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*Original Article*

## *Ovarian Tumors in Children: An 11-year Review*

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### **Abstract**

**Background:** Ovarian tumors in girls are important part of gynecological oncology. They may produce a wide range of clinical conditions according to nature, size and a time period of presentation.

**Objective:** To analyze the data of patients with ovarian tumors treated at Queen Sirikit National Institute of Child Health and compare between benign and malignant characteristics.

**Materials and Methods:** A retrospective study was conducted by reviewing of medical records of the patients with ovarian tumors treated at Queen Sirikit National Institute of Child Health between 2007 and 2017. Patients' data including demographics, clinical presentations, investigations, type of ovarian tumors, operative procedures and outcomes were collected and analyzed.

**Results:** Eighty-six patients were surgically treated for ovarian tumors during the study period. Benign and malignant tumors were classified in 74 (86%) and 12 cases (14%) respectively. Differences in clinical presentation, palpable abdominal mass was more frequent in malignant than benign masses (91.7% : 67.9%;  $p = 0.023$ ). Precocious puberty and abnormal vaginal bleeding were specific presentation in malignant tumor only. Cystic masses were more frequent in benign than malignant tumors (48.6% : 8.3%;  $p = 0.002$ ) and solid masses were more common in malignant than benign ovarian tumors (33.3% : 1.4%;  $p = 0.001$ ). Tumor markers including alpha-fetoprotein (AFP), b-human chorionic gonadotrophin (b-hCG) and lactic dehydrogenase (LDH) significantly elevated in malignant GCTs and SCSTs ( $p < 0.05$ ). Sizes of the tumors were not differentiated benign from malignant ovarian tumors. Almost all of the 84 cases with ovarian tumors were treated by oophorectomy or salpingo-oophorectomy. All 74 benign cases were alive. One case of the malignant group with T-cell lymphoma died one month after surgery and 4 cases lost to follow-up. The 2-year survival rate was 58.3%.

**Conclusion:** Benign ovarian tumors had more common occurrence 6 times than malignant ones. Presentations of palpable abdominal mass, solid tumor from imaging and elevation of serum tumor markers were strongly suspicious of malignant tumors of the ovary.

**Keywords:** Ovarian tumors, Children, Epithelial cell tumor, Germ cell tumor, Sex cord and stromal tumor, Cystadenoma, Teratoma, Granulosa-theca cell tumor, Follicular cyst

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## INTRODUCTION

Ovarian neoplasms are uncommon in the pediatric population but ovarian tumors in children and adolescent girls constitute an important part of gynecological oncology with an estimated incidence of 2-6 cases per 100,000 girls per year<sup>1</sup>. They may produce a wide range of clinical conditions according to their nature size and a time period of presentation. In general, 10% to 20% of all ovarian tumors in children are malignant<sup>2-6</sup> and they represent approximately 3% of cancers in girls with age under 15 years old<sup>7</sup>. World Health Organization has classified these tumors into 3 main groups based on derivation of embryonic histology, such as tumor of epithelial cells, germ cells and mesenchymal cells (sex cord and stromal cell tumor – SCST). Other malignancies may involve ovaries as the primary or secondary target organs, for example lymphoma and leukemia<sup>8,9</sup>.

In Thailand, there are minimal data regarding ovarian tumors in children. Herein, we are interested to review our experience of pediatric ovarian tumors in an 11-year period. The aim of this study was to analyze the data of our patients and compare between benign and malignant characteristics.

## MATERIALS AND METHODS

This study was retrospectively reviewed recording data of all female children aged under 15 years old who were diagnosed and underwent surgical procedures for management of ovarian tumors during January 2007 to December 2017 at Queen Sirikit National Institute of Child Health (QSNICH). All of the patients had histologic confirmation of various types of ovarian tumor from National Institute of Pathology. The patients, who were surgically treated due to ovarian tumors from the other hospital, were excluded from the study.

All of patients' data were obtained from the medical records including demographics, clinical presentations, imaging characteristics, tumor markers, operative findings and procedure, histopathology and outcomes of management. The study began after the proposal had been approved from the Ethic Committees of the institute (Document No.61-030).

The patients' personal information, clinical presentations, investigations and outcomes were analyzed using descriptive statistics with number, percent, range, mean and standard deviation (SD). Univariable associations were assessed by the Chi-square test for categorical

variables and using the Student t-test for continuous variables. A p-value of less than 0.05 was considered significant.

## RESULTS

Eight-six patients were enrolled in the study. Ovarian tumors were documented to be benign lesions in 74 patients (86%) and malignant lesions in 12 cases (14%). The ratio of benign to malignant ovarian tumors was 6:1.

Patients with benign and malignant tumors were found scattering in every age group (Table 1). Average ages at diagnosis of patients with benign and malignant tumors were not statistically different ( $7 \pm 4.2$  vs  $6.5 \pm 4.4$ ;  $p = 0.337$ ).

Palpable abdominal mass was the most common clinical presentation of both benign and malignant tumors, but it was more frequent in malignant than benign masses (91.7% vs 64.9%;  $p = 0.023$ ). Abdominal pain, nausea and vomiting were present in both groups with no different significance. Vaginal bleeding and precocious puberty were present only in one patient with malignant ovarian tumor (SCST). Positive findings of ovarian masses from prenatal ultrasound were proven to be benign lesion in every case.

Imaging investigations were begun with plain films of abdomen, ultrasound and computed tomographic (CT) scan. The obvious imaging characteristics of cystic mass were most common in benign tumor (Figure 1) while the findings of solid mass were most common in malignant tumor (Figure 2). These findings were considered statistically significant (Table 2). Imaging findings of mixed cystic and solid components, calcification in the mass and ascites could be found in benign and malignant lesions with no statistical difference. Torsion of benign ovarian tumor by ultrasound examination was noted in one case.

Assay of tumor markers was established for differentiation between benign and malignant lesions in many cases (55 in benign and 12 in malignant group). Normal serum alpha-fetoprotein (AFP) level is normally high in neonates and young infants. It gradually declines to normal level at 12 ng/ml/ at the age of 8 months old (set up normal level at our institute). Mean serum AFP levels of 55 benign lesions vs. 12 malignant lesions were 708.2 vs. 8454.8 ng/ml;  $p = 0.001$ . An elevation of serum AFP levels was noted in immature teratoma grade III (2 cases), mixed germ cell tumor (GCT) or teratoma

with yolk sac (endodermal sinus) tumors or malignant teratoma (2 cases) and dysgerminoma (1 case). Normal serum b-hCG level was < 5 mIU/ml at our institute. The mean serum b-hCG of benign vs. malignant group was 0.35 vs. 37.1 mIU/ml;  $p = 0.003$ . Elevation of serum b-hCG levels was noted in dysgerminoma (3 cases) and mixed GCT (1 case). Normal level of serum LDH at our institute was < 344 U/L. Mean serum LDH levels of benign and malignant groups were 690 vs. 4494.8 U/L;  $p = 0.012$ . Elevation of serum LDH level was noted in dysgerminoma (2 cases), mixed GCT (1 case) and granulosa thecal cell tumor (1 case).

All of the 86 patients underwent open laparotomy. Intraoperative findings revealed torsion of the ovarian tumors in 27 cases (31.4%) which were 15 with mature teratoma, 3 with malignant tumor and 9 with follicular and simple cysts. Diameter of the twisted tumors ranged from 4 to 28 cm (average 10.5 cm). They twisted in average 150 degrees from normal position. salpingo-oophorectomy was done in all of the 27 twisted ovarian tumors.

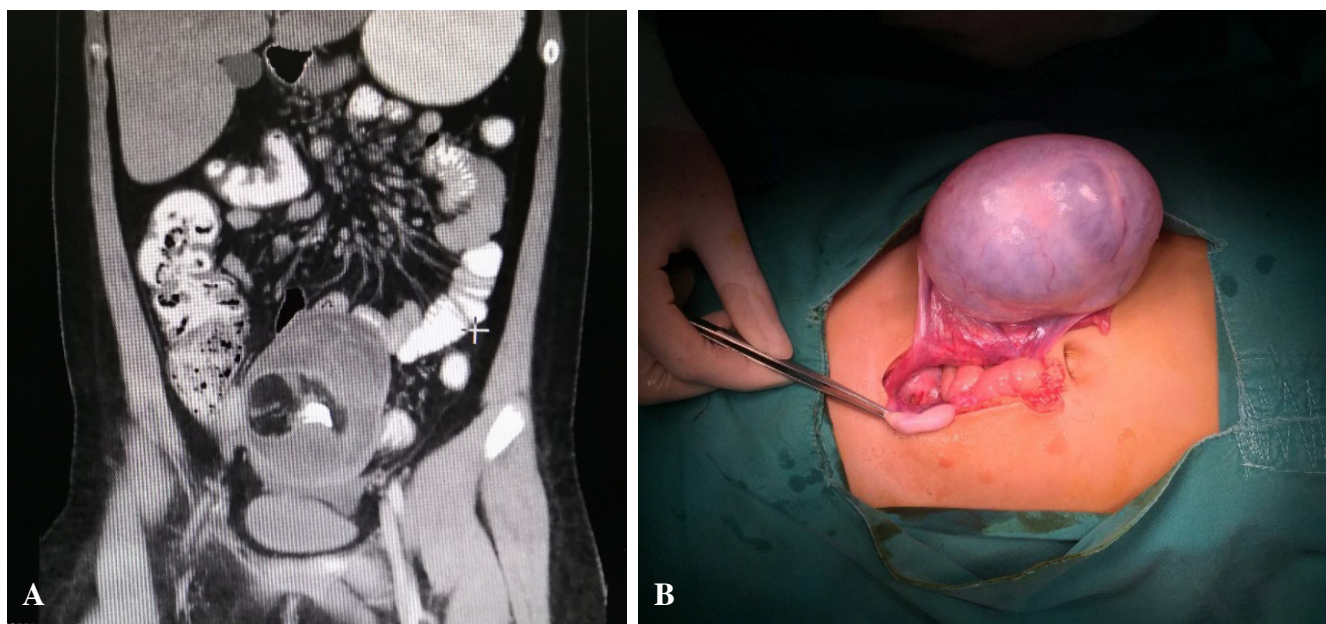
Operative procedures for the 86 patients were oophorectomy in 23 cases and salpingo-oophorectomy in 61 cases. Only ovarian biopsy was done in the remainder 2 cases because of bilateral simple ovarian cysts. Sizes of benign and malignant ovarian tumors were not statistically different (benign mean  $10.9 \pm 6.6$  cm, range 2.8 - 35 cm; malignant mean  $12.9 \pm 5.8$  cm, range 4.3 - 28 cm;  $p = 0.319$ ).

Postoperative course of all the 86 patients was uneventful. Mean length of hospital stay (LOS) was 7.5 days for the benign group and 16.4 days for the malignant group. LOS of the malignant group was longer than that of the benign group due to spending on chemotherapy administration. Pathological reports revealed type of ovarian tumors based on embryonic histology into 3 types with one miscellaneous tumor (Table 3). All of the epithelial cell tumors in 8 case were benign characteristics. Of the 51 cases with GCTs, 44 were benign (39 mature teratoma and 5 immature teratoma grade 1) and 7 were malignant (2 immature teratoma grad 3, 2 mixed GCTs and 3 dysgerminoma).

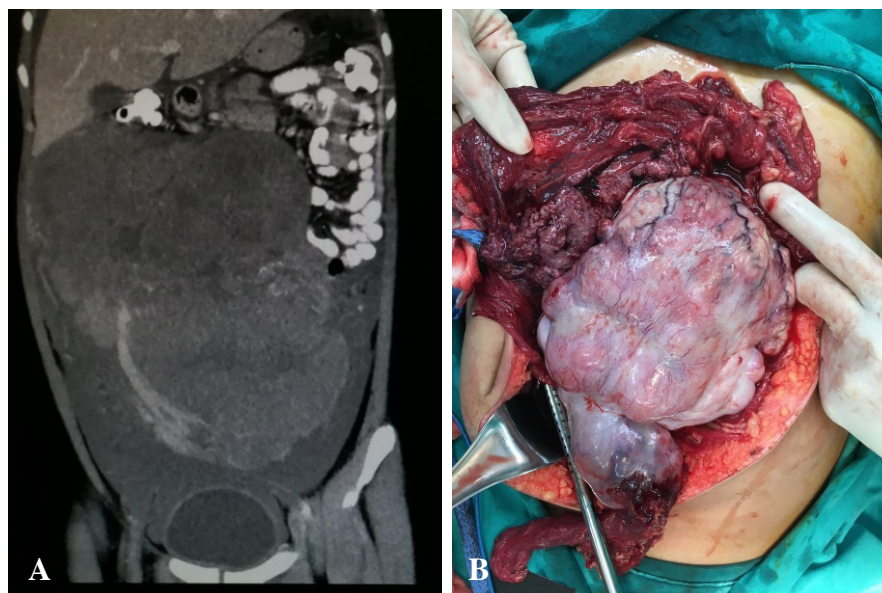
**Table 1** Comparison of demographic data and clinical presentations between patients with benign and malignant ovarian tumors

Patients' information	Benign group (N=74) cases (%)	Malignant group (N=12) cases (%)	p-value
<b>Age at diagnosis (years)</b>			
0 - 3	18 (24.3)	3 (25.0)	
3 - 6	11 (14.9)	2 (16.7)	
6 - 9	15 (20.3)	3 (25.0)	
9 - 12	16 (21.6)	1 (8.3)	
12 - 15	14 (18.9)	3 (25.0)	
range (mean $\pm$ SD)	0 - 15 (7 $\pm$ 4.2)	0.6 - 14 (6.5 $\pm$ 4.4)	0.337
<b>Clinical presentations</b>			
palpable abdominal mass	48 (67.9)	11 (91.7)	0.023
abdominal pain	22 (29.7)	2 (16.7)	0.321
nausea / vomiting	10 (13.5)	1 (8.3)	1.000
fever	4 (5.4)	1 (8.3)	0.547
vaginal bleeding	0	1 (8.3)	0.143
precocious puberty	0	1 (8.3)	0.270
presence of ovarian masses from prenatal ultrasound	12 (16.2)	0	0.053
<b>Side of the tumor</b>			0.111
right	37 (50.0)	8 (66.7)	
left	35 (47.3)	4 (33.3)	
bilateral	2(2.7)	0	





**Figure 1** A 12-year-old girl with mature teratoma; A, a cystic mass with calcification from a CT scan, B, a cystic mass from the operative finding.



**Figure 2** A 13-year-old girl with dysgerminoma and increased serum b-hCG level, A, CT abdomen with intravenous contrast showed ill-defined hypoechoic heterogeneous enhancing lobulated mass with ascites, B, solid multilobulated mass from the operative finding.

SCSTs were noted in 3 cases (juvenile granulosa-theca cell tumors) and all of them were malignant. Miscellaneous tumors included non-neoplastic ovarian mass (21 cases) and other malignant tumors (T-cell lymphoma and squamous cell carcinoma, one case each).

All of the 74 cases with benign tumors were alive. Mortality was noted in one of the 12 cases with malig-

nancy. She died one month after surgery due to bone marrow and brain metastasis from T-cell lymphoma. One case with dysgerminoma had tumor recurrence 3 months after surgery. She was sent to receive the second line chemotherapy at the other hospital and lack of communication later.

**Table 2** Comparison of imaging characteristics between benign and malignant ovarian tumors

Imaging findings	Benign (N=74) cases (%)	Malignant tumors (N=12) cases (%)	p-value
Cystic masses	36 (48.6)	1 (8.3)	0.002
Solid masses	1 (1.4)	4 (33.3)	0.001
Mixed cystic – solid masses	8 (10.8)	2 (16.7)	0.625
Calcification	17 (23.0)	3 (25.0)	0.554
Ascites	3 (4.1)	4 (33.3)	1.000
Torsion of the tumor	1 (1.4)	0	1.000

**Table 3** Classification of tumors in 86 pediatric patients based on pathohistology

Type of ovarian tumors	Benign (N = 74)		Malignant (N = 12)	
Epithelial cell N = 9 (10.5%)	- mucinous cystadenoma	5		
	- serous cystadenoma	3		
	- mixed mucinous-serous cystadenoma	1		
Germ cell N = 51 (59.3%)	- mature teratoma	39	- immature teratoma grade 3	2
	- immature teratoma grade 1	5	- dysgerminoma	3
			- mixed GCT	2
Sex cord and stromal cell N = 3 (3.5%)			- juvenile granulosa-theca cell tumors	3
Miscellaneous N = 23 (26.7%)	- follicular cyst	5	- T-cell lymphoma	1
	- simple cyst	16	- squamous cell carcinoma	1

Three case lost to follow-up one month after surgery. Seven cases with malignant tumor were alive now. The 2 -year survival rate was 58.3% (7 in 12 cases). Two cases were alive over than 5 years and 5 cases were doing well nearly 5 years after surgical treatment.

## DISCUSSION

Ovarian tumors in children represent a very heterogeneous group of histopathological entitles. GCTs represent over 80% of all ovarian tumors. Mature teratoma or dermoid cyst is the most frequent tumors of ovary with having benign behavior<sup>5,8,10</sup>. Epithelial tumors and SCSTs were reported in approximately 10% of all ovarian tumors, each<sup>5,11,12</sup>. Epithelial tumors, including mucinous, serous and mixed mucinous – serous cystadenoma, are rare before puberty and usually benign condition<sup>12</sup>. In the present study, GCTs were the most common ovarian tumors and noted about 60% of all the patients. Almost all of GCTs (86%) were benign and a minority (14%) were malignant, such as immature teratoma grade 3,

mixed GCTs and dysgerminoma. Epithelial cell tumors were noted in 10% and a low occurrence of SCSTs in 3.5% of our patients.

Similar to the previous studies, the most common clinical presentations were palpable abdominal mass and abdominal pain<sup>6,10,13</sup>. Precocious puberty, menstrual irregularity and abnormal vaginal bleeding related to estrogen secretion are commonly associated with SCSTs<sup>4,14</sup>. One case of this study had presented like this and the ovarian mass was proven to be juvenile granulosa-theca cell tumor. Nowadays, prenatal ultrasound has influence to detect intrauterine ovarian tumors and most of these are benign characteristics<sup>15</sup>. We found 16% of our patients noted to have ovarian tumors from ultrasound during maternal pregnancy care. All of these were benign conditions, mostly non-neoplastic ovarian tumors and mature teratoma.

Some investigators suggested that an increase in size of mass is associated with malignancy<sup>16,17</sup>. Traditionally, ovarian masses greater than 5 cm has been

used as the cutoff point for malignancy<sup>18</sup>, whereas some studies used 7.5 cm and 8 cm as the cutoff points for malignancy<sup>4,19</sup>. However, size of ovarian masses in the present study was not statistically different between benign and malignant tumors. Additionally, the greatest size of benign tumor was 35.2 cm, while the greatest size of malignant one was only 28 cm. Experiences from this study suggest that only size of the ovarian tumors cannot differentiate characteristic of tumors to be benign or malignant. Presence of solid components visualizing from imaging was also used as a predictor for malignancy. Cystic components and calcification in the masses could be used as a specific predictor for benign ovarian tumor. In addition, imaging investigation could demonstrate torsion of the ovarian tumor in a few cases, whereas real ovarian tumor torsion was discovered about one-third of all cases from the operative findings in the present study.

Spinelli<sup>20</sup> studied multiple tumor markers including AFP, b-hCG, CA-125, CA-19.9, LDH, neuron specific enolase (NSE) and carcinoembryonic antigen (CEA). He concluded that these markers were associated with ovarian malignancy, although they also elevated in some benign ovarian masses up to 20%. However, some malignant masses, such as pure dysgerminoma may not be demonstrated by any elevated tumor markers<sup>21,22</sup>. The weak point of the present study was a few tumor markers studied. We examined only 3 tumor makers including AFP, b-hCG and LDH. The results showed elevation of serum AFP and b-hCG tended to be highly specific for malignant ovarian masses and no benign mass was positive to both tumor markers. LDH was a non-specific tumor marker but it was positive in every case of malignant tumors.

Chabaud-Williamson<sup>23</sup> reported ovary-sparing surgery for the treatment of ovarian tumor and this technique could be safely performed in acute cases and incidental teratomas. Normal ovarian tissue could be identified and preserved with attempts. To the best of our practice, we do not have an experience in ovary-sparing surgery. We used salpingo-oophorectomy for surgical treatment both benign and malignant tumors without any problems. Outcomes of treatment were satisfactory. No mortality and serious complications occurred all of patients with benign ovarian tumor. Approximately 60% of patients with malignant tumor were doing well nearly 5 years after operation.

## CONCLUSION

Most of ovarian tumors (86%) in children were benign, and mature teratoma were predominantly occupied. Dysgerminoma and granulosa-theca cell tumor were the most common malignant ovarian tumors in older children. Difference of clinical presentations of the two groups were more often palpable abdominal mass, precocious puberty and abnormal vaginal bleeding in patients with ovarian malignant tumor, but positive findings of ovarian masses were common in benign ovarian tumor. For imaging characteristics, cystic mass was the indicator for benign lesion and hypoechoic heterogeneous or solid mass was suspicious of malignancy. Elevation of serum tumor marker levels (AFP, b-hCG and LDH) was a strong indicator for malignant tumors.

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## บทคัดย่อ **เนื้องอกของรังไข่ในเด็ก : การศึกษาในระยะเวลา 11 ปี**

โชติรส ไกรคง, พบ., สุรเนตร ลอวงศ์, พบ., อัจฉริยา ทองสิน, พบ.

กลุ่มงานศัลยศาสตร์ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี กรุงเทพฯ

**ความเป็นมา:** เนื้องอกของรังไข่ในเด็กหญิงมีความสำคัญในส่วนหนึ่งของเนื้องอกที่เกี่ยวข้องกับทางนรีเวชวิทยา เนื้องอกของรังไข่อาจจะแสดงออกทางคลินิก ในขอบเขตที่กว้างเกี่ยวกับธรรมชาติของเนื้องอก ขนาดของก้อนและระยะเวลาที่แสดงอาการ

**วัตถุประสงค์:** เพื่อวิเคราะห์ข้อมูลของผู้ป่วยที่มีเนื้องอกของรังไข่ที่รักษาในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี และเปรียบเทียบลักษณะของเนื้องอกรังไข่ชนิดไม่ร้ายแรงกับชนิดร้ายแรง

**วัสดุและวิธีการ:** เป็นการศึกษาย้อนหลังจากการทบทวนเวชระเบียนของผู้ป่วยที่เป็นเนื้องอกรังไข่ ที่รักษา ณ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี ระหว่าง พ.ศ. 2550 ถึง พ.ศ. 2560 โดยเก็บรวบรวมและวิเคราะห์ข้อมูลของผู้ป่วยเกี่ยวกับข้อมูลทั่วไป ลักษณะทางคลินิกการตรวจเพื่อวินิจฉัยชนิดของเนื้องอกรังไข่ วิธีการผ่าตัด และผลของการรักษา

**ผลการศึกษา:** ผู้ป่วย 86 ราย ได้รับการรักษาโดยการผ่าตัดเนื้องอกของรังไข่ในช่วงเวลาที่ศึกษา โดยจำแนกผู้ป่วยออกเป็น 2 กลุ่ม คือ ผู้ป่วยที่เป็นเนื้องอกชนิดไม่ร้ายแรงและผู้ป่วยที่เป็นเนื้องอกชนิดร้ายแรง จำนวน 74 ราย (ร้อยละ 86) และ 12 ราย (ร้อยละ 14) ตามลำดับ เนื้องอกชนิดไม่ร้ายแรงประกอบด้วย germ cell tumors – GCTs และเนื้องอกจากเนื้อเยื่อชั้นผิว (cystadenoma และเนื้องอกชนิดอื่นๆ (follicular and simple cysts) เนื้องอกชนิดร้ายแรงประกอบด้วย เนื้องอกร้ายแรงของ sex cord and stroma cell tumors และเนื้องอกชนิดอื่นๆ ความแตกต่างด้านลักษณะทางคลินิกพบว่าเนื้องอกชนิดร้ายแรงคลำก้อนในช่องท้องได้มากกว่าเนื้องอกชนิดไม่ร้ายแรง (ร้อยละ 91.7 : ร้อยละ 64.9;  $p = 0.023$ ) การเกิดภาวะเป็นสาวเร็วกว่าปกติ และเลือดออกทางช่องคลอดอย่างผิดปกติ พบได้ในผู้ป่วยที่เป็นเนื้องอกชนิดร้ายแรงเท่านั้น และการตรวจพบก้อนของรังไข่ด้วยการอัลตราซาวนด์ขณะทำการอยู่ในครรภ์มารดา เป็นเนื้องอกชนิดไม่ร้ายแรงทั้งสิ้น ก้อนที่มีลักษณะเป็นซิสต์ พบในเนื้องอกรังไข่ชนิดไม่ร้ายแรงมากกว่าชนิดร้ายแรง และก้อนที่เป็นก้อนแข็งพบในเนื้องอกรังไข่ชนิดร้ายแรงได้มากกว่าชนิดไม่ร้ายแรง สารส่อมะเร็งประกอบด้วย alpha-fetoprotein (AFP), b-human gonadotrophin (b-hCG) และ lactic dehydrogenase (LDH) สูงขึ้นอย่างมีนัยสำคัญทางสถิติในเนื้องอกรังไข่ชนิดร้ายแรงจาก GCTs และ SCSTs ( $p < 0.05$ ) ขนาดของก้อนของเนื้องอกไม่มีความแตกต่างกันระหว่างเนื้องอกชนิดไม่ร้ายแรง และเนื้องอกชนิดร้ายแรง เก็บรวบรวมข้อมูลของผู้ป่วย 86 ราย ได้รับการรักษาโดยวิธีการผ่าตัดเอารังไข่ข้างที่มีเนื้องอกออก หรือตัดรังไข่พร้อมกับท่อนำไข่ออกด้วย ผู้ป่วย 74 รายที่เป็นเนื้องอกรังไข่ชนิดไม่ร้ายแรง ยังมีชีวิตรอดทุกรายหลังการผ่าตัด ผู้ป่วย 12 รายที่เป็นเนื้องอกรังไข่ร้ายแรงมีเสียชีวิต 1 ราย หลังการผ่าตัด 1 เดือน เพราะมีการกระจายไปไขกระดูกและสมองของมะเร็งชนิด T-cell lymphoma ผู้ป่วยขาดการมาตรวจซ้ำ 4 ราย ดังนั้นอัตราการมีชีวิตรอดเมื่อครบ 2 ปี ของผู้ป่วยเนื้องอกมะเร็งรังไข่ในเด็กเท่ากับร้อยละ 58.3

**สรุปผลการศึกษา:** เนื้องอกรังไข่ชนิดไม่ร้ายแรงมีโอกาสพบได้มากกว่าเนื้องอกรังไข่ชนิดร้ายแรงถึง 6 เท่า การคลำก้อนได้ในท้องเป็นก้อนแข็งและระดับของสารส่อมะเร็งในเลือดสูงขึ้น เป็นข้อบ่งชี้ให้สงสัยว่าก้อนที่พบเป็นเนื้องอกของรังไข่ชนิดร้ายแรง