Cervical Cancer

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Epidemiology of Cervical Cancer in Young Women and Impact on Fertility

To date, cervical carcinoma is the second most common cancer in women worldwide. In the *Ferti*PROTEKT network, approximately 1.5% of consultations were due to cervical cancer [1]. Approximately one in four women worldwide are under 35 years of age at the time of initial diagnosis [2]. However, the incidence of cervical carcinoma has been steadily declining for decades in developed countries following the introduction of statutory early detection programmes. At the same time, malignant changes of the cervix in earlier stages are detected malginant changes of the cervix are detected earlier: One-third of all cervical cancers in developed countries are currently diagnosed at FIGO stage I [3].

Human papillomavirus (HPV) vaccination reduces the risk of cervical cancer in situ and cervical cancer [4]. However, vaccine efficacy is mainly depending on the vaccination coverage in the population.

In approx. 80% of cases, cervical cancer is a squamous cell carcinoma. However, adenocarcinoma, the histological subtype with a worse prognosis, affects young women in particular and is less likely to be detected by early screening [5].

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M. von Wolff, F. Nawroth (eds.), *Fertility Preservation in Oncological and Non-Oncological Diseases*, https://doi.org/10.1007/978-3-030-47568-0_10

Stage-Dependent Prognosis

The tumour stage is one of the most important parameters for estimating prognosis in cervical cancer. It has a very good prognosis in the early stages (Table 1). Other clear prognostic and risk factors for cervical cancer are lymph node involvement, lymphatic-, neoplastic vascular invasion, tumour grading, histological subtype and the resection margins. Patients without lymph node involvement have a 5-year survival rate of 90%, while proven pelvic lymph node involvement reduces the rate to 20–60%, depending on the location [5].

Influence of Treatments on Fertility

Cervical Carcinoma In Situ

Cervical carcinoma in situ does not limit fertility per se. Treatment should be performed in the way that is therapeutically appropriate. Adaptation of the cone and the technique, optimally with a large loop excision of the transformation zone (LLETZ), reduces the negative effect on the occlusive function of the cervix in subsequent pregnancies and thus in particular the risk of premature birth [8].

Cervical Cancer

Oncological treatment for cervical carcinoma can influence female fertility in many ways (Fig. 1).

Table 1 Characteristics and stage-dependent prognosis of cervical cancer, data from German cancer registries [6, 7]

	Diagnosis of cervical cancer in 2016 (*n*)	Median age at diagnosis (cervical cancer)	Relative 5 years survival rates (FIGO 2009)	Median age at diagnosis (carcinoma in situ)
Cervical cancer	4380	55 years	FIGO stage I: 94% FIGO stage II: 63% FIGO stage III: 54% FIGO stage IV: 23% All stages: 67%	34 years

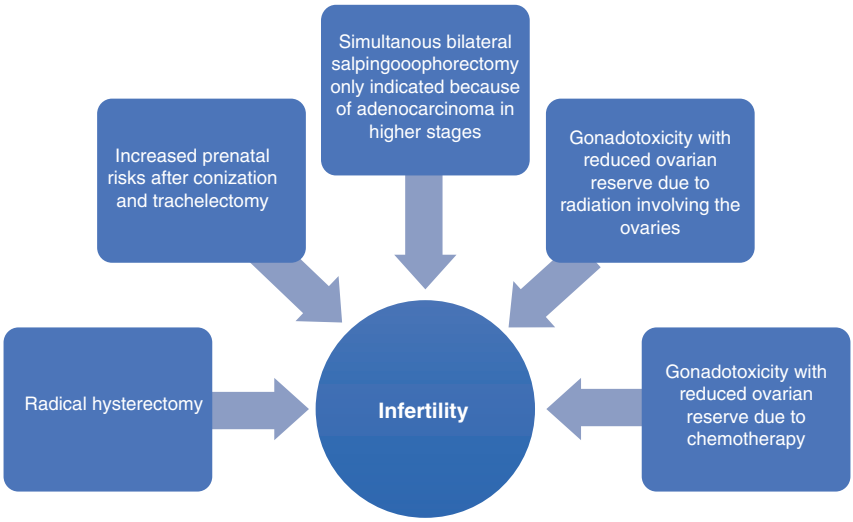

Fig. 1 Impairment of fertility as a result of cervical cancer and oncological treatment

Surgery

In early stages of cervical cancer, surgery is primarily indicated as a curative treatment and is equally effective as primary combined radiochemotherapy. Cervical treatment and therefore fertility-preserving therapy can only be permitted in early tumour stages up to a maximum of FIGO IB1b/IIA1 and tumour extension <2 cm can [9, 10]. The following recommendations are based on the currently valid German guidelines on cervical cancer and fertility maintenance in oncological disease [7, 11]. The Table 2 shows the flow chart of therapeutic decisions in young women with cervical cancer.

- In microinvasive stage FIGO IA1 with one risk factor, conisation—ideally as LLETZ (loop conisation) with R0 resection—primarily allows fertility to be maintained. For FIGO IA1 with L1 or FIGO IA2 and LO, a single sentinel node biopsy can be considered [12].
- In FIGO IA1 with two risk factors and from FIGO IA2 with one risk factor, the risk of lymph node involvement increases up to 5%. From these stages on, lymph node staging should be performed, ideally before the decision on fertility preservation. Radical trachelectomy according to Dargent [13] as a combination of tumour resection and complete staging as well as permanent cerclage is a special example of a surgical tumour treatment that is explicitly aimed at fertility. The post-operative residual cervix with a functional length of < or >10 mm is the most important influencing parameter on later obstetric complications. Vaginal sonography and MRI can be used to assess the risk of preterm birth [14].
- Under certain conditions—no other risk factors and small tumour volume (tumour <2 cm)—a radical trachelectomy can also be performed to treat FIGO IB1 and FIGO IIA1. Completion of surgery is recommended after pregnancy.

- Trachelectomy should not be recommended for neuroendocrine tumours or non-HPV-associated adenocarcinomas of the cervix.
- The uterine corpus should no longer be preserved for FIGO > IB1 cancers and radical hysterectomy, e.g. as total mesometrial resection (TMMR), is indicated [15]. The operation is performed according to the embryologically developed compartments and in a manner which protects the nerves. Even in the presence of risk factors, the TMMR treatment concept does not include adjuvant radiochemotherapy, only adjuvant chemotherapy. If radical hysterectomy is indicated, a bilateral salpingectomy should be performed, as the tubes belong to the uterovaginal (Müllerian) compartment.

Preservation of the ovaries is attempted, if possible, in cervical cancer patients. Even if there is evidence of adenocarcinoma, ovary preservation surgery can be performed in early stages after risk assessment. Various larger retrospective analyses of women with ovarian preservation and adenocarcinoma of the cervix FIGO stage I and II showed no significant differences in mortality [16]. Bilateral salpingo-oophorectomy should be considered from FIGO IB2 and adenocarcinoma onwards.

Combined Radiochemotherapy

If combined pelvic radiochemotherapy is necessary, the ovaries should be moved laterally and cranially outside the planned radiation field to protect the endocrine function. However, it is now also known that transposition of the ovaries itself can lead to a reduction in the ovarian reserve [17]. The gonadotoxic effect of pelvic radiotherapy depends on the total dose and the local dose calculated in the ovarian area, as well as the age of the woman during radiotherapy. At the age of 30, the radiation dose at which 97.5% of treated women experience complete ovarian failure (sterilisation) is 14.3 Gy [18] (see chapter “Indications for and Against Fertility Preservation”, Table 1). If the uterus is preserved and radiotherapy is performed, the uterus is no longer compatible with a later pregnancy. A uterine transplantation (see chapter “Further Fertility Preservation Techniques”) would then be an experimental approach, but it is particularly difficult in women who have previously undergone surgery and involves additional risks from the necessary immunosuppression [19].

Combined radiochemotherapy typically uses platinum-containing regimens for sensitisation to enhance the efficacy. Nevertheless, the gonadotoxic effect increases with the simultaneous irradiation of the pelvis.

Neoadjuvant Chemotherapy

Currently, neoadjuvant chemotherapy is only given in individual cases to enable uterus preservation after downstaging [20]. Ovarian tissue can be removed during laparoscopic lymph node staging [21] before the start of chemotherapy. However, this must be regarded as an experimental procedure.

In higher stages, active fertility preservation is not possible and endangers oncological safety.

Effectiveness and Risks of Fertility Preservation Therapy

Fertility-preservation therapy for cervical cancer is essentially limited to therapy which preserves the ovaries and uterine corpus. Although it is possible to carry out the fertility preservation measures listed in Table 2, these are often associated with considerable risks due to the increased probability of recurrence.

Metastasis of early cervical cancer into the ovaries is rare and is more likely to be found in the presence of risk factors such as deep infiltration and involvement of the uterine corpus. Nevertheless, adenocarcinoma in young women in particular is associated with an increased risk of ovarian metastasis [22]. This risk must be especially pointed out for adenocarcinoma with each ovarian preservation and cryopreservation. A meta-analysis of studies on cryopreserved ovarian tissue has not yet found an increased risk in women with cervical cancer, but the statement is limited due to the small number of cases and histological significance [23].

Other possible risks, which must be discussed individually with the patient as well as with the interdisciplinary teams (gynaecology oncology, radiotherapy and reproductive medicine), are shown in Table 2.

Conisation and trachelectomy can be performed as uterus-preserving and thus primarily fertility-preserving measures.

There have been several international studies in the past 15 years with higher case numbers which describe the oncological outcome and onset of pregnancy after trachelectomy. Recurrence rates after trachelectomy are reported to be <5% according to a Canadian publication [24]. However, the risk of recurrence after trachelectomy increases to 11% in women with primary tumours >2 cm. Pregnancies after trachelectomy are possible, and according to this analysis of more than 1200 treated

Table 2 Possible risks of fertility preservation for women with cervical cancer

Suggested oncological treatment	Options for fertility preservation	Possible risks
Radical hysterectomy	Preservation of uterus Cervical conisation Trachelectomy	Reduced oncological safety Increased risk of recurrence Obstetric risk after conisation and especially trachelectomy with increased risk of miscarriage and preterm birth
Bilateral salpingo-oophorectomy	Preservation of the ovary	Risk of ovarian metastasis (especially in adenocarcinoma)
Pelvic radiotherapy	Transposition of the ovaries	Alteration of ovarian function Chronic pain
Chemotherapy	Freezing of ovarian tissue	Transplantation of ovarian metastasis (especially in adenocarcinoma)

women, resulted in a live birth rate of 66.7%. A French study [25] also gives a comparable live birth rate after trachelectomy (70%) with a high proportion of premature births (38%).

Practical Approach

For women with a desire to have children and newly diagnosed early cervical carcinoma FIGO IA1 with risk factors, or up to IA2 without risk factors, fertility-preserving surgery with conisation is possible. Radical trachelectomy and ovarian preservation can be performed up to FIGO IB1 and FIGO IIA1 < 2 cm without risk factors. An increased risk of recurrence must be assessed in each individual case. The ovaries can be moved laterally prior to planned radiotherapy to maintain endocrine function.

If the ovarian reserve can be preserved in cervical cancer (possibly also by cryopreservation of ovarian tissue) but not the uterus, or if radiotherapy is required, there is theoretically—although not in Germany—the possibility of surrogacy. However, because of its ethical implications against legal regulations in many countries of the world, surrogate motherhood must be discussed in detail with the patient or the couple.

Experimental transplantation of the uterus (see chapter "Further Fertility Preservation Techniques") has also been reported [26, 27]. Also controversially discussed and classified as experimental is neoadjuvant chemotherapy for cervical cancer in higher stages, which should enable fertility-preserving surgery after downstaging (Fig. 2).

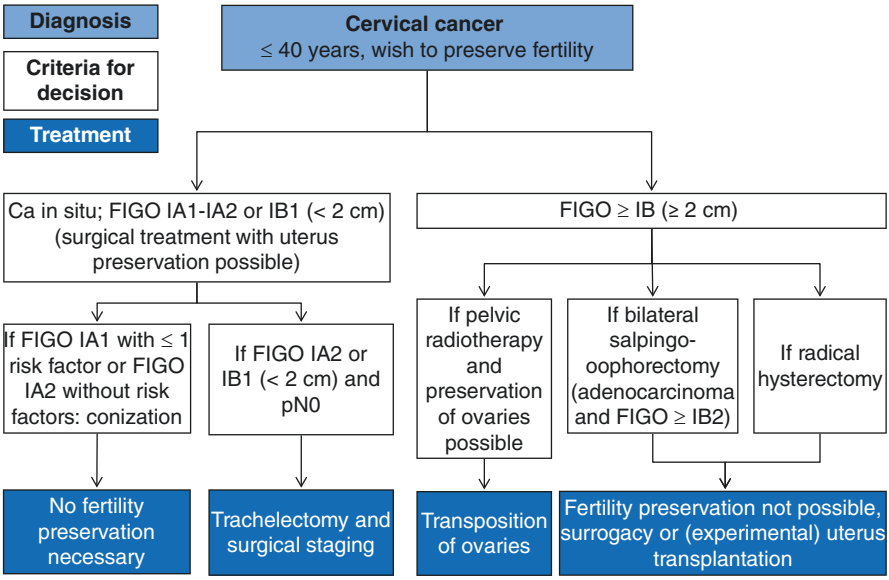

Fig. 2 Flowchart for fertility-preservation procedures in cervical carcinoma

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