Possibilities of Fertility Preservation in Young Patients with Ovarian Cancer

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Abstract. *Background: Ovarian cancer is a rare disease especially in young patients and surgical treatment often leads to loss of fertility. This study investigated the incidence of the different histological types and discusses the possibility of fertility preservation. Patients and Methods: A retrospective analysis of patients with an ovarian tumour under the age of 40 who presented either to the Women's University Hospital, Tuebingen or to centres of the FertiPROTEKT network was performed. Results: Out of 51 patients with ovarian cancer from Tuebingen, 21 (41.2%) were eligible for fertility-preserving surgery, 11 received chemotherapy and from those 4 (36.4%) chose a fertility preservation technique. From the FertiPROTEKT network, 26/41 patients (63.4%) decided to undergo fertility preservation. No complications and postponement of chemotherapy due to fertility preservation procedures were noted. Conclusion: With careful consideration of the risks, the correct indication and diligent aftercare, the realisation of conception is possible also for patients with ovarian cancer.*

Ovarian cancer is generally depicted as being a rare disease. However, it is the gynaecological tumour with the highest mortality rate and constitutes the fifth most common cause of death from cancer in women (1). As ovarian cancer is not associated with early symptoms, it is often diagnosed at a late stage (2, 3). Earlier stages as well as borderline ovarian tumors are often discovered incidentally, for example during laparoscopic cyst removal and are more often found in younger patients.

The following tumors can be distinguished corresponding to the original cells: epithelial ovarian tumours, sex cord stromal neoplasms and malignant germ cell tumours (2, 4).

Some data have shown that epithelial tumors more commonly occur at a younger age (5, 6). If the epithelial ovarian cancer is detected during stage I it is associated with a 5-year survival rate of 62-85% (6) and a 5-year survival rate of up to 90% can be expected for those suffering from a germ cell tumour. So far, no negative effects from the disease on the patients' children have been observed (7). Women of fertile age must, therefore, be informed about the possibility of fertility-preserving surgery and in the case of chemotherapy about further fertility preservation methods. The specific risks in view of the ovarian cancer must be considered and discussed for all these methods individually.

The *Ferti*PROTEKT network (www.fertiprotekt.eu) was established in 2006 to pool the expertise from reproductive medicine specialists, oncologists and rheumatologists, to implement national and international care structures and to develop treatment recommendations. Documentation of counselling and treatment is mandatory since 2007.

The following methods of ovarian protection are generally available: *GnRH-analogue treatment:* Ovarian damage from cytotoxic chemotherapy can be reduced by the administration of Gonadotropin-Releasing hormone (GnRH)-analogues which inhibit recruitment of the primordial follicle by suppressing gonadotropin release (9). *Ovarian tissue cryopreservation:* Ovarian tissue for cryopreservation with the possibility of later re-transplantation will be preferably removed by laparoscopy. In the case of premature ovarian failure, the ovarian tissue can be re-transplanted to an orthotopic site and spontaneous pregnancies have been reported in several diseases (8).

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Stimulation for cryoconservation of fertilised or unfertilised egg cells: To retrieve oocytes for cryopreservation, polyfollicular ovarian response is induced using high-dose stimulation treatment. The oocyte-retrieval is performed under ultrasound guidance and depending from the availability of a partner the oocytes are cryopreserved fertilized or unfertilized (9).

A detailed description of the various fertility preservation methods, the implementation, efficacy and risks have already been published as open access (9).

The aim of this study was to investigate the incidence of the different histological types of ovarian tumours in young women and to determine and discuss the possibility of fertility preservation in our patient collective. For this purpose, all women under the age of 40 who presented to the University Hospital for Women in Tuebingen with histologically confirmed ovarian cancer were retrospectively evaluated. For additional data regarding the utilization of fertility preservation methods in patients with ovarian cancer data from the *Ferti*PROTEKT network was added.

Materials and Methods

Patients of the Tuebingen University Hospital for Women. We retrospectively analysed all patients under the age of 40 who presented to and received treatment at the University Hospital for Women in Tuebingen for a histologically confirmed ovarian tumour between January 2001 and December 2010. Patients who presented for a second opinion or with a relapse were also included. The patient's age and pregnancy history, as well as the type of surgery - bearing in mind possible fertility preservation, subsequent chemotherapy if appropriate - were considered. Data relating to relapses or pregnancy after treatment were also collected.

The following histological groups were compiled:

Groups of ovarian tumours	Histological types of ovarian tumours
Epithelial tumours	- Serous ovarian tumour
	- Mucinous ovarian tumour
	- Endometrioid ovarian tumour
	- Clear cell ovarian tumour
	- Urothelial ovarian tumour (BRENNER tumour)
	malignant mixed mesodermal tumour (MMMT)
Gender cord stromal tumours	- Gender cord tumour (follicle, granulosa cells, Sertoli cells)
	- Stromal tumour (theca cells, fibroblasts, hilus cells)
	- Germ cell tumours
Malignant germ cell tumours	- Immature teratoma
	- Dysgerminoma
	- Yolk sac tumour
Others	

Patients counselled by centres of the FertiPROTEKT network. Data from women with ovarian cancer who were counselled in one of the centers of the *Ferti*PROTEKT network prior to planned chemotherapy between May 2007 and December 2012 were evaluated: age of the patients, pregnancy history, number and type of fertility preservation methods. Procedure-related complications and potential postponement of chemotherapy were included.

Results

Patients of the Women's university hospital Tuebingen. A total of 51 patients under the age of 40 with a malignant ovarian tumour were treated at the University Hospital for Women in Tuebingen between January 2001 and December 2013. The mean age of the patients was 29.3 years (range 16 to 40 years). Regarding the history of previous pregnancies, there was a mean of 0.8 pregnancies with 0.6 children, miscarriage had occurred in 5 (9.8%), pregnancy termination in 2 (3.9%) and unknown history on previous pregnancies in 3 (5.9%) patients.

Histology. 33 patients (64.7%) had epithelial tumours, 10 women (19.6%) had sex cord tumours and 7 (13.7%) had malignant germ cell tumour. The stage distribution is shown in Table I.

Surgical treatment and relapse. 21 (41.2%) patients underwent primary fertility preserving surgery, however 3 of them (5.9%) needed secondary ovarian cancer surgery because of relapse, inoperable relapse was found in 1 patient (2%) during surgery. 30 women (58.8%) underwent primarily total hysterectomy and bilateral adnexectomy due to a higher FIGO (International Federation of Gynecology and Obstetrics staging system) stage or completed family planning.

In the group of patients who received fertility preserving surgery 7 (33.3%) patients with epithelian tumour presented in FIGO stage I, divided in FIGO stage IA (57.1%) and FIGO IB (42.9%). For 10 patients (47.6%), with sex cord tumours, fertility preserving surgery was performed, 8 (80%) presented with FIGO I and 1 (10%) with FIGO II and III respectively. Three further patients (14.3%) had a germ cell tumour, 2 (66.7%) presented at FIGO stage I and 1 (33.3%) FIGO stage II. One patient (3.8%) suffered from a rhabdomyosarcoma.

From the patients who suffered a relapse after primary fertility preservation surgery 3 have had an epithelial tumour, one at FIGO stage IA and two at FIGO stage IC. One further patient had a FIGO stage II sex cord tumour.

Adjuvant chemotherapy. Adjuvant chemotherapy was applied in 90% (n = 27) of the patients who had non-fertility preserving surgery and in 52.4% (n = 11) of patients who underwent fertility preserving surgery.

Pregnancies after therapy. After successful treatment, a total of seven pregnancies were recorded in five patients. One patient had two miscarriages with a subsequent full-term

Table I. *Distribution of the tumour entities and FIGO stages of the Tuebingen patients.*

Tumour entity	FIGO stages of the patients treated in Tuebingen % and numbers (n)				
	FIGO I	FIGO II	FIGO IIII	FIGO IV	Total
Epithelial tumour	42.4% (n=14)	12.1% (n=4)	45.5% (n=15)	-	64.7% (n=33)
Sexcord tumour	80% (n=8)	10% (n=1)	10% (n=1)	-	19.6% (n=10)
Germ cell tumour	57.1% (n=4)	28.6% (n=2)	-	14.3% (n=1)	13.7% (n=7)
Rhabdo-myosarcoma	-	-	-	-	2% (n=1)

Table II. *Treatment choices of the counseled patients.*

Fertility preservation technique	Patients opting for this technique % and numbers (n)
GnRH-analogues alone	7.7% (n=2)
Ovarian tissue cryoconservation alone	61.5% (n=16)
Ovarian tissue cryoconservation + GnRH-a	7.7% (n=2)
Hormonal stimulation alone	15.4% (n=4)
Hormonal stimulation + GnRH-a	7.7% (n=2)
Fertility preserving treatments in total	n=26

pregnancy after recovering from a sex cord tumour treated with six adjuvant chemotherapy cycles of carboplatin/paclitaxel. Two pregnancies occurred in patients with epithelial tumours at FIGO stage IA without adjuvant chemotherapy. One patient decided to go for pregnancy termination without any relation to the diagnosis, and the cancer diagnosis was made during pregnancy in the other patient. This pregnancy continued normally. Two further women successfully carried their pregnancies to term, although one of them had previously suffered from FIGO stage IC epithelial tumour and the other from FIGO stage IA malignant germ cell tumour. Both patients underwent chemotherapy after surgery.

Of the 51 patients affected by ovarian cancer, 21 were eligible for fertility-preserving surgery and 7 (13.7%) were advised about possible fertility-preservation methods. Of these, 4 chose a fertility preservation technique: GnRH-analogue therapy was chosen once and ovarian tissue conservation three times.

FertiPROTEKT network data. Between May 2007 and December 2012, a total of 41 patients (including the 7 from our Center) were counselled within the FertiPROTEKT network on methods of fertility preservation prior to chemotherapy. Eighty percent (n=33) of the patients did not have children at the time of counselling, 3 (7.3%) had one child and one patient (2.4%) had two children. The parity of 4 women (9.8%) was unknown.

In total, 26 patients (63.4%) decided to undergo fertility preservation. 20% of the 15 women who decided against such measures already had a child.

The fertility-preservation methods chosen by the patients are shown in Table II. No complications and postponement of chemotherapy as a result of the fertility preservation procedures was noted. Data on pregnancies occurring after completed treatment could not be collected to date.

Discussion

Although ovarian cancer is usually seen in postmenopausal women, it is also present time and again in young women before their family planning is completed (5, 6). Several studies show that – when ovarian cancer is diagnosed at an early stage – a high survival rate of 62-85% for epithelial and up to 90% for germ cell tumours can be expected. This also applies for a fertility-preserving approach (6, 7, 10). In case of pregnancy, no relapse occurred and the children had a good outcome (10). Therefore counselling on fertility-preserving surgery as well as further fertility preservation methods before subsequent chemotherapy is important.

Regarding the protective effect and the risks of application of GnRH-analogue for fertility preservation in ovarian cancer, a Chinese study of 16 patients showed that there were fewer relapses after administration of a GnRH-analogue in addition to chemotherapy. All patients receiving GnRH-analogue had regular menstrual cycle 6 months after completion of the chemotherapy scheme and more spontaneous pregnancies occurred (11). Overall, there is little data about GnRH-analogue use and ovarian cancer. The present data suggest that it can be used in ovarian cancer and this data is also reflected in the *Ferti*PROTEKT network data.

Specific data about the relapse risk in ovarian cancer patients relating to ovarian tissue cryoconservation do not exist. The risk of a relapse after retransplantation of the cancer-affected organ must be discussed with each patient.

Stimulation for cryoconservation of fertilised or unfertilised egg cells is the most established procedure for fertility preservation. The malignancy does not affect the stimulation (12, 13). There is no data on the risk of relapse after stimulation treatment, nevertheless the short period of stimulation with subsequent chemotherapy appears to be justifiable but should still be discussed with each patient. To enhance the efficacy, combination of ovarian tissue cryoconservation and stimulation for cryoconservation of oocytes can be considered (14).

With 29.3 years, the evaluated patient collective from the Tuebingen University Hospital for Women was regarded as

rather young. The mean of 0.8 previous pregnancies reflect our society's trend towards postponement of starting a family (15). The histology distribution of our group showed – similar to the literature – that the largest proportion were epithelial tumours. Nevertheless, there were twice as many sex cord stromal tumours and germ cell tumours (2, 4).

A total of 41.2% underwent fertility-preserving surgery, 4 of these suffered a relapse. The majority (47.6%) of patients who received preserving surgery had a sex cord tumour (one relapse), followed by 33.3% with an epithelial tumour (3 relapses). The smallest proportion were germ cell tumours. Out of this data we conclude that fertility-preserving surgery could be performed on a large proportion of our patients without an increased risk of relapse. This is supported by another study, evaluating data from 94 patients. With the correct indication, there was no negative effect on the overall survival (OS) and disease-free survival (DFS) (10). Approximately half the patients had to undergo postoperative adjuvant chemotherapy, most commonly those with an epithelial tumour.

Only seven women were preoperatively advised on methods of fertility preservation, and more than half of them decided to undergo treatment. The reasons for the low number of counselling is that the *Ferti*PROTEKT network was not established before 2007 with the subsequent implementation of counselling on fertility preservation and the lack of a possibility of fertility preservation for advanced disease.

The high number of fertility preservation procedures found in the *Ferti*PROTEKT network's data reveals the urgency of the need for counselling. More than half of the patients decided to undergo fertility-preservation treatment. A study evaluating the development of the wish to conceive after chemotherapy showed that prior to cancer, 35% had at least 1 child, compared with 46% currently childless. Of those currently childless, 76% wish to have children in the future (16).

In summary, the issue of fertility preservation is very important in patients with ovarian cancer. The patient's wishes must be weighed against the risk. The realisation of having a child is often an option, especially in the early stages. Counselling on the methods of fertility preservation has to be provided before adjuvant chemotherapy. After chemotherapy, the patient should wait at least 6 months before a pregnancy to eliminate the effect of the chemotherapy on the oocytes, as folliculogenesis takes about 6 months. With careful consideration of the risks, the correct indication and diligent aftercare, the realisation of pregnancy is possible for patients with ovarian cancer.

Conflicts of Interest

The Authors confirm that there are no conflicts of interest.

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