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# Autonomous Ovarian Cysts in a Girl: A Rare Case of Precocious Puberty

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**ABSTRACT**

Precocious puberty (PP) is defined by development of secondary sexual characteristics before eight years old in girls. Autonomous ovarian follicular cysts in prepubertal girls are rare but the most common cause of gonadotropin-independent PP. Current management is debated.

We report a case of PP due to an autonomous ovarian cyst in a 3-year-old girl with a month history of vaginal bleeding and breast development; the patient underwent surgical intervention.

There is no consensus as to the superiority of surgical versus pharmaceutical management in the autonomous ovarian cysts in prepubertal girls. Surgical management should be deferred as long as possible to permit a spontaneous resolution of cysts. If a surgical intervention is made, conservation of normal ovarian tissue is mandatory.

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## Introduction

Precocious puberty (PP) is defined by development of secondary sexual characteristics before eight years old in girls. It is classified as gonadotropin-dependent, central precocious puberty (CPP) or true precocious puberty and peripheral or precocious pseudopuberty (PPP), that is gonadotropin-independent. In the majority of cases early puberty is of central origin, whereas if there is a peripheral hormonal secretion it can be classified as pseudoprecocious puberty. Autonomous functional ovarian follicular cysts in prepubertal girls are rare but the most common cause of gonadotropin-independent precocious puberty [1]. Current management of this condition is debated. We report a case of precocious pseudopuberty in a 3-year-old girl. A review of literature was performed.

## Case

A 3.5-year-old girl was brought to our hospital for evaluation of PP, with a month history of vaginal bleeding and breast development without other symptomatology. Family history was negative for endocrinopathy or early sexual development. On physical examination, she had bilateral enlarged breasts (Tanner stage 3) with minor pigmentation of areola (Figure 1). No development of pubic or axillary hair were observed. The clitoris was of normal size according to age. No signs of McCune-Albright syndrome (MAS) neither café-au-lait spots, adenoma sebaceous, neurofibromas or bony deformities were observed. On initial laboratory evaluation, the basal plasma estradiol level was 1292 pg/ml, the plasma luteinizing hormone (LH) was <3 mIU/ml and the follicle-stimulating hormone (FSH) was < 3 mIU/ml. Serum tumor markers were normal. Bone age was estimated at 3.5 years.

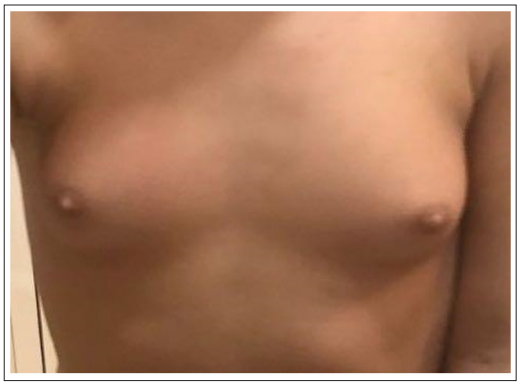

**Figure 1:** Physical Examination at the Presentation; Bilateral Enlarged Breasts (Tanner Stage 3)

The first ultrasonographic study of the abdomen showed a 22 x 24 x 28 mm cystic mass in the left adnexal location; the uterus was enlarged, with its length of 50 mm and an endometrial line visualized. The magnetic resonance imaging (MRI) of the brain was normal, no anomalies of pituitary gland was observed. Pelvic MRI showed a normal right ovary and a left cystic polylobulated septated ovarian mass, surrounded by physiological ovarian follicles.

A gonadotropin releasing hormone (GnRH) stimulation test revealed a prepubertal response with no appreciable rise of plasma LH or FSH. The patient was followed with both clinically and laboratory evaluation for two month and no variations or improvements are observed. Because the psychological distress of the family and the persistence of clinical symptoms, the patient underwent surgical intervention. A laparoscopic assisted transumbilical extracorporeal ovarian cystectomy was performed (Figure 2, Figure 3). An intraoperative frozen section excluded the possibility of malignancy. Definitive pathologic evaluation demonstrated benign follicular cysts.

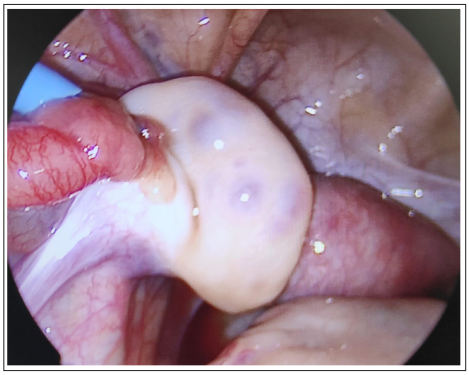

**Figure 2:** Laparoscopic Finding Shows a Left Cystic Polylobulated Ovarian Mass

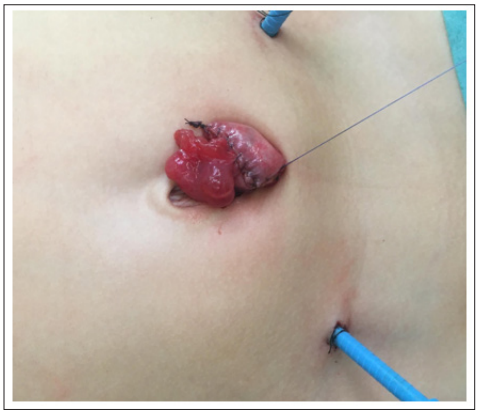

**Figure 3:** Appearance of The Ovary After Transumbilical Extracorporeal Ovarian Cystectomy

Her postoperative course was uneventful; the plasma estradiol level at 24 hour after surgery was < 24.52 pg/ml and vaginal bleeding was stopped. She was discharged on postoperative day 1. At one month follow-up, breast development was almost completely regressed (Figure 4), and estradiol concentration had returned to a prepubertal range (< 5 pg/ml). At follow-up of 6 months, no relapses are observed.

**Figure 4:** Physical Examination at One-Month Follow-Up: Breast Development was almost Completely

**Discussion**

Ovarian cysts occur in 2-5% of prepubertal girls. As a result of exposure to maternal hormones, most neonatal ovarian cysts spontaneously resolve during the first months of life [2]. Autonomous ovarian cysts are present in 5% of the girls with ovarian cysts and cause PPP [1] . The ranging age where PPP in girls may develop is from 2 years old, the upper limit considered for maternal estrogen effect or for increased levels of gonadotropins after birth due to immaturity of the hypothalamic-pituitary-ovarian axis, to 8 years old, the cut off for normal pubertal development [3]. PPP is gonadotropin-independent and it is less common than CPP. It is important to distinguish an autonomous ovarian cyst from cysts that are associated with secondary sexual changes in CPP [3]. The diagnosis of PPP due to autonomous ovarian cysts is based on the history, clinical presentation, laboratory findings, and imaging. It is a rare condition and there are not many published reports about it [3]. A search conducted on Pubmed, Scopus and Web of Science showed only 33 cases of PPP due to autonomous ovarian cysts, with the characteristic described in Table 1.

**Table 1: Summary of Reported Cases of Girls with Autonomous Ovarian Cysts**

| | Authors (Year Reported) | Age (years) | Breast development | Vaginal discharge or bleeding | Pubic hair | Cyst diameter (mm) | Management | Number of episodes | Time of total resolution (months) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Kosloske et al. [4] (1984) | 3.7 | Y | Y | N | 9 | Oophorectomy | 1 | - |
| 2 | Kosloske et al. [4] (1984) | 6.0 | Y | N | N | 11 | Cystectomy | 1 | - |
| 3 | Lyon et al.[5] (1985) | 2.8 | Y | Y | Y | 38 | Cystectomy | 1 | - |
| 4 | Lyon et al.[5] (1985) | 4.6 | Y | Y | N | - | Conservative | 3 | 23 |
| 5 | Lyon et al.[5] (1985) | 4.2 | Y | Y | N | 27 | Conservative | 2 | 1 |
| 6 | Lyon et al.[5] (1985) | 5.0 | Y | Y | N | - | Oophorectomy | 1 | - |
| 7 | Fakhry et al.[6] (1988) | 5.0 | Y | Y | N | 33 | Cystectomy | 1 | - |
| 8 | Fakhry et al.[6] (1988) | 6.4 | Y | Y | N | 55 | Conservative | 1 | 2 |
| 9 | Millar et al.[1] (1993) | 3.0 | Y | Y | N | 27 | Conservative | 1 | - |
| 10 | Millar et al.[1] (1993) | 4.0 | Y | N | N | 55 | Conservative | 1 | - |
| 11 | Millar et al.[1] (1993) | 4.5 | N | Y | N | 45 | Cystectomy | 2 | 6 |
| 12 | Millar et al.[1] (1993) | 8.0 | Y | N | N | 50 | Cystectomy | 1 | - |
| 13 | Rodriguez-Macias et al.[7] (1999) | 6.9 | Y | Y | Y | 65 | Oophorectomy | 1 | 1 |
| 14 | Rodriguez-Macias et al.[7] (1999) | 5.9 | Y | Y | Y | 30 | Conservative | 2 | 11 |
| 15 | Rodriguez-Macias et al.[7] (1999) | 2.2 | Y | N | N | 25 | Conservative | 1 | 1 |
| 16 | Rodriguez-Macias et al.[7] (1999) | 5.4 | Y | Y | Y | 50 | Conservative | 2 | 2 |
| 17 | Rodriguez-Macias et al.[7] (1999) | 2.6 | Y | Y | Y | 46 | Conservative | 5 | 26 |
| 18 | Engiz et al.[8] (2008) | 8.0 | Y | Y | N | 54 | Conservative † | 2 | 6 |
| 19 | de Sousa et al.[9] (2008) | 5.3 | Y | Y | N | 40 | Conservative † | 5 | 20 |
| 20 | de Sousa et al.[9] (2008) | 4.7 | Y | Y | N | 60 | Oophorectomy | 1 | - |
| 21 | de Sousa et al.[9] (2008) | 6.3 | Y | Y | N | 30 | Conservative † | 3 | 12 |
| 22 | de Sousa et al.[9] (2008) | 4.7 | Y | Y | N | 35 | Conservative † | 3 | 12 |
| 23 | Brauner et al.[10] (2010) | 3.3 | Y | Y | N | 50 | Conservative † | 1 | 5 |
| 24 | Brauner et al.[10] (2010) | 5.6 | Y | Y | Y | 60 | Conservative † | 2 | 7 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 25 | Brauner et al.[10] (2010) | 6.6 | Y | Y | N | 41 | Conservative † | 1 | 3 |
| 26 | Chae and Rheu[11] (2013) | 5.9 | Y | Y | N | 54 | Cystectomy | 1 | - |
| 27 | Dhivyalakshmi et al.[12] (2014) | 4.0 | Y | Y | N | 45 | Oophorectomy | 1 | - |
| 28 | Dhivyalakshmi et al.[12] (2014) | 4.5 | Y | Y | N | 30 | Conservative | 1 | - |
| 29 | Dhivyalakshmi et al.[12] (2014) | 2.5 | Y | Y | * | 20 | Conservative | 1 | - |
| 30 | Honda et al.[13] (2016) | 2.8 | Y | Y | Y, * | 16 | Conservative | 3 | 50 |
| 31 | Chehade et al.[14](2017) | 6.5 | Y | Y | N | 42 | Conservative | 1 | 2 |
| 32 | Fu et al.[15] (2019) | 5.0 | Y | Y | N | 32 | Conservative | 1 | 1 |
| 33 | Fu et al.[15] (2019) | 2.3 | Y | Y | Y, * | 45 | Cystectomy | 1 | - |

Y = yes; N = no; * = Axillary Hair; † = Medical Treatment

Like in our case, among clinical symptoms, girls present with signs of oestrogenisation, such a rapid bilateral breast development and vaginal discharge (or bleeding), reported in 97% and 88% respectably in the literature. Other rarer possible signs are pubic or axillary hair development, reported in 27% of the cases, and swelling of labia minor [4-15].

The laboratory findings in an autonomous ovarian cyst are elevated estrogen levels with low gonadotropins. As in our case, highly elevated estrogen levels with low basal GnRH stimulated gonadotropin levels suggest PPP. In most cases, like our case, bone age is not advanced [4-15]. Moreover, in our case MRI examination of the pituitary gland confirmed a gonadotropin-independent source of estrogen.

Pelvic ultrasound examination can demonstrate unilateral or bilateral ovarian cyst. The diameter of the ovarian cyst is important, as a diameter less than 1 cm is clinically insignificant and represents follicular activity within the prepubertal ovary [1]. Larger cysts in prepubertal girls are a pathological sign and should be correlated closely with other clinical and biochemical data. The size of cysts described in literature varied in the range 9-65 mm , with an average of 39 mm [4-15].

In our case, the pelvic MRI showed the ovarian cyst surrounded by physiological ovarian follicles; at ultrasound scan, the presence of normal ovarian tissue adjacent to the cyst or tumor tissue it is the "ovarian crescent sign", that may be used to help exclude an invasive ovarian malignancy in adnexal mass [16]. In our cases, all serum tumor markers were negative.

Autonomous ovarian cysts represent a self limiting disorder and no treatment often is necessary. They can go to a spontaneous regression after 2 or 3 months from the onset of symptoms. In some cases, no regression is observed and for this reason management is debated. The possibilities included surgical treatment and conservative treatment, that can include a "wait & see" approach or medical treatment [3, 4].

The main indications to surgery are persistence of clinical symptoms, increasing of ovarian cyst dimensions, torsion or recurrence [3,4]. In 5 cases reported in the literature, the patient underwent an oophorectomy; in some of these cases the surgical indication for this procedure is not clear, but in our opinion it is not justifiable, unless malignancy is suspected [4,5,7,9,12]. Sometimes, a parents and child distress without resolution of clinical symptoms in 2 or 3 months can encourage a surgical treatment, such as in our case [7-9]. The data on the clinical course of our patient therefore, confirms the option of surgery like a valid option. Furthermore, always avoiding an oophorectomy, the choice of an assisted laparoscopy is an excellent choice because it allows to explore both ovaries and perform the cystectomy in complete safety through a transumbilical extracorporeal surgery; all this with an excellent aesthetic result.

From the literature review it emerged that 21 girls (64%) were treated conservatively [4-15]. At the follow-up, no relapses are observed in our patient. In literature, one or more relapses were observed in 11 cases among the girls treated conservatively and in only one case underwent a cystectomy. Time at relapse varies from 1 month to 50 months, with a median time of 6 months [4-15].

Recurrent autonomous ovarian cyst can be a symptom of the McCune-Albright syndrome (MAS), which in its classic form consists of at least 2 features of triad: polyostotic fibrous dysplasia, café au last skin pigmentation and autonomous endocrine hyperfunction. MAS is due to post zygotic activating recurrent mutations in the guanine nucleotide binding protein (G protein) alpha subunit [17]. Precocious pseudopuberty is usually the first manifestation of MAS in children. Clinical evidence for MAS may appear years later, in the course of recurrent autonomous cysts; for this reason it is necessary a large follow-up, with clinical evaluation and molecular studies in some cases [13]. In case of clinical suspicion, a molecular DNA analysis must be indicated to confirm the diagnosis. From the literature review, 3 out of 33 cases of autonomous ovarian cysts were found to be MAS [7,13].

PPP in girls with MAS is usually treated with aromatase inhibitors; currently the third generation aromatase inhibitors are used, such as anastrozole and letrozole [18]. Other options used in MAS are tamoxifen and cyproterone acetate, like estrogen receptor agonists [10,19,20].

In fact, the medical treatment is described above all in cases of progression to CPP. Similar treatment options are reported in girls with autonomous ovarian cysts but only case or limited series are reported [9,10]. Out of the total 7 cases that emerged from the review of the literature in which a pharmacological treatment was carried out, 5 of them are cases in which the complete resolution of the PPP occurred after several months, on average 9.2 months (range 3-20 months ) [8-10]. In 3 cases the Authors opted for treatment with GnRh agonists after onset of CPP and in other 3 cases the treatment with cyproterone acetate seemed to be more effective ; it is still only three cases found in the literature [9, 10].

## Conclusion

In conclusion, there is no consensus as to the superiority of surgical versus pharmaceutical management in the autonomous ovarian cysts in prepubertal girls. Surgical management should be deferred as long as possible to permit a spontaneous resolution of autonomous ovarian cysts. However, if a surgical intervention is made, a conservation of normal ovarian tissue is mandatory. A large follow-up is always necessary.

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