledge about PP in infancy based on the literature review and 2 cases of male infants with scrotal hair during minipuberty.

Results: Isolated hair in the pubic region in a boy during the period of minipuberty requires differential diagnosis. After excluding serious aetiology, it seems to be a mild, self-limiting variant of precocious puberty. The phenomenon is probably a result of increased sensitivity of the hair follicles to transiently increased androgen concentration.

Conclusions: Isolated pubic hair in infancy as a mild, self-limiting variant of precocious puberty in infants should be a diagnosis of exclusion. The condition resolves spontaneously, but it absolutely requires further follow-up to exclude serious aetiology in the case of puberty progression.

Key words:
infancy, precocious puberty, pubic hair, minipuberty, premature pubarche.

Streszczenie

Wprowadzenie: Izolowane przedwczesne *pubarche* u chłopców w okresie *minipuberty* może nastręczać wiele trudności diagnostycznych. Powodem jest mała częstość występowania, a co za tym idzie ograniczona liczba badań na ten temat oraz brak ściśle określonych norm laboratoryjnych z powodu fizjologicznej zmienności stężeń hormonów gonadotropowych i androgenów w tym okresie.

Materiał i metody: W pracy przedstawiono aktualną wiedzę dotyczącą przedwczesnego pubarche u niemowląt, opierając się na przeglądzie piśmiennictwa, oraz dwa opisy przypadków niemowląt płci męskiej, u których *pubarche praecox* wystąpiło w przebiegu *minipuberty*.

Wyniki: Owłosienie w okolicy łonowej u chłopca w okresie *minipuberty* wymaga diagnostyki różnicowej. W przypadku wykluczenia patologii wydaje się, że może być łagodnym wariantem przedwczesnego dojrzewania płciowego, które prawdopodobnie jest wynikiem zwiększonej wrażliwości mieszków włosowych na przejściowe zwiększone stężenie androgenów.

Wnioski: Przedwczesne *pubarche* w okresie *minipuberty*, jako łagodny wariant przedwczesnego dojrzewania płciowego, jest rozpoznaniem z wykluczenia i ustępuje samoistnie, jednak bezwzględnie wymaga okresowej kontroli, aby w przypadku progresji dojrzewania wykluczyć poważną etiologię.

Słowa kluczowe:
niemowlę, *minipuberty*, owłosienie łonowe, przedwczesne dojrzewanie, *pubarche praecox*.

Introduction

Premature pubarche (PP) is defined as the presence of pubic hair before the age of 8 years in girls and 9 years in boys. It occurs mainly between 6 and 8 years of age, mostly in girls [1–5]. It results from premature secretion of adrenal androgens; less frequently, from late-onset congenital adrenal hyperplasia (CAH) or androgen-producing tumours [1]. Infants with PP are described relatively rarely. Different terminology related to the age, e.g. "pubic hair in infancy", "scrotal or labial hair in infancy", or "premature pubarche in infancy", is used in the literature to describe the condition [2–8]. In this study, we aimed to present current knowledge about PP in infancy based on the literature review and 2 cases of male infants with scrotal hair

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during minipuberty. We attempt to discuss the necessary tests required when premature pubic hair is found as an isolated sign of puberty in a child in the first year of life. This is vital, on the one hand, to prevent the patient from undergoing unnecessary diagnostics and, on the other, not to overlook the potentially serious cause of this condition.

Patient 1

A 6-month-old male infant was referred to an endocrinologist due to the presence of pubic hair, which appeared at the age of 4 months, without other disturbing symptoms. The child was born in term with appropriate weight and length in good condition (40 weeks, 3600 g, Apgar 10). He had been healthy thus far; no exposure to exogenous androgens was reported. The child's parents were not related and were healthy. In a physical examination several dark hairs were found at the base of the penis (Tanner stage G1P2), without other signs of androgenization. The volume of the testes was below 2 ml, the penis was not enlarged; the scrotum was not hyperpigmented; there was no body odour, armpit hair, or acne. The boy's body weight was normal for his age. In laboratory studies, basal gonadotropins were slightly elevated, and testosterone, 17-hydroxyprogesterone (17OHP), and dehydroepiandrosterone (DHEAS) were appropriate for the age of the child (Table I).

Ultrasound examination of the abdomen, adrenal areas, and testicles showed no abnormalities. After 3 months of monitoring, spontaneous hair regression occurred – there was only one dark hair on the scrotum, and the concentration of gonadotropins decreased. At the age of 12 months, pubic hair was no longer observed. Based on the clinical picture, PP in the course of minipuberty was diagnosed.

Patient 2

A 4-month-old male infant was referred to an endocrinologist due to the appearance of pubic hair, with no other alarming symptoms. The boy was born in the 39th week of pregnancy complicated by gestational diabetes, with a birth weight of 3980 g, in good condition – Apgar 10. The boy had been developing properly thus far. In the physical examination, several single hairs on the scrotum were found (Tanner stage G1P2), without other features of androgenization. In laboratory studies, higher concentrations of gonadotropins (FSH 2.12 U/l, LH 0.67 U/l) and testosterone (19.79 ng/dl) were found, corresponding to minipuberty. Initial 17-OHP concentration was mild and transiently increased, together with normal DHEA, which allowed exclusion of CAH and adrenal tumour. The evolution of hormone concentrations and other findings of the boy are presented in Table II.

Ultrasound showed a normal image of the abdominal organs and testicles. At the age of 6 months, the boy had no progression of puberty, and at the age of 12 months, with normalization of androgen concentrations, the hair had resolved. Based on the clinical presentation, the diagnosis of PP in the course of minipuberty was made. At the age of 12 and 24 months, the boy did not show any signs of puberty.

Table I. Laboratory tests of patient 1

Parameter	Age [in months]		Reference ranges for prepubertal period
	6	9	
FSH [U/l]	2.09	1.11	0.2–2.8
LH [U/l]	0.82	0.17	0–0.4
Testosterone [ng/dl]	< 2.5	< 2.5	12–21
Cortisol [μg/dl]	10.64		6.2–19.4
17-OHP [ng/ml]	1.32		0.1–2.0
DHEA-S [μg/dl]	31.57		3.4–124
TSH [μIU/ml]	1.2		0.73–8.35
AFP [ng/ml]	109.1	51.07	0–28
β-HCG [mIU/ml]	0.1		0–2.6

FSH – follicle-stimulating hormone; LH – luteinizing hormone; 17-OHP – 17-hydroxyprogesterone; DHEA-S – dehydroepiandrosterone sulphate; TSH – thyroid-stimulating hormone; AFP – α-fetoprotein; β-HCG – human chorionic gonadotrophin β subunit.

Discussion

Premature pubarche is a condition that can have different causes. Disorders that may be the reasons for the presence of premature pubic hair include congenital adrenal hyperplasia, androgen secreting tumours, premature adrenarche, central precocious puberty, or exogenous exposure to androgens [4]. Accompanying symptoms and signs that indicate the need for deeper diagnosis include the following: rapid progression of androgenization, testicular enlargement, penis enlargement, body odour, acne, advanced bone age, and growth acceleration [4]. Therefore, it is important to decide how broad a diagnosis is necessary if scrotal hair is an isolated disorder in a boy in the first year of life, and when PP can be a sign of physiological minipuberty.

Reports of gonadal activity in the prenatal and infancy period began to appear in the 1970s [9] and its physiology is still not fully understood [10–12]. Before puberty the hypothalamic-pituitary-gonadal axis is activated twice: in the middle of foetal life and in the first months after birth [10, 13, 14]. In foetal life, in the middle of pregnancy, gonadotrophins reach high concentrations; however, due to the increasing levels of placental oestrogens, and in male foetuses probably also testosterone, their suppression occurs [10, 15]. After delivery, as the level of placental hormones has decreased, the hypothalamic-pituitary-gonadal axis is unlocked, and as a result we observe changes known as minipuberty [15, 16]. In boys, concentrations of LH and FSH, testosterone, 17-OHP, and androstenedione reach

Table II. Laboratory tests of patient 2

Parameter	Age [in months]					Reference ranges for prepubertal period
	4	6	9	12	24	
FSH [U/l]	2.12					0.2–2.8
LH [U/l]	0.67					0–0.4
Testosterone [ng/dl]	19.79	2.53		0.087		12–21
Cortisol [μg/dl]		9.4				6.2–19.4
ACTH [pg/ml]		26.67				7.2–63.6
17-OHP [ng/ml]	5.04	2.61	2.84	1.27	0.84	0.1–2.0
DHEA [ng/ml]		0.732				< 2.9
TSH [μIU/ml]	2.241			4.03		0.73–8.35
AFP [ng/ml]	248.2	187.1	39.1	14.5	2.98	< 28
β-HCG [mIU/ml]	< 0.1					0–2.6
Na [mmol/l]	138	139				129–143
K [mmol/l]	4.7	4.57				4.1–5.3

FSH – follicle-stimulating hormone; LH – luteinizing hormone; ACTH – corticotropic hormone; 17-OHP – 17-hydroxyprogesterone; DHEA – dehydroepiandrosterone; TSH - thyroid-stimulating hormone; AFP – α-fetoprotein; β-HCG – human chorionic gonadotrophin β subunit; Na – sodium, K – potassium

maximum values in the first 3 months of life and then decrease to pre-pubertal values at about 6-9 months of age [15, 17]. In small for gestational age and preterm infants the response seems to be stronger and more prolonged, because of immaturity of the hypothalamic feedback [13, 14]. It was reported that in extremely low-birth-weight infant females the excessive hormonal response manifested with recurrent vaginal bleeding, which spontaneously resolved over time [18]. In both sexes, it is vital for future reproductive capacity [19]. In the case of males, transient stimulation of the testes is important for priming Leydig and Sertoli cells and gonocyte-to-spermatogenic stem cell (also called spermatogonia) transformation, which serve as a lifetime source of spermatogenesis [14, 16, 19, 20]. It plays pivotal roles in brain masculinization and the development of sexual orientation [7, 10, 11, 14, 15]. Moreover, minipuberty provides a temporary window for diagnosis and potential treatment in infants with disorders of sex development [13]. Effective treatment for micropenis could be advised during minipuberty, but it is not clear whether gonadotropin therapy in children with congenital hypogonadotropic hypogonadism would improve fertility in the future [16].

In older children, PP is most often a manifestation of the maturation of the zona reticularis of the adrenal gland, known as premature adrenarche [1, 21]. In infants, however, it appears to be more complex. Observations indicate that pubarche in children under the age of 2 years is associated with the activation of the hypothalamic-pituitary-gonadal axis, rather than with adrenal stimulation [2, 5]. The concentration of gonadotropins and testosterone in the first 3 months of life in male infants may reach pubertal values; it then decreases, reaching the pre-pubertal level in the second half of year [10, 22]. The researchers of the COPENHAGEN Minipuberty Study (2016–2018) aimed to establish continuous reference curves for reproductive hormones in healthy female and male infants to evaluate the hypothalamic-pituitary-gonadal axis during minipuberty [12, 19]. A follow-up of 119 boys revealed that gonadotropins and Leydig cell products – total testosterone and insulin-like factor 3 – peak at around one month of age. Sertoli cell markers – inhibin B and anti-Mullerian hormone – and testicular volume peak at around 4 to 5 months [19].

Also, androgens secreted during this period by the foetal zone of the adrenal cortex, such as dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS), and androstenedione, significantly increase the pool of androgens in the blood in infants of both sexes [23]. In target tissues, e.g. in the skin, they are converted to more potent testosterone and dihydrotestosterone (DHT), which manifests by sebaceous gland hyperplasia often found in infants, acne, or pubic hair [23–25]. Pubic hair in this age is rare. Kaplowitz *et al.* state that among 104 children who were referred to the author due to the features

of precocious puberty, 8% were infants with pubarche, and the ratio of boys to girls in this group was 3 : 5 [8]. In another study, in a group of 216 children diagnosed with PP, only one boy and 21 girls were under the age of 2 years [5]. The authors found no association between the occurrence of pubic hair in this age group and obesity or intrauterine growth retardation (IUGR), as was the case in the group of older children. Moreover, in the youngest participants of the study, they observed slightly higher concentrations of DHEAS and androstenedione in relation to age and gender. However, according to the authors, the results did not indicate premature adrenarche [5]. The described condition was considered a consequence of the hypersensitivity of the androgen receptor to physiologically transiently increased concentrations of androgens originating from both the testes and adrenal glands. Another reason would be increased activity of 5-alpha reductase in the hair follicles within the scrotum during the minipuberty period [6, 23, 26–29]. These phenomena are also responsible for other skin manifestations of androgenization observed in infants, i.e. sebaceous gland hyperplasia and acne [22–25]. Characteristics of isolated PP in infants are summarized in Table III.

The arguments presented above confirm the observations of other researchers. In a study of 11 infants with PP, all had normal growth, normal hormone test results, and bone age. At the average age of 11 months, the regression of hair was noted [6]. In another observation, the average age of 9 infants with isolated scrotal hair was 4.5 months. The boys were not exposed to exogenous hormones and did not show other features of hyperandrogenism. The results of hormonal tests (testosterone, 17-OHP, androstenedione, and DHEAS), which were performed in 6 of them, were normal for their age. By 12 months of age, the hair had receded in all the patients [7]. Similarly, in research by Tatli *et al.* and Montane *et al.*, in 6 and 7 infants with isolated scrotal hair, respectively, no hormonal disorders were found, and the hair disappeared spontaneously [30, 31].

Another interesting report suggests the possibility of family occurrence of PP [28]. In Pakistani-origin twins, pubic hair appeared at one month of age and gradually developed up to the age of 6 months, after which it remained stable until the 9th month, when the monitoring ends. The results of additional tests (testosterone and 17-OHP concentration) were adequate to the age, the bone age was consistent with the boy's chronological age, and abdominal ultrasound examinations were normal [28]. A 7-month-old patient was also described with a 3-month history of pubic hair. In the child, the concentration of LH was 1.5 mIU/ml, testosterone – 25.2 ng/dl, and 17-OHP – 2.48 ng/ml, with normal bone age. After 6 months, pubarche spontaneously resolved [4].

Bourayou *et al.*, proved that minipuberty was the cause of PP in 21 out of 23 studied male infants. In 2 boys, however, central precocious puberty (CPP) was diagnosed as a sign of an organic disease as magnetic resonance imaging (MRI) revealed hypothalamic hamartoma. It should be noted that in these 2 patients, the pubic hair reached a more advanced stage than in isolated PP Tanner stage, i.e. P3. Neither pubertal testosterone concentration nor pubertal gonadotropins increase after the gonadoliberin stimulation (gonadotropin-releasing hormone, GnRH) was a differentiating test between children with CPP and those with isolated PP [2]. In another study, in 3 out of 5 infants with scrotal hair, additional exposure to gestagens taken by the mother was described, dydrogesterone during pregnancy and desogestrel during breastfeeding [27]. However, the significance of this exposure remains unclear because dydrogesterone does not exhibit an androgenic effect, while metabolites of desogestrel used during pregnancy could cause virilization in the foetus. The intake of the substance during lactation seems to be safe [32].

All the authors agree that, in a patient with PP, it is first necessary to conduct a thorough physical examination [2, 4]. Regarding the scope of necessary diagnostic tests, the opinions are divided. Charkaluk *et al.* recommend excluding true precocious puberty if there are no other signs of puberty, i.e. enlargement of mammary glands or increase of testicular volume, and the normal concentration of androgens and their metabolites (testosterone, androstenedione, 17-OHP) [5]. Bourayou *et al.*, however, underline the need to interpret the results of hormonal tests in relation to age. In minipuberty, a pubertal response to GnRH is possible, as the authors described in 9 out of 13 boys diagnosed with isolated PP [2]. The proposed diagnostic algorithms in patients with PP suggest that, in the absence of other features of hyperandrogenism, the testing should be limited to resting serum 17-OHP, bone age, and growth rate assess-

Table III. Characteristics of isolated PP in infants

1. Time: pubic hair appears most often in the first half-year of the child's life [7, 28, 30]
2. Location: hair limited to the skin of the pubis, scrotum, or labia majora [26]
3. Intensity: Tanner's P2 stage [2]
4. Coexisting signs: without other features of puberty (i.e. acceleration of growth rate, enlargement of the testicles, penis, clitoris, or nipples) [5, 8, 29]
5. Hormonal tests: possible increase in the level of gonadotropins, testosterone, or oestradiol during the minipuberty period; possible pubertal increase in gonadotropins in the LH-RH test [2]; sometimes slightly increased DHEAS concentration [22, 29]
6. Imaging tests: normal ultrasound of the abdominal cavity with the assessment of the adrenal glands and ultrasound of the gonads [28]
7. Course: in most infants, spontaneous pubic hair loss by 12 months of age [6, 7, 29–31]

PP – premature pubarche; LH-RH – luteinizing-hormone-releasing hormone; DHEA-S – dehydroepiandrosterone sulphate

ment. At a basal 17-OHP concentration of < 6 nmol/l (2 ng/ml), only periodic monitoring is recommended, with no indication for an ACTH test [1, 3]. However, these recommendations do not take into account the specificity of the infancy period. The cut-off point for 17-OHP has been determined in a group of patients with an average age of 6.6 years [1]. According to other researchers, it is advisable to assess the concentrations of testosterone, 17-OHP, and ACTH [2]. At high testosterone concentrations, it is advised to determine tumour markers: chorionic gonadotropin and alpha-fetoprotein, and perform an GnRH test [2]. The authors note that in the case of enlarged testicles (> 3 ml) or breast development, the presence of skin lesions (e.g. the café-au-lait type), ocular lesions, or enlarged head circumference, it is necessary to perform an GnRH test and head MRI in order to search for an organic disease [2]. The authors of the publications present very different positions regarding the diagnostic pathway. According to some, the diagnosis of minipuberty as the cause of PP in a male infant should be a diagnosis of exclusion [27]. Therefore, the occurrence of a condition during this period requires urgent diagnosis and further monitoring of patients [26, 27].

In contrast, there are opinions that isolated pubic hair in infancy is a mild disorder and, under certain conditions, follow-up without intensive diagnosis is sufficient [6, 8, 21, 28]. According to others, hair limited only to the scrotum is a mild variant of precocious puberty, but the occurrence of hair in the area of the perineal skin indicates the need for a broad diagnosis and search for the cause, e.g. CAH [26]. Based on the cases of 8 patients and a review of the literature, Zimmerman *et al.* claim that, in the absence of other alarming signs in the physical examination or acceleration of growth in the history, watchful waiting without hormonal testing is sufficient [29]. In the series of 5 infants, the concentration of basal 17-OHP and after stimulation of ACTH, the concentrations of testosterone, DHEAS, androstenedione, LH, and FSH were assessed. The only deviation found was a slightly higher concentration of DHEAS originating from the foetal layer of the adrenal glands [29]. The remaining 3 children did not have testing except for clinical follow-up. It was noted that PP in infancy is a self-limiting condition that usually resolves before 12 months of age [29, 30]. The authors of the publication agree on the necessity to monitor the further development of the child and the progression of puberty [5, 6].

Summary

Isolated PP in infancy may be the reason for many diagnostic difficulties. This is due to the low incidence and, therefore, the limited number of studies on this subject and the lack of strict laboratory standards because of the physiological variability of gonadotropic hormone and androgen concentrations during minipuberty. Based on the literature and the authors' own observations, it may be concluded that isolated hair in the pubic region in a boy during the period of minipuberty is a mild, self-limiting variant of precocious puberty and probably occurs as a result of increased sensitivity of the hair follicles to transiently increased androgen concentration. The condition resolves spontaneously, but it absolutely requires further follow-up to exclude serious aetiology in the case of puberty progression.

References

1. Armengaud JB, Charkaluk ML, Trivin C, et al. Precocious pubarche: distinguishing late–onset congenital adrenal hyperplasia from premature adrenarche. J Clin Endocrinol Metab 2009; 94: 2835–2840. doi: 10.1210/jc.2009-0314
2. Bourayou R, Giabicani E, Pouillot M, et al. Premature pubarche before one year of age: distinguishing between mini-puberty variants and precocious puberty. Med Sci Monit 2015; 21: 955–963. doi: 10.12659/MSM.893139
3. Ghizzoni L, Gasco V. Premature pubarche. Horm Res Paediatr 2010; 73: 420–422. doi: 10.1159/000308178
4. Grob F, Goecke C. Premature pubarche in an infant: nonclassical congenital adrenal hyperplasia or mini-puberty variant? Clin Pediatr Endocrinol 2017; 26: 193–195. doi: 10.1297/cpe.26.193
5. Charkaluk ML, Trivin C, Brauner R. Premature pubarche as an indicator of how body weight influences the onset of adrenarche. Eur J Pediatr 2004; 163: 89–93. doi: 10.1007/s00431-003-1358-9
6. Nebesio TD, Eugster EA. Pubic hair of infancy: endocrinopathy or enigma? Pediatrics 2006; 117: 951–954. doi: 10.1542/peds.2005-1227
7. Papadimitriou A, Beri D, Nicolaidou P. Isolated scrotal hair in infancy. J Pediatr 2006; 148: 690–691. doi: 10.1016/j.jpeds.2005.12.046
8. Kaplowitz P. Clinical characteristics of 104 children referred for evaluation of precocious puberty. J Clin Endocrinol Metab 2004; 89: 3644–3650. doi: 10.1210/jc.2003-031532
9. Forest MG, Cathiard AM, Bertrand JA. Evidence of testicular activity in early infancy. J Clin Endocrinol Metab 1973; 37: 148–151. doi: 10.1210/jcem-37-1-148
10. Lanciotti L, Cofini M, Leonardi A, et al. Up–To–Date Review About Minipuberty and Overview on Hypothalamic–Pituitary–Gonadal Axis Activation in Fetal and Neonatal Life. Front Endocrinol (Lausanne) 2018; 9: 410. doi: 10.3389/fendo.2018.00410
11. Becker M, Hesse V. Minipuberty: Why Does it Happen?. Horm Res Paediatr 2020; 93: 76–84. doi: 10.1159/000508329
12. Ljubicic ML, Busch AS, Upners EN, et al. A Biphasic Pattern of Reproductive Hormones in Healthy Female Infants: The COPENHAGEN Minipuberty Study. J Clin Endocrinol Metab 2022; 107: 2598–2605. doi: 10.1210/clinem/dgac363
13. Pepe G, Calafiore M, Velletri MR, et al. Minipuberty in born small for gestational age infants: A case control prospective pilot study. Endocrine 2022; 76: 465–473. doi: 10.1007/s12020-022-03003-0
14. Lucaccioni L, Trevisani V, Boncompagni A, et al. Minipuberty: Looking Back to Understand Moving Forward. Front Pediatr 2021; 8: 612235. doi: 10.3389/fped.2020.612235
15. Kurtoğlu S, Başţuğ O. Mini puberty and its interpretation. Turk Pediatri Ars 2014; 49: 186–191. doi: 10.5152/tpa.2014.2038
16. Nordenström A. Potential impact of mini–puberty on fertility. Ann Endocrinol (Paris) 2022; 83: 250–253. doi: 10.1016/j.ando.2022.06.002
17. Garagorri JM, Rodríguez G, Lario–Elboj AJ, et al. Reference levels for 17–hydroxyprogesterone, 11–desoxycortisol, cortisol, testosterone,

dehydroepiandrosterone sulfate and androstenedione in infants from birth to six months of age. Eur J Pediatr 2008; 167: 647–653. doi: 10.1007/s00431-007-0565-1
18. Kida A, Nakada Y, Kitano H, Ueno Y. Extreme mini–puberty in an extremely low-birth-weight infant. Pediatr Int 2021; 63: 1245–1247. doi: 10.1111/ped.14586
19. Busch AS, Ljubicic ML, Upners EN, et al. Dynamic Changes of Reproductive Hormones in Male Minipuberty: Temporal Dissociation of Leydig and Sertoli Cell Activity. J Clin Endocrinol Metab 2022; 107: 1560–1568. doi: 10.1210/clinem/dgac115
20. Shima Y. Functional Importance of Mini–Puberty in Spermatogenic Stem Cell Formation. Front Cell Dev Biol 2022; 10: 907989. doi: 10.3389/fcell.2022.907989
21. Kaplowitz P. Diagnosing children with signs of early puberty: knowing when to test and when to just monitor. Expert Rev Endocrinol Metab 2016; 11: 297–299. doi: 10.1080/17446651.2016.1191350
22. Kuiri–Hänninen T, Sankilampi U, Dunkel L. Activation of the hypothalamic-pituitary-gonadal axis in infancy: minipuberty. Horm Res Paediatr 2014; 82: 73–80. doi: 10.1159/000362414
23. Kuiri–Hänninen T, Haanpää M, Turpeinen U, et al. Transient postnatal secretion of androgen hormones is associated with acne and sebaceous gland hypertrophy in early infancy. J Clin Endocrinol Metab 2013; 98: 199–206. doi: 10.1210/jc.2012-2680
24. Lucaccioni L, Trevisani V, Boncompagni A, et al. Minipuberty: Looking Back to Understand Moving Forward. Front Pediatr 2021; 8: 612235. doi: 10.3389/fped.2020.612235
25. Herane MI, Ando I. Acne in infancy and acne genetics. Dermatology 2003; 206: 24–28. doi: 10.1159/000067819
26. Bragonier R, Karabouta Z, Crowne L. Transient scrotal hair growth in infancy. Postgrad Med J 2005; 81: 412. doi: 10.1136/pgmj.2004.029892
27. Janus D, Wojcik M, Tyrawa K, Starzyk J. Transient isolated scrotal hair development in infancy. Clin Pediatr (Phila) 2013; 52: 628–632. doi: 10.1177/0009922813480845
28. Leung AK, Hegde HR, Stephure DK. Scrotal hair in identical twin infants. Int J Dermatol 2005; 44: 1042–1044. doi: 10.1111/j.1365-4632.2005.02264.x
29. Zimmerman C, Houk CP, Lee PA. Scrotal Hair in Infancy: Outcome Verification of an Isolated Condition Needing Minimal Assessment. Clin Pediatr OA 2018; 3: 138. doi: 10.4172/2572-0775.1000138
30. Tatlı ZU, Gul U, Hatipoglu N, Kurtoglu S. Scrotal hair in infancy: A case series. Pediatr Dermatol 2017; 34: e331–e333. doi: 10.1111/pde.13284
31. Sentchordi Montane L, Quintanar Rioja A, Ayala Bernardo de Quirós L, et al. Vello escrotal en lactantes [Scrotal hair in infants]. An Pediatr (Barc) 2008; 68: 146–148. doi: 10.1157/13116231
32. Dutta DK, Dutta I. Desogestrel mini pill: is this safe in lactating mother? J Indian Med Assoc 2013; 111: 553–555