Special Article

Gynecologic Tumors during Childhood and Adolescence

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The majority of genital tumors are similar in almost all of the cell types but the frequency is different between children, adolescents, and female adults. The primary site of tumor is similar to the adults, however, the potential of malignant occurrence is higher among children and adolescents. The outline of this article covers clinical manifestation, differential diagnosis, investigation, and management in the particular disease/condition. The challenges of gynecology in children and adolescents are the complexity of physical and mental health, so the approach needs delicate skill and reasoning. Because they are not in full adulthood but in the transitional stage, the multidisciplinary and meticulous approach and management is a substantial issue. Balance and flexibility are the main key of this medical care. Extreme surgical intervention leading to over treatment or ignorance and carelessness leading to under quality of care are challenges facing the doctor.

Keywords: *Gynecologic tumor, Childhood, Adolescence*

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Although gynecologic tumors in children are rare events, they should be included in the differential diagnosis because of the high incidence of malignancy in those tumors compared with adult. Genital tumors must be considered whenever a child is found to have a genital enlargement, virilization, premature sexual maturation, abdominal pain, abdominal mass, chronic genital ulcer, non-traumatic swelling of the external genitalia, foul-smelling bloody discharge, or tissue protruding from the vagina[1]. Proper investigation can quickly evaluate the course of gynecologic problems. Because of progress in tumor markers, diagnostic imaging techniques, chemotherapy regimens, and surgical techniques, the prompt and precise detection of either benign or malignant tumors can lead to both cure and preservation of fertility with conservative surgery whenever possible[2].

Hassan et al reviewed 71 cases of genital tumors. The most common tumor was ovary (80.3%), follow by uterine (16.9%) and cervical (2.8%). From the ovarian tumors; 77.2% of cases were found to be benign; 15.8% malignant and 7% borderline. Malignant tumors were found to be germ cell (44.5%), epithelial (22.2%), stromal (11.1%), lymphoma (11.1%), and mixed (11.1%)[3]. In Thailand, Data from the Department of Obstetrics and Gynecology, Prince of Songkla University revealed that 45 cases underwent surgery for gynecologic tumors during period from January 1996 to December 2005, among ovarian in the origin is the most common conditions[4] (Table 1).

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Vulva tumors

Vulva tumors are very uncommon in children when compared with adult due to the lack of accumulated influence of environmental factors including the exposure to sexual transmitted infection such as human papilloma virus[5]. The common benign tumors of child and adolescent include hemangiomas, simple cysts of the hymen, benign granulomas of the perineum, and condylomata acuminata[2,5].

These are nearly always innocent and comprise retention cysts of the hymen or paraurethral glands in the newborn and benign new growths such as li-

Table 1. Gynecologic tumors underwent surgery in women aged less than 20 years

Organ	Diagnosis	Mean age (yrs)	Number (%)
Vulva	-	-	0 (0)
Vagina and cervix	Endodermal sinus tumor of vagina	1	1 (2.22)
Uterine	Malignant mullerian tumor	18	1 (2.22)
Ovary	Functional or benign		
	- Rupture corpus luteum cyst	18	4 (8.89)
	- Mature teratoma	15.88	16 (35.56)
	- Endometriotic cyst	18	2 (4.44)
	- Serouscystadenoma	13.5	2 (4.44)
	Borderline		
	- Mucinouscystadenocarcinoma	12.5	2 (4.44)
	Malignant		
	- Dysgerminoma	14.33	3 (6.66)
	- Endodermal sinus tumor	16	7 (15.56)
	- Immature teratoma	15.67	3 (6.66)
	- Malignant teratoma	16	1 (2.22)
	- Granulosa cell tumor	15	1 (2.22)
	- Mucinouscystadenocarcinoma	12	2 (4.44)
Total			45 (100)

poma and hemangioma in older children. Retention cysts of the hymen can be left alone to disappear of their own accord. Lipoma can easily be removed if large enough to warrant this but hemangioma is best left alone. Treatment is reserved for lesions that fail to regress, or develop complications such as bleeding or ulceration[5]. Although malignant tumors arising from vulva of this age group is a very rare, sarcoma botryoides (rhabdomyosarcoma) and endodermal sinus tumors have been reported[6-9].

Vaginal and cervical tumors

In this age group, the most common neoplasm of the lower genital tract is sarcoma botryoides, follow by endodermal sinus tumors, and clear cell adenocarcinoma[10]. These disorders are nearly always malignant.

The age of the patient give some help in the diagnosis. The endodermal sinus tumors or yolk sac tumors are most commonly seen in the very young child below age of 3 years[10]. The clear cell adenocarcinoma often associated with a history of antenatal exposure to diethylstilbestrol (DES)[10,11]. The age of the DES-exposed patients has varied from 7 to 34 years with the highest frequency from 14 to 22 years[11]. Sarcoma botryoides is an embryonal variant usually found in the vagina of infants and early childhood. It is seen predominantly in children less than 2 years of age[10]. The onset of sarcoma botryoides from the uterine cervix is very rare with a peak incidence in the second decade[10,12].

The gross and histologic features of vaginal endodermal sinus tumors are similar to those tumors of ovarian origin. Typically, they are tan or white soft vaginal masses, polypoid. Schiller-Duval bodies, PAS-positive globules, and positive staining for α-fetoprotein should be present and assist in diagnosis. Tumor marker can be helpful in endodermal sinus tumors and α-fetoprotein is generally considerably raised[10,13]. Sarcoma botryoids has a typical "grape-like" appearance due to a layer of spindle cells pushing up beneath the mucosa in polypoid masses. These lesions are usually clinically visible, but occasionally the only symptom the patients may present with is unexplained vaginal bleeding or abdominopelvic mass[1,10,12]. The clear cell adenocarcinoma may have cells of this type as its name implies or may have a hob-nailed appearance.

Bleeding or blood-tinged discharge in child is the most common presentation demanding examination under anesthesia. Vaginoscope or cystoscope can be inserted through the hymen easily. With the fluid

running continuously, the physician can have an excellent view and take a number of biopsies. The inspection may reveal an obvious malignant tumor or something that appears to be a benign lesion such as polyp.

The biopsy should be followed by diagnostic tools to determine the degree of local and distant spread of the growth. Once the nature and extent of the tumor is determined, treatment can be started. The management of rhabdomyosarcoma has progressed from radical surgery to neoadjuvant chemotherapy followed by surgery or radiotherapy[1,10,12,14]. Initial treatment should be with combination chemotherapy, usually vincristine, actinomycin-D, and cyclophosphamide. Further surgical excision or radiation therapy may be necessary after the course of chemotherapy[14,15]. A similar regimen of chemotherapy and surgery can be used for the endodermal sinus tumors[10,16]. For the clear cell adenocarcinoma, radical surgery was a management of choice. Adjuvant radiation or chemotherapy may be necessary in some cases[10]. In recent years, neoadjuvant chemotherapy for reduced tumor size followed by surgery and radical abdominal trachelectomy for retained fertility has been reported[17,18]. Although the condition is still very serious, results of treatment of vagina and cervical malignancies as nowadays much better than earlier.

Uterine tumors

Uterine tumors are rare in this age group. However, when tumors of the uterus are found in children and adolescents, they are likely to be malignancy. Endometrial cancer usually occurs after menopause, 15% of cases occur in premenopausal women, and just over 1% of patients are diagnosed at an age younger than 40[19]. Only a few cases of endometrial cancer have been reported in adolescent[20,21]. Uterine sarcomas account for less than 4% of all malignancies of the uterine corpus. Endometrial stromal sarcoma (ESS), mixed mesodermal tumor (MMT), and leiomyosarcoma (LMS) are the three major histologic types[22]. Uterine LMS tends to occur in younger women than does MMT. Although some series have shown a higher number of LMS (32%) than MMT (9%) in premenopausal patients, uterine LMS is very rare during childhood and adolescence[22,23]. LMS of the uterus in a girl has been reported, as is its sudden presentation as a pelvic mass[24].

Ovarian tumors

Ovarian tumors are infrequently seen in children and adolescents, but they are the most common genital tumors in this age group of patients[2,25,26]. The incidence varies according to the age of the patients, with less than 5 % occurring in children and adolescent patients[26,27]. Benign neoplasm or functional are the most common ovarian masses in this age group. Approximately thirty to twenty percent of ovarian tumor are malignant[2,28,29]. Malignant neoplasm require proper preoperative evaluation and staging by operative treatment. If malignancy can be rule out, cysts or functional ovarian cysts can often be successfully treated by expectation and observation. The ovarian tumors are pathologically classified into three main categories: germ cell tumors, stromal tumor, and epithelial tumors[2]. In adults, the epithelial tumors are the most common ovarian neoplasm in 80% of cases, while germ cell tumors develop frequently throughout early childhood to adolescence[2,26].

Functional cysts

Functional cysts can presents as follicular, corpus luteum, and theca lutein cysts. Ultrasonography is more specific in the diagnosis of follicular cyst than a corpus lutein cyst. Because of a corpus luteum cyst is often complex on sonography, which invokes a larger differential diagnosis, including ectopic pregnancy, endometriosis, and neoplam[30]. Functional cysts are benign, unilocular, usually will resolve in 4-8 weeks[25]. Combined estrogen and progesterone oral contraceptive pill may or may not be given during period of follow-up. However, large cysts may rupture and cause peritonitis. It may require operative intervention to control bleeding[29].

Benign ovarian tumors

Mature cystic teratomas (dermoid cyst) was the most common, and follow by cystadenoma[26,29]. Mature cystic teratomas may contain tissue derived from all three germ cell layers, with ectodermal derivatives such as teeth and hair most commonly encountered. As a result, mature cystic teratomas commonly demonstrate intraabdominal calcifications on X-ray[25]. Patients with mature cystic teratomas are usually asymptomatic unless complications such as torsion or rupture occur. Malignant transformation occurs in 0.17% to 2% of benign teratomas patients. Patients who develop malignant transformation are typically postmenopausal[31]. Functional teratomas occur in 5% to 20% of benign teratoma and most commonly presence of thyroid tissue. A diagnosis of struma ovarii is made on thyroid tissue more than 20% of benign ter-

atomas; it could be present signs and symptoms of thyrotoxicosis[25,32,33]. The treatment for an ovarian mature cystic teratomas diagnosed in a child or adolescent is similar in adults. Recurrence after conservative surgery is 4%[34]. Benign epithelial tumors include serous cystadenomas and mucinous cystadenomas. These lesions tend to be smooth and well circumscribed[35]. In this age group, serous cystadenomas more common than mucinous cystadenomas[30]. For stromal tumors, fibromas are common in child and adolescent, account for 4% of all ovarian tumors and 0.5% to 2% of all ovarian tumor in this age group. Forty percent of these tumors larger than 10 cm present with ascites[25,32,36]. Thecomas are rarely found in adolescent. These tumors are more common in the late 30s and are associated with estrogen production[32].

Malignant ovarian tumors

Ovarian cancer, specific to child and adolescent patients include germ cell and juvenile granulose cell tumors. Ovarian cancer is an insidious disease. Because of non-specific symptoms ovarian cancer are frequently diagnosed in advanced stage. Whereas ovarian cancers in adults normally present with non-specific symptoms such as abdominal distension and abdominal pain are frequently diagnosed in advanced stage, 65% of ovarian cancers in adolescents present with acute or sub-acute pain associated with cyst accident[28]. Malignant germ cell tumor exhibits an extremely rapid growth pattern. According to the anatomical situation at this age, the most common sign is abdominal pain or mass. Sudden onset of abdominal pain may be the sign of torsion or rupture[37]. Tumor markers are extremely useful in the differential diagnosis, follow the patient's response to therapy and monitor for recurrence of disease[25,28,30,35]. It may be particularly helpful in adolescent patients with suspected ovarian malignancy. Alpha fetoprotein is reliable marker for endodermal sinus tumors, embryonal tumors, mixed germ cell tumors, and rarely by immature teratomas. Similarly, human chorionic gonadotrophin (hCG) is produced by embryonal tumors and choriocarcinomas. Inhibin a good tumor marker for granulosa cell tumors[25,28,30,35]. Lactic dehydrogenase (LDH) levels have been noted to be elevated in many cases of dysgerminoma[38]. CA-125 was the first widely available monoclonal antibody against epithelial ovarian cancer. The specificity of CA-125 is poor[25].

Malignant germ cell tumors included dysgerminomas, endodermal sinus tumors, embryonal carcinomas, mixed germ cell tumors, chroriocarcinomas, and immature teratomas. Mixed germ cell tumors are composed of two or more germ cell components. Dysgerminomas and endodermal sinus tumors are more common in this age group[25,26,30,35]. Of all germ cell malignancies, dysgerminomas has the most significant incidence of bilaterality. These tumors present are bilateral in 9% to 15% of patients[25,30,35], in contrast to all other ovarian germ cell tumors, which are usually unilateral[25]. Dysgerminomas can be associated with gonadal dysgenesis and androgen insensitivity. Therefore, premenarchal patients should be identified karyotype[28,39]. Immature teratomas are rare and account for 20% of tumors in the first two decades of life. These tumors are normally unilateral but are often associated with a mature cystic teratoma in the contralateral of ovary[28]. Pure ovarian choriocarcinoma are extremely rare tumors. These tumors present in patients younger than 20 years of age, with 50% exhibiting signs of isosexual precocity[25,28]. Embryonal carcinomas are an extremely rare, generally large (10-15 cm), unilateral masses and occur at mean age of 14 years[25,28,32].

For malignant stromal tumors, juvenile granulosa cell tumor was the most common, follow by Sertoli-Leydig cell tumors[32,40]. The juvenile granulosa cell tumor is presents with signs and symptoms of isosexual precocity secondary to increased estrogen secretion by the tumor (80% of patients). Sertoli-Leydig cell tumors account for less than 0.2% of all tumors and cause virilization in the female patient secondary to androgen production[25]. Deepened voice, hirsutism, clitoromegaly, breast atrophy, and acne are common signs and symptoms[2,25,32].

Epithelial ovarian cancers are even more uncommon in young patients but remains part of the differential diagnosis of any ovarian tumors. For epithelial ovarian neoplasm in this age group are frequently borderline tumors and or well differentiated tumor in an early stage[41].

Treatment for child and adolescent patients with ovarian malignancy, preservation of the ovarian and fertility function should be considered. With development of effective chemotherapy for ovarian cancer, perspective operation should be carried out[2,25,37,42]. The surgical approach to germ cell or stromal ovarian cancer confined to a single ovary should aim to preserve fertility and ovarian function.

Advanced disease is not usually accompanied by contralateral ovarian disease, conservative surgery by retained the uterus and contralateral ovary should be preferred[2,42,43]. Chemotherapy for malignant germ cell tumors should be with combination chemo-

therapy, usually bleomycin, etoposide, and cisplatin. For malignant sex cord stromal tumors, cisplatin-based chemotherapy may require in those with metastasis or recurrent disease[25,30,40]. Treatment of epithelial ovarian cancer in adolescent generally adheres to the principles of adult management, with more emphasis on anatomic preservation[2,30].

Conclusion

Although gynecologic tumors are infrequently seen in childhood and adolescence, they should be included in the differential diagnosis. The incidence of malignant of tumors is higher than in adult. Therefore, the detection of these lesions is worrisome to patients, her families, and physicians. Early correct diagnoses could be reached by physical examination, imaging, tumor marker, pathologic examination (including frozen section) and should follow by individual therapy. However, preservation of fertility with conservative surgery is essential.

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เนื้องอกทางนรีเวชในวัยเด็กและวัยรุ่น

จิตติ หาญประเสริฐพงษ์, วีระพล จันทร์ดียิ่ง

ในเด็กและวัยรุ่นก็เช่นเดียวกับในวัยผู้ใหญ่ที่เนื้องอกทางนรีเวชส่วนใหญ่มีความคล้ายกันในแง่ของชนิดทางพยาธิวิทยา แต่ความซุกอาจแตกต่างกันอย่างชัดเจน ส่วนตำแหน่งปฐมภูมิของเนื้องอกคล้ายกับในผู้ใหญ่ เพียงแต่เนื้องอกในเด็กและวัยรุ่นมีศักยภาพที่เป็นมะเร็งสูงกว่า ขอบเขตเนื้อหาในบทความนี้ ประกอบด้วยลักษณะทางคลินิก การวินิจฉัยแยกโรค การตรวจเพิ่มเติม การดูแลรักษาโรคหรือภาวะนั้น ๆ ความท้าทายของปัญหาทางนรีเวชเด็กและวัยรุ่นนั้นคือ ความซับซ้อนทั้งในเชิงกายภาพและสุขภาพจิต ดังนั้นการเข้าหาปัญหาจำเป็นต้องอาศัยทักษะและเหตุผลที่ละเอียดอ่อน โดยข้อเท็จจริงแล้วเด็กและวัยรุ่นไม่ใช่ผู้ใหญ่ ทว่าอยู่ในช่วงระยะผ่านเปลี่ยนการเข้าหาโดยทีมสหวิทยาการและการจัดการที่ละเอียดอ่อนเป็นเนื้อที่สำคัญยิ่ง ทัศนคติต่อการสร้างสมดุลและยืดหยุ่นในการดูแลรักษาเป็นกุญแจสำคัญในการดูแลรักษาทางการแพทย์ โดยไม่จำเป็นต้องผ่าตัดอย่างถอนราก อันนำไปสู่การดูแลรักษาที่มากเกินความจำเป็น ในขณะที่อีกด้านหนึ่ง การละเลยและไม่เอาใจใส่มักนำไปสู่คุณภาพการดูแลรักษาที่ต่ำกว่ามาตรฐาน