

Problems in gynaecologic oncology in girls and young women—an outline of selected issues

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Objective: The aim of the study was to present selected oncological problems among girls and young women. **Mechanism:** Malignant ovarian cancers grow faster in girls. Due to the lack of an anatomic barrier, they spread rapidly from the pelvis to the organs in the entire peritoneal cavity. High-grade cancers may be associated with an insufficient immune response that controls the early tumour growth. **Findings and brief:** Paediatric cancers represent about 1% of all diseases; fortunately, in developmental age gynaecology this is not a frequent problem, yet its significance requires intense specialist actions. Although they most often occur in adult women, malignant lesions may also affect girls (e.g., cervical germ cell tumour). Therefore, the importance of early detection of neoplastic ovarian lesions at any age is emphasised. Cervical cancer is also an oncological issue in developmental age gynaecology (the immature metaplastic epithelium is particularly sensitive to the oncogenic effects of HPV (Human Papillomavirus)), hence any prophylaxis, especially vaccinations, are of great importance in this respect). Apart from typical genital cancers, there can also be cancers where the genitourinary system is just one of the possible locations. **Conclusions:** Fortunately, cancers are not frequent in developmental age gynaecology, yet the significance of this problem requires intense specialist actions.

Keywords

Girls; Oncology; Gynaecology

1. Introduction

Paediatric cancers represent about 1% of all diseases, so cancers are not frequent in developmental age gynaecology. Although oncological problems in girls are indeed rare, specialist and preventive measures in relation to such cancers are of great importance.

2. Cervical cancer vs developmental age

There is irrefutable evidence of a relationship between early onset of sexual activity and the risk of developing in this article cervical cancer—the immature metaplastic epithelium is particularly sensitive to the oncogenic effects of HPV (Human Papillomavirus), and in this context prophylaxis in

developmental age gynaecology cannot be overestimated. A vaccination programme is of great importance in this respect [1].

Currently, both in Poland and worldwide, there are three registered vaccines for the prevention of cervical cancer: the 4-valent vaccine protecting against HPV types 16, 18, 6 and 11—Silgard (MSD), the bivalent vaccine containing VLP antigens for HPV 16 and HPV 18—Cervarix (GSK), and the 9-valent vaccine protecting against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58—Gradasil 9 [2].

The key role of all the aforementioned vaccines is the long-term persistence of the antibody titre in those who have been vaccinated, compared to serologically positive women. Importantly, both vaccines are highly protective against HPV infection, providing protection even throughout the entire period of female sexual activity. It is now known that Silgard and Cervarix do not require a fourth booster dose after 60 months, and anti-HPV vaccines create immune memory [3–6].

According to the recommendations of the Polish Society of HPV Infections Prophylaxis (Polskie Towarzystwo Profilaktyki Zakażeń HPV) on using anti-HPV vaccines:

- vaccines are recommended for girls aged 12–15 years;
- vaccines can be administered to girls as young as 9 (quadrivalent vaccine) and 10 years of age (bivalent vaccine), and to boys aged 9–15 years (quadrivalent vaccine);
- vaccines are recommended for girls and women aged 16–25/26 years before exposure to HPV infection [7].

The Polish Paediatric Society (Polskie Towarzystwo Pediatriczne, PTP) and the Polish Society of HPV Infections Prophylaxis recommend HPV vaccination, which should be included in the mandatory vaccination schedule. Silgard should be administered in the following pattern: 1 day, after 2 months, and 6 months after the first dose; Cervarix—day, after a month, and 6 months after the first dose [8–10].

● As part of their cancer prevention activities, the World Health Organisation called on all international institutions involved in cervical cancer prevention programmes for action toward the elimination of cervical cancer as a public health problem. These activities are intended to reduce the incidence of cervical cancer to ≤ 4 cases/100,000/year by the end of the century. European countries can reach this goal by 2055 to 2059. The following “90-70-90” targets must be met by 2030 will place all countries on the path toward elimination:

- 90% of girls up to 15 years of age fully vaccinated with HPV vaccine,
- 70% of women screened with a high-performance test two times per life by 35 and 45 years of age,
- 90% of women identified with cervical disease receive treatment and care [11–13].

It should be strongly emphasized that although cervical cancer is extremely rare in children and screening is not recommended by most societies until women are 30, it is worth developing the habit of regular gynecological checks in girls, which is important in shaping the right attitudes towards oncological prophylaxis in the future, including cervical cancer prophylaxis. It is hoped that in the future, the combination of screening tests with vaccination of anti-oncogenic HPV strains will reduce the incidence of cervical cancer.

3. The specificity of ovarian cancers in girls

It should be emphasized that ovarian proliferative processes: both malignant and benign, primary and secondary are in the form of a tumour or cyst. Benign hormone-induced lesions also take the form of cysts. Indeed, elevated gonadotropin concentrations during puberty result in a constant response from the ovaries, which may be expressed by the formation of so-called functional ovarian cysts that usually resolve spontaneously and require no treatment. Such lesions should not occur during the so-called hormonal silence, i.e., in childhood and prepubertal periods. An enlarged ovary during this period always requires careful diagnostic procedures, as it may suggest a malignant cancer [14].

Apart from follicular cysts, corpus luteum cysts may appear during puberty, a few years after menarche. They have a higher recurrence-rate than follicular cysts.

Malignant ovarian cancers grow faster in girls. Due to the lack of an anatomic barrier, they spread rapidly from the pelvis to the organs in the entire peritoneal cavity. High-grade cancers may be associated with an insufficient immune response that controls the early tumour growth. When considering treatment, the long-term effects of radical surgery, chemotherapy or radiotherapy on the girl's future growth need to be taken into account. Ovarian cancers from all groups of cancers encountered in adults may occur in girls (although most of them are very rare) [14].

Except for complicated cases and hormonally active tumours, ovarian cancers do not show any specific symptomatology and are tricky. The presumptive symptoms are less

pronounced and for a long time are not recognised by the patient, or they are misleading and do not convince the doctor to issue a referral to consult a gynaecologist.

Malignant gynaecological cases account for 2%, and two-thirds of them are formed in ovaries. Primary germ cell cancers predominate among malignant ovarian cancers. The growth of rare ovarian cancer in girls is slower than in adults and is easier to recognize at the early stages of the disease. By performing even malignant ovarian tumours surgery, healthy tissue should be maximally spared, as it has hormonal and reproductive significance. Permanent postoperative control is needed to possibly detect cancer recurrences [15].

The percentage of malignant ovarian cancers in the group of girls and young women is 10–30%; and 60% of these are malignant tumours from the primary germ cell (germinal) [16].

It is estimated that gonadal tumours account for 7% of ovarian malignancies, therefore they are considered rare. Tumours belonging to this specific group develop both from female and male gonad components as well as from stromal cells and fibroblasts. Granulosa cell tumors (GCT—granulosa cell tumor) account for as much as 70% of malignant gonadal tumours: 95% in the mature form and 5% in the juvenile form, probably associated with precocious puberty [17].

Gonadal tumours also include thecomas and fibromas, Sertoli–Leydig cell tumours as well as very rare tumours, such as gynandroblastoma, sex cord tumours with annular tubules and sclerosing stromal tumours.

The histological structure of sclerosing stromal tumours shows both male and female gonadal endocrine cells. For this reason, these tumours often show hormonal activity which is reflected in the clinical course of the disease. It is also worth mentioning here that there are some fortunately rare metastatic tumours, which can also occur in girls, e.g., Burkitt-lymphoma [18, 19].

In Poland, 40 to 90 germ cell tumours in children and adolescents under 18 years of age are diagnosed annually. They are more frequent in females. It should be noted that two peaks of the disease are observed: in children between 1–6 years of age and during puberty, and in young adults [20].

Clinical symptoms of germ cell tumours depend on the location of the primary focus, metastases, and the clinical stage of the disease. In 90% of cases, the primary focus is located outside of the skull, in children most often in the sacral region of the spine, and then in the ovaries, testicles, retroperitoneal space (the posterior part of the abdominal cavity), mediastinum, neck, at the base of the skull and intracranially, constituting 10% of the diagnosed tumours.

Large-sized ovarian tumours cause increased abdominal circumference. In addition, abdominal pain, pressure on adjacent organs (urinary tract, gastrointestinal tract), or symptoms of “acute abdomen” due to ovarian torsion can occur [20].

In infancy and early childhood, the symptoms of tumours in the sacral region of the spine depend on the tumour

growth. Deformation of the sacral and rectal region is the effect of tumour growth outside the sacral bone; defecation and emiction disorders as well as neurological symptoms are the effect of the tumour growth inside the pelvis, whereas tumours located in the mediastinum region in infants are diagnosed during increasing respiratory failure as a consequence of the tumour mass increase, while in older children initially they do not give any symptoms.

Germ cell tumours can spread to the lungs, liver, lymph nodes, brain and bones.

4. Treatment in ovarian cancers

Any symptoms reported by the patient as “abdominal pain, gastrointestinal discomfort” without determining a general or surgical cause, require diagnostic implementation to exclude ovarian cancer [21–23]:

- If a lesion is found in the adnexa, a medical history should be taken and a physical examination needs to be carried out, with special attention given to the risk factors for malignant tumours, cases of ovarian or breast cancer in the family, the stage of puberty, symptoms of virilisation or premature puberty, and non-specific symptoms of the disease, such as abdominal circumference, reduced appetite, feeling of fullness, abdominal pain, pain in the small pelvis, urgent and/or frequent urinary pressure, and bleeding from the reproductive tract.

- Ultrasonography is the basic and first imaging examination in the assessment of genital organs, regardless of age group. However, it should be strongly emphasised that paediatric patients and adolescents pose a particular challenge due to the limitations of transabdominal imaging and complex social problems closely related to the sexual health of adolescents. A normal uterus in an ultrasound examination is directed backwards towards the bladder, most often in the midline, and fully visible with a properly filled bladder.

- In the sagittal section, the length and thickness of the uterus is assessed, while its width is assessed in the transverse section. In the prepubertal period, the uterus is tubular or conic in shape, the thickness of the uterine body is smaller than or equal to the thickness of the cervix [24]. It should be remembered that an enlarged pear-shaped uterine body is a symptom of the growth of this organ in the peripubertal period. The endometrium in the sagittal US image in the prepubertal period is not visible or takes the form of a linear hyperechoic structure less than 1 mm thick. The thickness of the uterine mucosa in older girls shows high variability in the menstrual cycle, from 4–16 mm [25];

- The use of a colour Doppler is necessary, but with the frequency between 3–6 cm/s, ensuring adequate penetration;

- Computed tomography (CT) or magnetic resonance imaging (MRI) is indicated in the case of complex lesions or suspicion of metastases in patients with malignant tumours, depending on the patient’s condition, availability of particular methods and assessment of the associated risks and potential benefits. CT is also performed to determine the clinical stage

of the disease, evaluating the structures of the chest and abdominal cavity for metastases in the lungs and liver, as well as enlarged lymph nodes. MRI, on the other hand, shows soft tissues, but due to the long duration of the examination, it is necessary to use anaesthesia in infants and young children. Among the imaging methods, in the case of suspected ovarian neoplastic lesions, CT in cancer diagnosis is of particular importance.

- Visibility of the gastrointestinal tract through oral administration of a contrast agent;

- Determination of β -human chorionic gonadotropin (β -hCG) and α -fetoprotein (AFP) concentration, lactate dehydrogenase (LDH) activity, 125 cancer antigen (CA-125) and carcinoembryonic antigen (CEA).

- Genetic testing: tumours of germinoma type are the most common cancers in young girls (<10 yrs.). They are usually associated with XY gonadal dysgenesis, so it is advisable to test Y-DNA.

Ultrasound images of malignant lesions of the ovaries (teratoma malignum, carcinoma embryo, dysgerminoma) are unfortunately not very characteristic and they are not much different from benign lesions, such as mature forms of teratomas or dermoid cysts of the ovary. Of course, in the late stages of cancer, infiltrates are found in the surrounding tissues and the presence of fluid in the peritoneal cavity, as well as the presence of metastases.

Due to the asymptomatic course in the early stages of tumour growth in developmental gynaecology, there is a need for preventive ultrasound examinations, and in the case of suspected malignant lesions assessment of tumour markers concentration and histopathological verification should be performed [26–29].

It needs to be borne in mind that the clinical picture of adnexal tumours varies depending on the aetiology of the lesion. Ultrasound examination is particularly important among studies that differentiate functional changes from ovarian tumours. Physiological changes that cause the development of ovarian cysts may cause pain when there is ovary torsion.

The presence of bilateral small-cystic formations in the ovaries during an ultrasound examination may arouse a suspicion of Stein-Leventhal syndrome [30]. Any enlargement of the ovary in a girl may suggest a malignant tumour and requires careful consultation. Gynaecological and ultrasound examinations performed at the beginning of the next menstrual cycles, allow to recognize physiological follicular cysts. Corpus luteum cysts do not occur for about 2 years after the first menarche. If the cysts persist in the next cycle, laparoscopic diagnostics and determination of tumour markers in the blood are necessary. Surgical treatment is necessary when a cyst ruptures, because there is heavy bleeding and peritoneal irritation followed by shock.

5. Treatment

Prognostic factors in germ cell tumours in children include: clinical stage, serum tumour marker concentration, histological classification of germ cell tumour, location of primary focus, and response to treatment.

Mild germ cell tumours are treated only by surgery, while malignant germ cell tumours in children are treated by surgery and chemotherapy. In case of residual lesions, radiotherapy and therapy with autologous haematopoietic cell transplantation are also applied.

Radical surgical procedures are performed when the location and size of the tumour allows for its complete removal without injury to the patient. Postponed tumour removal or removal of the residual lesion in the primary focus area or metastases take place after completion of first-line chemotherapy. In selected cases of tumours of germinoma type, radiotherapy is applied [31, 32].

Many years of disease-free life are found in 74–87% of patients treated with various therapeutic protocols currently used worldwide. Treatment results vary depending on the histological type, serum marker concentration, primary focus location and clinical stage.

The prognosis is better for tumours of germinoma and immature teratoma types (more than 90% of long-term remissions), but worse for yolk sac tumours (70% of long-term remissions). The prognosis is better for gonadal than non-gonadal tumours [33].

In some children who recovered from germ cell tumours, symptoms of pulmonary fibrosis, renal dysfunction and ototoxicity are observed, whereas in men endocrine disorders related to sex hormones occur. In the group of high-risk patients there is also a problem of myocardial injury after treatment with certain groups of medications. In patients who recovered from childhood terminal cancer there is also an increased risk of secondary cancers.

6. Other oncological problems in developmental age

In adolescent gynaecology, apart from typical genital cancers, there can also be cancers where the genitourinary system is just one of the possible locations.

An example of such a cancer is rhabdomyosarcoma, which belongs to a soft tissue cancers originating from undifferentiated embryonic mesenchymal cells, capable of differentiating into striated muscles, often without a direct relationship to the muscle. Although the causes of this cancer are unknown, genetic factors are thought to affect the development of some of its forms. Symptoms and clinical picture associated with cancer location can occur at any age also in girls. Sarcomas most often manifest in the head and neck region –36% of tumours; in the genitourinary system –23%; and in limbs –19% [34].

The American Cancer Society in *Cancer Facts and Figures* reports that in 2019, 11,060 new cases of malignant cancers

were diagnosed in children under 15 years of age, and 1190 died as a result of these diseases [35].

Summing up, malignant gynaecological cases account for 2%, and two-thirds of them are formed in ovaries. Primary germ cell cancers predominate among malignant ovarian cancers. Cancers that belong to all groups of cancers found in adults can be identified in girls, although most of them appear rarely. The course of development of malignant ovarian cancers in girls is particularly insidious in nature, so doctors of any specialization must be aware of this in order to make a proper diagnosis. Despite the dynamic progress of medicine, ovarian cancer remains a serious diagnostic and therapeutic problem.

The search for an ideal method for early recognition of malignant ovarian lesions is underway.

These changes, although most often occur in mature women may, what is highlighted, affect girls, (e.g., germ cell tumours). Hence the importance of early detection of ovarian cancer at all ages should be emphasized once again. All preventive measures are important here.

Although reproductive cancers among girls and young women are not frequent, the gravity of these problems make prevention actions, early diagnosis and modern therapies extremely important.

Author contributions

KP-R and GJ-B analyzed the data; WK, MG-P and PM performed the review and editing. KP-R, GJ-B, WK, MG-P, PM, MP-M wrote the paper. All authors read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest. KP-R is our reviewer board, given his role as the reviewer, had no involvement in the peer-review of this article and has no access to information regarding its peer-review.

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