

## An intriguing case of precocious puberty due to an ovarian mass in an infant

Ciekawy przypadek przedwczesnego dojrzewania płciowego spowodowanego guzem jajnika u niemowlęcia

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### Abstract

We present a rare occurrence of precocious puberty (PP) probably due to an autonomous ovarian cyst in a 15-month-old girl who presented to us with growth spurt, breast and pubic hair development, and vaginal bleeding over the last few months. The clinical presentation was suggestive of central precocious puberty (CPP). However, the rapid progression of pubertal changes and occurrence of menarche at breast Tanner stage 2 indicated peripheral precocious puberty (PPP). Due to uncertainty of clinical diagnosis, investigations were conducted for CPP as well as PPP. The basal and peak stimulated LH concentrations were  $< 0.3$  IU/l and  $< 2$  IU/l, respectively, indicating PPP. However, the peak LH : FSH ratio was  $> 1$ , which is consistent with CPP. Abdominal imaging revealed an ovarian mass, which was laparoscopically excised, but the true nature of the mass could not be ascertained because the excised specimen showed only haemorrhage and features of ovarian torsion on histopathological examination. Regression of pubertal development occurred over a three-month period postoperatively.

### Key words:

precocious puberty, pseudopuberty, central precocious puberty, autonomous ovarian cyst.

### Streszczenie

W pracy przedstawiono rzadki przypadek przedwczesnego dojrzewania płciowego (PP) spowodowanego prawdopodobnie autonomiczną torbielą jajnika u 15-miesięcznej dziewczynki, u której stwierdzono przyspieszony wzrost, rozwój sutków i owłosienia łonowego oraz krwawienie z pochwy w ciągu ostatnich kilku miesięcy. Obraz kliniczny sugerował centralne przedwczesne dojrzewanie płciowe (CPP). Jednak szybki postęp zmian okresu dojrzewania i wystąpienie pierwszej miesiączki w drugim stadium rozwoju według skali Tannera wskazywały na obwodowe przedwczesne dojrzewanie płciowe (PPP). Ze względu na niepewność diagnozy klinicznej przeprowadzono badania zarówno pod kątem CPP, jak i PPP. Stężenia podstawowe i szczytowe stymulowanej lutropiny (LH) wynosiły odpowiednio  $< 0,3$  IU/l i  $< 2$  IU/l, wskazując PPP. Aczkolwiek szczytowy stosunek LH do FSH  $> 1$  był zgodny z CPP. Obrazowanie jamy brzusznej wykazało guza jajnika, który został wycięty laparoskopowo, ale nie można było ustalić prawdziwej natury guza, ponieważ pobrany wycinek wykazał jedynie krwawienie i cechy skrętu jajnika w badaniu histopatologicznym. Regresja rozwoju pokwitania nastąpiła w ciągu 3 miesięcy po operacji.

### Słowa kluczowe:

przedwczesne dojrzewanie płciowe, rzekome przedwczesne dojrzewanie płciowe, przedwczesne dojrzewanie centralne, autonomiczna torbiel jajnika.

## Introduction

Precocious puberty (PP) is classified into gonadotropin-dependent, also known as central (or true) PP (CPP), and gonadotropin-independent or peripheral (or pseudopuberty) PP (PPP). Central PP is more common than PPP, with an estimated occurrence of approximately 1 in 5000–10,000 in the general population [1]. In girls, PPP is usually due to increased peripheral oestrogen production from an autonomous ovarian cyst, a germ cell tumour, or McCune Albright syndrome [1, 2]. Although ovarian cysts occur commonly (2–5% of prepubertal girls), only 5% secrete oestrogens, and the consequent estimated risk of PPP is 1 in 400 (0.25%) [1]. Autonomous ovarian cysts may occur at any age, and may regress spontaneously or after treatment and recur at a later age [1].

Very rarely, sustained oestrogen production from the cysts may lead to activation of hypothalamic-pituitary-ovarian (HPO) axis and cause CPP [1, 3]. The occurrence of CPP is usually observed in girls who suffer recurrences of ovarian cysts and may require surgical removal or gonadotropin-releasing hormone agonist (GnRHa) therapy [3]. Such presentations are usually seen in girls older than five years [3]. We recently managed a girl with an ovarian mass, who had onset of PP below one year of age. The rarity of such an occurrence and the challenges in the aetiological workup prompted us to report this case.

## Case report

A 15-month-old girl was brought to us for evaluation of PP. Her parents had noticed enlargement of breast buds four months earlier, followed by the appearance of pubic and axillary hair almost simultaneously and episodic vaginal bleeding two months later. Until presentation, she had had two episodes of vaginal bleeding, each lasting for 4–5 days. Her parents also reported a noticeable growth spurt over the last four months. She had no history of behavioural change, headache, visual disturbances, seizures, head injury, cranial irradiation, abdominal pain, or distension. There was no history of any drug intake or use of oestrogen in the child or by any of the family members. She weighed 2.75 kg at birth and was otherwise developmentally normal.

On examination, her weight was 10.8 kg and height 82.0 cm, with 0.30 and 1.63 z-scores, respectively, on WHO growth charts, 2007. She did not have goitre, café-au-lait spots, adenoma sebaceum, neurofibromas, or bony deformities. Her systemic and genitalia examination was unremarkable. The Tanner stage was B2, P3, and A+ (Fig. 1A–C). Her visual field and acuity were normal. The bone age (BA) was advanced at three years (Greulich and Pyle's method). A clinical diagnosis of CPP was made initially.

Laboratory investigations revealed normal basal serum concentrations of luteinising hormone (LH) (0.1 IU/l, normal range 0.01–3.5 IU/l) and follicle stimulating hormone (FSH) (0.1 IU/l, normal range 0.12–8.7 IU/l). Serum oestradiol (E2), prolactin, triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) levels were 5 pg/ml (normal range 8.7–21.7 pg/ml),

16.1 ng/ml (normal range 4.79–23.3 ng/ml), 1.08 ng/ml (normal range 0.8–2.0 ng/ml), 6.34 µg/dL (normal range 4.8–12.7 µg/dl), and 1.29 mIU/ml (normal range 0.27–4.7 mIU/ml), respectively. Serum α-fetoprotein (α-FP) and human chorionic gonadotropin (hCG) concentrations were 2.3 ng/ml (normal < 7 ng/ml) and < 0.1 IU/l (normal ≤ 0.8 IU/l), respectively.

Since basal LH levels were < 0.3 IU/l, a GnRH stimulation test was performed after injecting 100 µg of aqueous triptorelin acetate. The stimulated serum LH concentrations were 1.02, 1.30, 1.51, and 1.44 IU/l at 30, 60, 90, and 120 minutes, respectively; the corresponding FSH concentrations were 0.63, 0.87, 1.02, and 1.09 IU/l, respectively. The low stimulated values of LH (the cut-off for diagnosis of CPP is > 5 IU/l) suggested PPP. However, the peak LH : FSH ratio of > 1 favoured CPP. In view of the “mixed” response to GnRH stimulation, further aetiological investigations for both CPP and PPP were planned.

The contrast-enhanced magnetic resonance imaging (CEMRI) of the brain was normal. The pelvic ultrasonogram revealed a heterochoic mass measuring 5.4 × 5.0 cm in the left adnexal location. The uterus measured 2.5 × 1.5 × 2.0 cm. Pelvic CEMRI showed a heterogeneous mass measuring 5.1 × 5.1 × 5.8 cm in the mid-abdomen extending from the lower margin of the L2 vertebral body to the lower margin of the L5 vertebral body along with a curved structure along the left lateral margin of the lesion, and peripheral haemorrhage suggestive of a non-enhancing, enlarged ovary with torsion (Fig. 2a). Serum adrenocorticotropin, cortisol, dehydroepiandrosterone sulphate, growth hormone, testosterone, and progesterone were all within normal range for the child's age.

The child underwent laparoscopic left salpingo-oophorectomy. Per operatively, the left ovary was found to be grossly enlarged with a complete twist of the pedicle and was densely adherent to surrounding structures (Fig. 2b). The histopathological examination of the excised mass showed extensive areas of haemorrhagic infarction, fibrocollagenous tissue, and hemosiderin laden macrophages with the fallopian tube adherent to the haemorrhagic mass (Fig. 2c). There were focal areas of calcification. No tumour tissue was identified. These features were consistent with ovarian torsion.

The child's parents started noticing regression of secondary sexual characteristics two months after surgery. There was no recurrence of vaginal bleeding. At three-month follow up, breast Tanner stage was B1 and serum LH, FSH, and E2 concentrations were 0.1 IU/l, 1.7 IU/l, and < 5 pg/ml, respectively. At her latest evaluation at three years of age, her weight and height were 14.8 kg (0.44 z-score) and 94.4 cm (–0.28 z-score), respectively. BA was three years.

## Discussion

Our case presented a diagnostic challenge in that the appearance of secondary sexual characteristics was in consonance, and hence the initial consideration was CPP. However, the rapidity of progression and occurrence of menarche at breast Tanner stage 2, which usually occurs at breast tanner



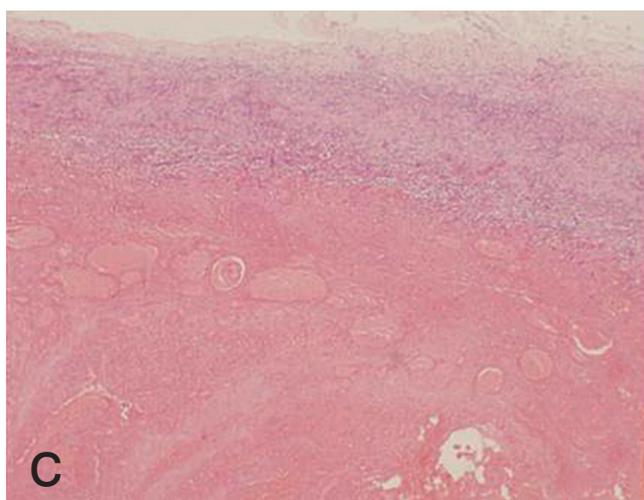
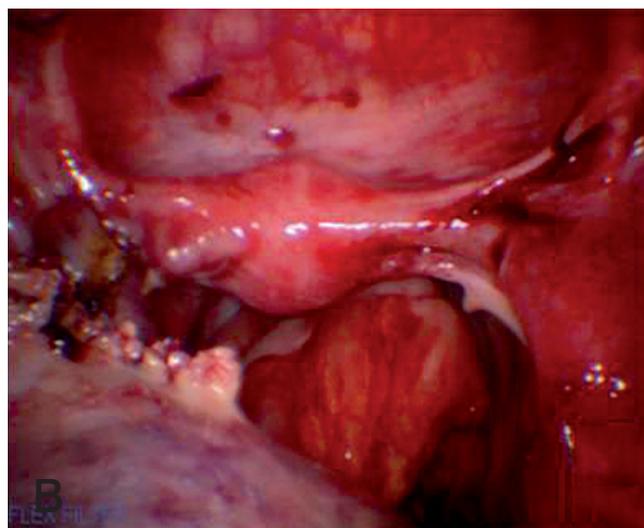
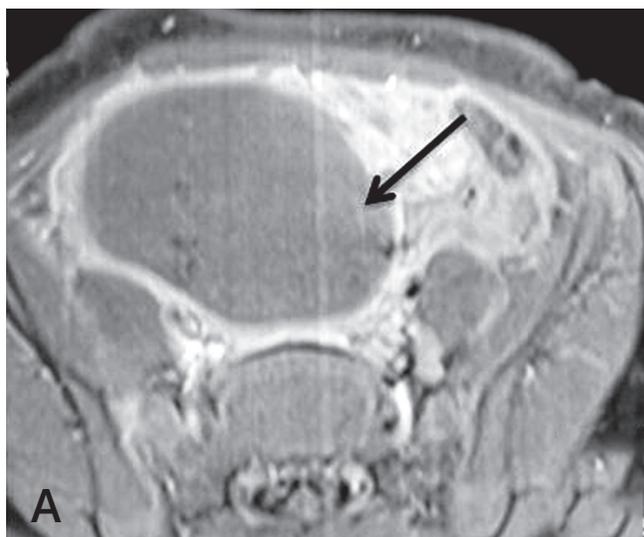
**Figure 1A–C.** Clinical photographs of the infant showing Tanner staging at the time of initial presentation

stage 3 or 4 in normal pubertal development, was a clue to PPP [1]. Such a rapid progression is due to acute exposure to oestrogens, usually from an ovarian source, most commonly due to an autonomous ovarian cyst [1]. The patients usually have high concentrations of serum oestrogens at the time of presentation [1]. The low serum oestradiol in our patient could be due to the change in the functional status of the ovarian mass. The occurrence of vaginal bleeding in most cases of autonomous ovarian cysts is due to oestradiol withdrawal, which usually happens after cyst resolution [1]. The presence of haemorrhagic infarction and features of ovarian torsion on histopathology in our patient also indicated non-functionality. We presume that our patient had an autonomous ovarian cyst that produced high concentrations of oestrogens, initially resulting in PP and fast skeletal maturation followed by haemorrhagic infarction causing oestrogen withdrawal bleeding. The rudimentary ovarian tissue on histopathology suggests that the

ovary may have become necrosed, as happens generally in children with ovarian torsion [4]. The occurrence of ovarian torsion in our patient also indicates the presence of a pre-existing ovarian pathology, most commonly an ovarian cyst [4].

The results of GnRH test were equivocal in our patient. The LH : FSH ratio of  $> 1$  is rare in girls under three years of age [5]. Such a ratio may rarely be observed in patients with untreated PPP and is due to chronic androgen excess that may activate the HPO axis and cause CPP [6]. However, the overall very low response of LH and FSH to the GnRH stimulus makes CPP less likely in our patient.

Autonomous functional ovarian follicular cysts are the most common cause of PPP in girls [1, 3]. Ovarian neoplasms are rare in children and include germ cell tumours, surface epithelial stromal tumours, sex cord–stromal tumours (SCSTs), and miscellaneous tumours such as gonadoblastoma, malignant lymphoma, small cell carcinoma, and soft-tissue tumours [7, 8].



**Figure.** A) Pelvic CEMRI showing a midline mass periperipheral hemorrhage and features of ovarian torsion. B) Per-operative photograph of the mass. C) Microphotograph showing extensive hemorrhage and infarction of the ovary with a thin rim of normal tissue at the periphery. Hematoxylin-eosin stain (original magnification  $\times 20$ )

The oestrogen-producing ovarian tumours such as SCSTs and gonadoblastomas may cause isosexual PPP as an initial manifestation [7, 8]. The tumour markers are usually elevated in these cases [8]. The rare causes of PP such as prolonged untreated hypothyroidism were ruled out by investigations in our case [9, 10].

The presence of features of torsion on imaging and histopathology were unexpected because the classical clinical features of ovarian torsion such as abdominal pain, nausea or vomiting, and abdominal tenderness were absent in our patient [4]. Another interesting feature was the accelerated skeletal maturation caused by HPO axis activation, which happened during initial presentation. Such a phenomenon is usually observed in patients who have prolonged exposure to oestrogens and at least two episodes of autonomous cyst formation [1, 3].

The decision for surgical removal was taken primarily because of suspicion of malignancy because the exact nature of the ovarian mass could not be ascertained after initial investi-

gations, and because of features of ovarian torsion on imaging. a rapid progression of pubertal changes with height acceleration and BA advancement at presentation favoured a malignant mass [7, 8]. However, a conservative approach may be preferred in cases of ovarian cysts because surgical treatment does not always prevent recurrence [1, 3]. The current recommendations also favour attempts to perform ovarian-sparing resections even for malignant ovarian tumours [8].

The occurrence of true PP in girls below one year of age is rare, and most cases described in the literature were due to an ovarian neoplasm [7, 8, 11, 12]. To the best of our knowledge, ours is the first infant to develop PP due to an autonomous ovarian cyst.

In conclusion, a rapidly progressive precocious puberty in an infant may occur due to an autonomous ovarian cyst. The normal oestrogen and gonadotropin levels at the time of presentation may indicate non-functionality of the cyst due either to auto-regression or ovarian torsion and haemorrhage.

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