Management of Ovarian Cancer in Adolescents and Young Adults

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Norihito Yoshioka and Nao Suzuki

Abstract

About 70,000 young people (ages 15–39) called adolescents and young adults (AYAs) are diagnosed with cancer each year in the United States. The numbers of cancers in AYAs are about six times compared with in children ages 0–14. The past 20 years have seen great improvements in cancer treatment for both children and adults. However, the AYAs with cancer typically do not receive as much attention as children and older adults, and marked improvements in the outcomes of cancer treatment in AYAs have not yet been seen. Therefore, cancer treatments for AYAs must be considered by the specialist.

The clinical study of cancer in AYAs has only just begun. As cancer patients of AYAs often suffer from particular types of cancers and exhibit different therapeutic outcomes from those seen in children and adults today.

In this chapter, we will focus on AYAs and review the management of ovarian cancer in this age group.

Keywords

Adolescent • Ovarian cancer • Treatment

15.1 Introduction

The past 20 years have seen great improvements in cancer treatment for both children and adults. However, marked improvements in the outcomes of cancer treatment in adolescents and young adults (AYAs), who comprise the age group

N. Yoshioka, M.D., Ph.D. (✉) • N. Suzuki, M.D., Ph.D.
Department of Obstetrics and Gynecology, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan
e-mail: yoshi531@marianna-u.ac.jp

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between children and adults, have not yet been seen [1]. Cancer strategies for this age group have been recently prioritized with the aim of improving the survivorship of AYAs. Adolescent girls and young women in particular span the age gap between the fields of pediatrics and gynecology, combining the characteristics of both. Therefore, cancer treatments for both of these age groups must be considered.

It was believed that those people diagnosed with cancer in adolescence or young adulthood between 1975 and 1980 had a better prognosis than the younger or older generations. However, establishment of a range of new treatments and clinical trials improved the survival rate for both children and regular adults, without any corresponding improvements in the survival rate for AYAs. This means that survival rates for the latter generations have become comparatively worse [1]. One possible reason for this is the lack of clinical trials of cancer treatments in AYAs [1]. As a result, the National Cancer Institute (NCI) and the Livestrong Foundation's Adolescent and Young Adults Oncology Progress Review Group collaborated between 2004 and 2005 in carrying out a 10-year study on AYA cancer patients in the United States. Therefore, the clinical study of cancer in AYAs has only just begun. As cancer patients of this age group often suffer from particular types of cancers and exhibit different therapeutic outcomes from those seen in younger children and older adults today, cancer in AYAs is an important topic for research. In this chapter, we will focus on AYAs, who comprise the age group between children and adult women and review the management of ovarian cancer in this age group.

15.2 Definition of Adolescent and Young Adult

AYAs are often defined as individuals aged between 15 and 39 years, but this may vary in different studies [2, 3]. Recent definitions of AYAs are summarized in Table 15.1. The Surveillance, Epidemiology, and End Results (SEER) Report published by the NCI in 2006 defined adolescent and young adult oncology patients as those aged 15–29 years [2]. However, in the report of the NCI's Adolescent and Young Adult Oncology Progress Review Group and the 2016 National Comprehensive Cancer Network (NCCN) Guidelines, they were defined as those aged 15–39 years [2]. Thus, the current mainstream view is to regard those aged 15–39 years as AYAs and to deal with them separately from both younger children and older adults. In our description in this chapter, we will regard AYAs as those aged between 15 and 39 years.

Table. 15.1 Definition of adolescent and young adult

SEER (NCI)	15–29-year-old
Adolescent and young Adult Oncology Progress Review Group	15–39-year-old
NCCN	15–39-year-old

15.3 Cancer in AYAs Worldwide Including Ovarian Cancer

In the United States, 70,000 AYAs are diagnosed with cancer every year, which is seven times more than the number of cancer patients aged under 15 years [4]. In 2014, there were 5330 cancer diagnoses and 610 cancer deaths among adolescents [5]. Keegan et al. used the SEER 13 registry data from 2002 to 2006 to report the 5-year survival rates for various cancers in 45,232 children, AYAs, and older adults [2]. According to that study, the most common cancers among AYAs were breast carcinoma (14.4%), thyroid carcinoma (12.1%), and melanoma (11.2%). The cancers with the best 5-year survival rates were thyroid carcinoma (99.7%), testicular cancer (96.1%), and melanoma (95.5%). Those with the worst 5-year survival rates were hepatic carcinoma (22.8%), gastric carcinoma (26.3%), and pancreatic carcinoma (33.0%), while the other forms of cancer for which the 5-year survival rates were under 50% included high-grade astrocytoma, lung carcinoma, rhabdomyosarcoma, and acute myeloid leukemia. Ovarian cancer occurred in 919 AYAs of the 45,232 included in the study (2.0%), with a 5-year survival rate of 79.5%, which is a much better outcome than the 41.4% 5-year survival rate for older adults aged over 40 years. Thus, survival rate for ovarian cancer in AYAs is not lower than that for other cancers and is higher than that in older adult women. This high survival rate in AYAs suggests that the choice of treatment method should prioritize improving the quality of life (QOL) of the patients.

15.4 Incidence of Ovarian Cancer in AYAs in Japan

As shown in Table 15.2 the Gynecological Cancer Committee carried out a study on 2832 ovarian cancer patients who had started treatment in 2009 at 182 institutions according to clinical statistics. Patients who underwent preoperative chemotherapy and those whose stage was unknown were excluded. Included patients were classified into one of three age groups (under 19, 20–39, and over 40 years), and their ovarian cancer stage was compared. Of the total 2832 patients with ovarian cancer, 25 (0.88%) were aged under 19 years, 283 (10.0%) were aged 20–39 years, and 2524 (89.1%) were aged over 40 years, with the latter accounting for over 90% of the cases. Proportion of patients aged under 39 years with ovarian cancer was 10.88%, and those aged under 19 years was only 0.88%, indicating that this disease is extremely rare in the latter age group. An investigation of the characteristics of ovarian cancer by age group found that of the 2524 patients aged over 40 years, 1152 (45.6%) had Stage I, 275 (10.9%) had Stage II, 884 (35.0%) had Stage III, and 213 (8.5%) had Stage IV cancers. Stages I and III were the most common cancer stages, which is also similar to the general statistics for ovarian cancer, with little difference between the proportions of Stage I and Stage III patients. Of the 308 patients aged under 39 years, 204 (66.2%) had Stage I, 27 (8.8%) had Stage II, 66 (21.4%) had Stage III, and 11 (3.6%) had Stage IV cancers. For the patients aged over 40 years, most cancers were discovered at either Stage I or III, but among those aged under 39 years, a higher proportion was discovered at Stage I. In terms of the

Table 15.2 Characteristics of ovarian cancer stage by age group (Data of JSOG)

	Age	~19		20 ~ 39		40~		Total
FIGO stage		case	%	case	%	case	%	
I	A	8	32	76	26.8	446	17.6	530
	B	1	4	1	0.4	24	1.0	26
	C(b)	4	16	68	24.0	381	15.1	453
	C (1)	0	0	5	1.8	27	1.1	32
	C (2)	1	4	13	4.6	116	4.6	130
	C(a)	4	16	23	8.1	158	6.3	185
II	A	0	0	3	1.1	28	1.1	31
	B	0	0	4	1.4	29	1.1	33
	C(b)	0	0	11	3.9	62	2.5	73
	C (1)	0	0	0	0	7	0.3	7
	C (2)	0	0	3	1.1	59	2.3	62
	C(a)	0	0	6	2.1	90	3.6	96
III	A	1	4	5	1.8	50	2.0	56
	B	0	0	10	3.5	97	3.8	107
	C	4	16	46	16.2	737	29.2	787
IV		2	8	9	3.2	213	8.4	224
total		25		283		2524		2832

substaging of Stage I ovarian cancers among those aged under 39 years, 84 patients (27.2%) had Stage IA, 2 (0.6%) had Stage IB, and 118 (38.3%) had Stage IC cancers, with Stage IC tending to be more common. Further, an investigation of those aged under 19 years (25 patients) found that 18 (72%) had Stage I, 0 (0%) had Stage II, 5 (20%) had Stage III, and 2 (8%) had Stage IV cancers, with a higher proportion of Stage I cancers compared with the other two age groups.

Figure 15.1 shows a summary of the yearly numbers of ovarian cancer patients reported by the Gynecological Cancer Committee of the JSOG (2003–2014) [6, 7]. An investigation on the 49,513 ovarian cancer patients registered in these annual patient reports found that 4895 (9.9%) were AYAs (this statistic included those aged under 15 years as AYAs). These 4895 AYA patients were then classified according to whether their tumor was epithelial, sex cord-stromal, germ cell, or others, and the results were plotted on a graph by age group (Fig. 15.1). As shown in Fig. 15.1, there were 363 ovarian cancer patients aged under 19 years, accounting for 7.4% of AYA ovarian cancer patients. Germ cell tumors were present in 285 cases (78.5%), followed by epithelial tumors in 64 cases (17.6%). There were 1128 ovarian cancer patients aged 20–29 years, accounting for 23.0% of AYA ovarian cancer patients. Epithelial tumors were present in 639 cases (56.6%), followed by germ cell tumors in 471 cases (41.6%). There were 3404 ovarian cancer patients aged 30–39 years, accounting for 69.5% of AYA ovarian cancer patients. Epithelial tumors were present in 2995 cases (88.0%), followed by germ cell tumors in 354 cases (10.4%).

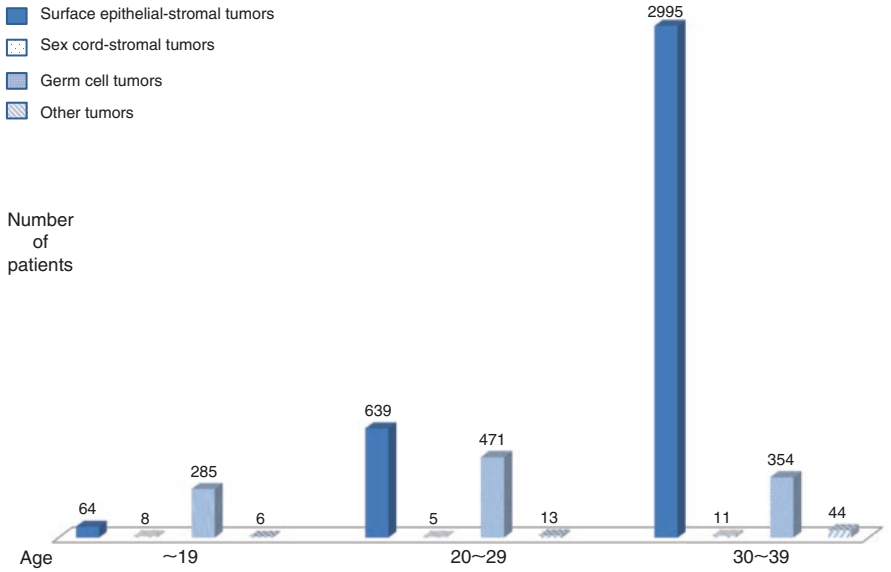

Fig. 15.1 Pathological characteristics of ovarian cancer in AYAs (Data of JSOG)

Bringing together all the AYA ovarian cancer patient data available to date, AYAs account for approximately 9.9% of all ovarian cancer patients, with the highest proportion aged 30–39 years (69.5%), followed by those aged 20–29 years (23.0%) and under 19 years (7.4%). Almost all cancer tumors in AYA ovarian cancer patients were either epithelial tumors or germ cell tumors. Epithelial tumors accounted for the great majority of cancers among those aged 30–39 years, which is similar to ovarian cancer patients aged over 40 years. For those aged 20–29 years, epithelial tumors and germ cell tumors accounted for around half of the cases each. Those aged under 19 years, however, exhibited different characteristics from those aged 20–29 years, with germ cell tumors accounting for 78.5% of the cases.

15.5 Treatment of AYA Ovarian Cancer Patients

From the perspective of improving survivorship, the most important point in the treatment of AYA ovarian cancer patients is to spare their fertility. AYAs are generally defined as those aged between 15 and 39 years, and as members of this age group who may either be considering pregnancy in the future or already want to have children, treatment methods must always be chosen with the conservation of fertility in mind.

The recommended basic fertility-sparing surgical technique for ovarian cancer patients is the ipsilateral salpingo-oophorectomy with omentectomy and laparoscopic cytology. Ipsilateral ovarian biopsy with para-aortic lymph node or pelvic lymph node dissection or biopsy and intraperitoneal biopsy may also be performed

as staging laparotomy [8, 9]. Because most AYA ovarian cancer cases are known to comprise either epithelial tumors or germ cell tumors, we will provide an overview of the fertility-sparing surgery for patients with these two types of cancer tumors.

15.5.1 Treatment of Epithelial Tumors

The Japan Clinical Oncology Group (JCOG) reported data from a joint study carried out in 30 institutions in 2010 [10]. Their analysis covered 211 Stage IA or Stage IC ovarian cancer patients who underwent fertility-sparing treatments. They found that fertility-sparing surgeries are recommended for ovarian cancer patients with highly differentiated (G1) or moderately differentiated (G2) Stage IA non-clear cell carcinoma [10]. They also reported that fertility can be spared in cases of Stage IA ovarian clear cell carcinoma or G1/G2 Stage IC non-clear cell carcinoma with ipsilateral lesions as long as an adjuvant chemotherapy is performed [10]. However, the fertility-sparing surgeries are not recommended for G3 Stage I non-clear cell carcinoma and Stage IC clear cell carcinoma patients [10, 11]. Although it may be possible to preserve fertility by carrying out an adjuvant chemotherapy, this may be assumed to deplete the ovarian reserve, depending on the patient's age. Ovarian toxicity of anticancer agents will be discussed below.

15.5.2 Treatment of Germ Cell Tumors

Germ cell tumors are rare tumors that account for less than 5% of all malignant ovarian cancers [11, 12]. However, as these tend to occur in the younger age group (10–29 years) [11, 13], are highly sensitive to chemotherapy, and are ipsilateral in over 95% of the cases [11, 14], they do not frequently provide opportunities to consider the issue of conserving the fertility of AYA ovarian cancer patients. When sparing fertility, detailed peritoneal investigation in addition to ipsilateral salpingo-oophorectomy with omentectomy and laparoscopic cytology is recommended. Some experts consider that tumor debulking is useful for patients with Stage III or IV advanced cancers, but organ damage and combined resection must be avoided and chemotherapy must be started as soon as possible. Fertility-sparing surgeries are not believed to affect the prognosis of patients with advanced cancers [15], and for younger individuals such as AYAs, a procedure that preserves ovarian function and fertility should be chosen. If the patient does not wish to conserve her fertility, the procedure for the initial surgery for ovarian carcinoma should be followed. Germ cell tumors grow rapidly; therefore, it is important that they be diagnosed early and their treatment be started rapidly.

BEP (bleomycin, etoposide and cisplatin) therapy with bleomycin, etoposide, and cisplatin is strongly recommended as a postoperative adjuvant chemotherapy [11, 16–19]. A study of malignant ovarian germ cell tumors in the early 1970s, before the development of the current chemotherapy, found that the cure rate for patients with advanced cancers who underwent surgery alone was almost 0% and

that for those with Stage I cancer, it was only 5–20% [20]. Subsequent clinical trials of BEP therapy for testicular germ cell tumors, which are ten times more common than ovarian germ cell tumors, resulted in its establishment as the standard treatment for ovarian germ cell tumors as well. The reported cure rate of BEP therapy for ovarian germ cell tumors is almost 100% for early-stage tumors and over 75% even in advanced cases [18], making it highly effective as postoperative adjuvant chemotherapy. Although there are some concerns about the ovarian toxicity of chemotherapy, BEP therapy does not include any drugs that are severely toxic to the ovaries [21]. Chemotherapy can be omitted for Stage IA undifferentiated germ cell tumors and G1 Stage I immature teratomas [15, 22]. In such cases, prognosis is reportedly good if a treatment strategy of rigorous monitoring and the use of BEP therapy in the event of recurrence is followed [20]. Thus, fertility-sparing surgeries are the treatment of choice for such germ cell tumors in AYAs, and the use of BEP therapy as a postoperative adjuvant chemotherapy or recurrence therapy is recommended.

15.6 Fertility Preservation Treatment in AYAs

Young cancer patients and those with autoimmune diseases may suffer from irreversible reproductive dysfunctions from the anticancer agents or radiotherapy used to treat them. The concept of oncofertility, bringing together the fields of oncology and reproductive medicine to resolve gonadal failure, loss of fertility, and other reproductive issues following cancer treatment, was proposed by Woodruff et al. in 2006. Conservation of fertility must always be a matter of concern for cancer patients in the AYA age group, and oncofertility treatment is very often indicated. Here, we will describe the current status and future prospects of the oncofertility treatment required for ovarian cancer in AYAs.

15.6.1 Chemotherapy-Induced Ovarian Toxicity

Although surgery is an important treatment for ovarian cancer, anticancer drug therapy is also extremely important. In AYA cancer patients, it is both important to perform fertility-sparing surgeries and to consider gonadal toxicity if chemotherapy is required. However, the gonadal tissue is extremely vulnerable to chemotherapy, and the resulting damage is permanent. Oligomenorrhea, amenorrhea, anovulation, and other forms of ovarian dysfunction resulting from the use of chemotherapy are termed “chemotherapy-induced amenorrhea” and occur with a reported incidence of 20–100% [23]. Frequency of chemotherapy-induced amenorrhea has been found to depend on the choice of drug used, duration of treatment, and its total dose [24]. Incidence of premature menopause is reportedly lower in younger patients, who still have a large number of primordial follicles remaining, than in older adults [25]. Table 15.3 [26] shows the risk categories for the ovarian toxicity of anticancer agents. Alkylating agents are the best-known cytotoxic anticancer agents, and

Table 15.3 Classification of chemotherapy-induced ovarian toxicity

Risk	Chemotherapy
High risk	Cyclophosphamide
	Ifosfamide
	Dacarbazine
Intermediate risk	Cisplatin
	Carboplatin
	Doxorubicin
	Etoposide
Low risk	Actinomycin D
	Vincristine
	Methotrexate
	Fluorouracil
	Bleomycin
No data	Paclitaxel
	Docetaxel
	Gemcitabine
	Irinotecan

cyclophosphamide and ifosfamide are among the most commonly used drugs of this type. As shown in Table 15.3, cyclophosphamide is classified as a particularly high-risk agent, as it causes severe ovarian toxicity and is believed to entail a high risk of refractory infertility [27]. Risk of cyclophosphamide-induced amenorrhea increases after the age of 35 years and reportedly exceeds 80% over the age of 40 years [28]. These drugs are seldom included in the regimens currently used for ovarian cancer treatment. Doxorubicin, the best-known anthracycline anticancer agent, exerts its antitumor effect by suppressing RNA and DNA biosynthesis. As shown in Table 15.3, it is categorized as an intermediate risk agent and may be included in second-line and subsequent regimens. Doxorubicin-induced ovarian toxicity results in amenorrhea in 96% of women aged 40–49 years [23], but its incidence in younger age groups was reportedly less than 10% [29]. Platinum-based anticancer agents, which act by inhibiting DNA replication and inducing apoptosis, include cisplatin, carboplatin, and nedaplatin. The only reports of ovarian toxicity involve cisplatin, for which the incidence of amenorrhea is reportedly related to the total dose administered [30]. Basic experiments have also shown that cisplatin reduces the ovulation rate in rats and diminishes the concentrations of anti-Mullerian hormone (AMH) and inhibin-α in the blood [31]. BEP therapy, as described above as the first treatment of choice for germ cell tumors, includes cisplatin and is used to treat AYAs [16–19]. A study on 41 Stage I germ cell tumor patients treated with BEP therapy after fertility-sparing surgeries found that normal menstrual cycles were preserved in 71.4% of the cases, and no patient developed primary ovarian insufficiencies (POI) [32]. Thus, fertility may be comparatively well preserved following BEP therapy.

Taxane anticancer agents, such as paclitaxel and docetaxel, are used in the standard regimens for the treatment of surface epithelial-stromal tumors. Animal experiments in rats have also shown that paclitaxel reduces the number of primordial ovarian follicles [33] but does not exert severe ovarian toxicities in this animal

model [34]. Further, a prospective study that compared anthracycline and taxane anticancer agents found that the incidence of amenorrhea was higher when taxanes were used [35]. However, as shown in Table 15.3, they are classified in the risk category of "no data." Thus, more data must be gathered on their effect on fertility after chemotherapy for ovarian cancer.

15.6.2 Radiotherapy-Induced Ovarian Toxicity

As described above, surface epithelial-stromal and germ cell tumors account for the vast majority of ovarian cancers in AYAs. These forms of ovarian cancer are mainly treated by surgery and chemotherapy, with radiotherapy used in only a few cases. If complete remission is not achieved after initial treatments for surface epithelial-stromal tumors, then maintaining the patient's QOL is prioritized, with complaints of pain particularly requiring proactive treatments. Further, radiotherapy for palliative purposes is reportedly effective [36, 37]. Among germ cell tumors, one tumor for which radiotherapy is effective is dysgerminoma. Like the seminoma in the testes, dysgerminoma is highly sensitive to radiation, and until the late 1980s, radiotherapy was frequently used to treat patients with this type of tumor. From then on, good therapeutic outcomes were obtained from chemotherapy, and as radiotherapy makes fertility preservation difficult and causes acute toxicity to organs such as those in the gastrointestinal tract, it is now very seldom used to treat dysgerminoma. Thus, it is now rare for AYAs to undergo radiotherapies for ovarian cancer. In this chapter, we will also describe radiation-induced ovarian toxicities in general.

The testes and ovaries, which are the gonads responsible for reproductive function, are exceptionally sensitive to radiation. Toxicity is induced by far lower doses of radiation than those tolerated by many other healthy tissues. When these tissues fall within the radiation field, it has an extremely strong effect, and even outside the radiation field, the threshold is often exceeded by trace amounts of scattered radiation. Radiation exposure of 4–6 Gy in adults and 10–20 Gy in children is generally regarded as sufficient doses to reduce ovarian function, and studies have found that irreversible ovarian failure is caused by radiation exposure exceeding 18.5 Gy at age 10 years, 16.5 Gy at age 20 years, and 14.3 Gy at age 30 years [38]. Generally, the best-known disease for which ovarian function is affected by radiotherapy is leukemia, in which patients undergo 12 Gy total body irradiation (TBI) before bone marrow transplantation. Other situations for which ovary management is a matter of great concern during treatment planning include total pelvic irradiation for cervical cancer, Wilms tumor in children, neuroblastoma, and postoperative irradiation for abdominal rhabdomyosarcoma. The ovaries can be preserved in some cases of cervical cancer in young women. If the ovaries have been spared, ovarian displacement should be considered to move the ovaries out of the radiation field to avoid their exposure during postoperative radiotherapies. Ovarian function after ovarian displacement is generally good [39], with reported rates of ovarian function maintenance of 41 [40], 50 [41], 60 [42], and 71% [43]. If the radiation dose to the displaced

ovaries is less than 3 Gy, ovarian function is reportedly maintained in 90% of the patients [41], although measures must be taken to anchor the ovaries after their displacement.

15.7 Fertility Preservation Treatment

Although the prevalence of cancer has been recently increasing, development of multimodal therapies has enabled many patients to overcome their disease. In particular, the 5-year survival rate for pediatric cancer patients aged under 15 years and for those in the AYA age group now exceeds 80%, and consideration of fertility preservation in younger cancer patients is progressing on a daily basis. From the viewpoint of improving the survivorship and QOL of younger cancer patients, the use of fertility preservation treatments before multimodal therapies are implemented is one method of avoiding fertility loss. There are three possible choices of fertility preservation methods in women: cryopreserved embryos, cryopreserved eggs, and cryopreserved ovarian tissue. Which of these is chosen will depend on considerations including (1) the type of cancer, (2) how advanced it is, (3) the types of anticancer agents used, (4) when chemotherapy is started, (5) age at the start of treatment, and (6) whether or not the patient is married. Each method has its own advantages and disadvantages and must be implemented with a full understanding of its indications and precautions, including the medical and social contexts. It is important to inform patients that fertility preservation treatment does not guarantee that pregnancy can be achieved and that its use in cancer patients entails some risk. Additionally, we should obtain their full understanding. It is also imperative to prioritize cancer treatments above all else and to offer fertility preservation treatments in such a way that the treatment of underlying diseases is not delayed, with the doctors only providing it if they judge it to be feasible. As ovarian cancer means that cancer cells are present in the ovarian tissue itself, ovarian tissue cryopreservation is contraindicated because of its risk of minimal residual disease (MRD) development. However, the first live birth resulting from an embryo generated by the harvesting of immature oocytes from surgically extracted ovarian tissue, in vitro maturation and fertilization, and subsequent embryo implantation has been recently reported in a case that indicates the potential for oncofertility treatment use in advanced medical institutions [44].

Conclusion

Ovarian cancer in AYAs has specific characteristics compared with the same disease in other age groups. Preservation of fertility must always be taken into account when considering treatments, but this must be handled carefully as this is an area in which sufficient evidence has yet to be established. Close collaboration between pediatricians and obstetricians/gynecologists, including during the post-treatment period, is required in the future to gather evidence on the treatment of ovarian cancer in this age group and provide better treatment.

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