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Fertility preservation during oncological treatment

1. *Quality of evidence:*
   I — Evidence obtained from properly designed and conducted randomized clinical trials or meta-analyses of randomized clinical trials
   II — Evidence obtained from properly designed and conducted prospective observational studies (non-randomized cohort studies)
   III — Evidence obtained from retrospective, observational, or case-control studies
   IV — Evidence obtained from experience gained in clinical practice and/or expert opinions
2. *Recommendation categories:*
   A — Indications confirmed unequivocally and extremely useful in clinical practice
   B — Indications likely to be potentially useful in clinical practice
   C — Indications defined individually

Introduction

The number of new cancer cases is increasing worldwide. Early diagnosis of cancer and appropriate therapy improve prognosis. One of the more serious effects of oncological treatment is the impairment of reproductive functions, leading to temporary or permanent infertility. Fertility protection in children and adults of reproductive age receiving oncological treatment is part of standard oncological care.

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Genetic basis of cancer in children and people of reproductive age

According to the data from the National Cancer Registry, 146 200 new cancer cases and 99 900 cancer-related deaths were registered in 2020 [1]. Cancer transformation is driven by abnormalities in genetic information, leading to acquisition of new, specific biological cell features [2, 3]. The first critical genetic abnormality can occur in any cell of the body and initiate neoplastic transformation in a specific location. These sporadic, non-hereditary changes account for about 75% of all cancers. If the abnormality occurs in the reproductive cells, it will be passed on to subsequent generations, leading to a hereditary cancer risk syndrome. Hereditary mutations affect 5–10% of all cancers [4, 5]. Most often, these abnormalities are inherited as autosomal dominants, rarely autosomal recessives. Identification of the hereditary burden of increased cancer risk syndrome improves medical care and allows taking preventive measures for the affected person and their family members [6]. On this basis, information should also be provided about the risk of passing a critical mutation to offspring and about possibilities of reducing this risk [7].

Recommendations

1. Access to clinical genetics consultation should be provided to any person suspected of having a hereditary cancer risk syndrome (IV, A).
2. Each carrier of a hereditary mutation (child and adult) with increased risk of cancer development should receive oral and written information about the risk of passing a critical mutation to offspring and the possibilities of reducing it by *in vitro* fertilization with genetic preimplantation diagnostics (IV, A).

Fertility counseling

All cancer patients of reproductive age, regardless of sex, cancer type and stage, should have access to fertility counseling before starting oncological treatment and preferably immediately after a cancer diagnosis.

The conversation with the patient and possibly his/her partner should take into account the patient's situation, procreative plans, having a partner, and possible genetic predisposition. Patients should be provided with information on the possibility of preserving fertility, the optimal time to try to conceive, course of pregnancy, and impact of oncological treatment on future offspring. Counseling should also be offered to patients who, at the time of diagnosis, do not plan to have children in the future. Individual management is determined by an interdisciplinary team consisting of an oncologist, a specialist in reproductive medicine, and a psychologist [8, 9].

Recommendations

1. Every cancer patient of reproductive age, regardless of sex, cancer type, and stage, should be informed about the risk of reproductive impairment before starting oncological treatment and should receive advice from a reproductive medicine specialist on how to reduce this risk (III, A).
2. Counseling about fertility preservation should take into account the patient's situation, sex and gender, age, cancer type and stage, type of planned treatment, possible genetic burden, and procreation plans (III, A).
3. Information on fertility preservation should be provided to the patient orally and in writing, and his/her decision should be documented in the medical records (IV, A).

Gonadotoxicity of oncological treatment

The gonadotoxic effect of standard anticancer treatment in men and women is quite well understood. Less is known about the risks associated with new treatments.

Surgery

Surgical treatment of women

Surgical procedures in the treatment of gynecological cancers have a direct impact on female reproductive potential [10–12]. The only way to have children after hysterectomy is to use surrogacy, but this method is not legally available in Poland.

Fertility-sparing treatment for ovarian cancer and borderline ovarian tumors

Fertility preservation involving unilateral adnexectomy while preserving the uterus is possible in patients with stage IA or IC1, low-grade serous, endometrial, or mucinous ovarian cancer (OC) with expanding growth [13].

Uterine preservation with unilateral adnexectomy may also be considered in selected, younger patients with stage IB OC with low risk of invasion and normal endometrial biopsy; however, data on this approach are scarce. In borderline tumors and stage IA mucinous carcinoma, unilateral oophorectomy is performed. In stage IB, when tumors occur in both ovaries, enucleation of the tumor from one or even both ovaries may be considered [14].

Fertility-sparing treatment for endometrial cancer

Fertility-sparing treatment may be used in patients with atypical hyperplasia/intraepithelial neoplasia of the endometrium or endometrial cancer grade G1. In these patients, uterine curettage or hysteroscopic

endometrial biopsy should be performed and medroxyprogesterone acetate (400–600 mg/day) or megestrol acetate (160–320 mg/day) should be used. Treatment with a levonorgestrel-releasing intrauterine device (IUD) with or without gonadotropin-releasing hormone analogs may also be considered. After 6 months, curettage of the uterine cavity, hysteroscopy, and imaging should be performed. No response to treatment is an indication for standard surgery. In the case of a complete response, the patient can try to become pregnant. Maintenance therapy should be considered in responding patients who wish to delay pregnancy. If hysterectomy has not been performed, a clinical evaluation should be performed every 6 months. After the patient has ended her procreation plans, it is recommended to perform a hysterectomy with removal of the ovaries and fallopian tubes (Salpingo-oophorectomy); ovarian sparing is debatable [15].

Fertility-sparing treatment for cervical cancer

Fertility-sparing treatment can be used in patients with squamous cell cervical carcinoma or adenocarcinoma up to 2 cm in size. It is not recommended in rare more malignant histological subtypes, for example, neuroendocrine tumors and adenocarcinomas unrelated to human papillomavirus (HPV) infection. If this procedure is planned, the first step should be the evaluation of the sentinel node. Patients with T1a1 and T1a2 N0 stages can undergo conization and simple trachelectomy. Radical trachelectomy (type A) may be considered at stages T1a1 and T1a2 N0 with vascular infiltration. Radical trachelectomy (type B) should be performed at stage T1b1 N0 with a lesion ≤ 2 cm and infiltration of the vascular spaces. There is no need for routine hysterectomy after the termination of reproductive plans [16].

Surgical treatment of men

Unilateral orchidectomy is routinely used as the first step in the treatment of primary testicular cancers. Resection of retroperitoneal lymph nodes, prostatectomy, cystectomy, pelvic exenteration, resection of the lower anterior colon, or any similar deep pelvic surgery may damage the vas deferens, ejaculatory duct, or seminal vesicles, which together form the testicular duct system. These procedures may also cause damage to the cavernous nerve with erectile dysfunction, damage to the autonomic nerves with impaired ejaculation, and physical interruption or obstruction of the seminal tract, as well as erectile dysfunction and/or dysfunction of the autonomic nerves [17].

Recommendations

1. All women of childbearing potential starting treatment should undergo individual fertility risk assessment by a multidisciplinary team (IV, A).
2. Fertility-preserving surgery may be considered in patients with stage IA or IC1, low-grade serous, endometrial, or mucinous ovarian cancer with expanding growth (III, C).
3. Fertility-sparing treatment may be used in patients with atypical hyperplasia/intraepithelial neoplasia of the endometrium or endometrial cancer of grade G1 (III, C).
4. Fertility-preserving treatment may be considered in patients with HPV-related cervical squamous cell carcinoma or adenocarcinoma up to 2 cm in size with negative margins and N0 disease (III, C).
5. Sperm cryopreservation should be considered before any testicular or other pelvic surgery (III, A).

Radiotherapy

Reproductive cells are particularly sensitive to ionizing radiation. Even small doses of radiotherapy reduce the number of male and female reproductive cells and may cause mutagenic changes. The damaging effect depends on the initial germ cell quality, irradiation dose, fractionation, and irradiated area (Tab. 1). A dose > 0.2 Gy affecting the gonads impairs spermatogenesis, and > 4 Gy causes irreversible changes. At doses of 1 to 2 Gy, spermatogenesis can be expected to return to a normal level after about 1 to 3.5 years [18]. A single dose is more gonadotoxic than several smaller fractions [19]. Irradiation of retroperitoneal lymph nodes results in dispersion of part of the dose to the vicinity of testicles, which justifies shielding them [20].

Administration of a dose of 2 Gy to the ovaries accelerates follicular atresia and reduces their pool. At the age of 15, a dose of 16 Gy causes permanent sterilization, and at the age of 30, it is 12 Gy. Radiotherapy of the pelvic area leads to abnormal development, growth, and trophic disorders of the uterus, vagina, and ovaries [21]. Irradiation also affects the elasticity of the uterus, which can lead to an abnormal course of pregnancy (miscarriage, abnormal placental development, premature birth, or uterine rupture), and in girls, it can cause abnormal development of the uterus.

In the case of total body irradiation (TBI) before hematopoietic stem cell transplantation, the risk of premature ovarian and testicular failure reaches 90% and is irreversible in most cases [22].

Central nervous system irradiation may cause secondary hypogonadism; doses of 30–40 Gy lead to secondary ovarian and testicular failure in 80% of patients. Damage to pituitary cells can be a significant cause of abnormal secretion of growth hormones, sex hormones, and adrenal and thyroid hormones. The consequence of brain irradiation may also be hyperprolactinemia caused by a deficiency of the inhibitory neurotransmitter dopamine. It affects 20–50% of women

Table 1. Risk of gonadotoxicity after radiotherapy in women depending on dose and age

Total dose and irradiation area	Risk of gonadotoxicity in the prepubertal period	Risk of gonadotoxicity in women aged 15–40 years	Risk of gonadotoxicity in women > 40 years of age
< 6 Gy per abdomen/pelvis	Moderate	None	None
15 Gy per abdomen/pelvis	High	Low	Moderate
25–50 Gy per abdomen/pelvis	High	Moderate	High
50–80 Gy per abdomen/pelvis	High	Moderate	High
CNS and spinal cord irradiation	Moderate	Moderate	Moderate
Whole body irradiation	High	High	High

CNS — central nervous system

and about 5% of children and is usually asymptomatic [23–24].

Irradiation of the thyroid area may cause hormonal disorders, disrupting the menstrual cycle.

Recommendations

1. Irrespective of the planned dose of radiotherapy to the testicular area, semen preservation is recommended before it starts (III, A).
2. In patients irradiated to the pelvic area, a testicular shield should be used (III, A).
3. In women of childbearing potential, ovarian transposition and freezing of oocytes, embryos, or ovarian fragments should be considered before starting radiotherapy (III, A).
4. In patients receiving whole-body irradiation, one of the available methods of fertility protection should be considered (III, A).
5. Due to the risk of secondary hypogonadism, it is advisable to use one of the available methods of fertility protection before starting brain irradiation (III, A).

Chemotherapy

Cytotoxic drugs can damage gonadal function and reduce fertility in children and people of reproductive age [25–28]. Chemotherapy-induced fertility disorders in women are most often manifested by amenorrhea at various times after its completion, possibly in combination with postmenopausal hormone levels [27].

In breast cancer, amenorrhea occurs in approximately 80% of patients receiving the combination of docetaxel and cyclophosphamide or doxorubicin and cyclophosphamide followed by a taxoid. At the same time, there is a deep and long-term decrease in anti-Mullerian hormone (AMH) levels [29, 30]. Dose-dense chemotherapy regimens used in breast cancer patients do not increase the risk of amenorrhea compared to the standard regimen [31].

In Hodgkin lymphoma, premature ovarian failure due to chemotherapy occurs in about 40% of women. In women aged 15–40, the cumulative risk of premature ovarian failure after treatment with and without alkylating drugs is 60% and 3–6%, respectively [32]. In patients with non-Hodgkin's lymphoma receiving CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOPE3 (CHOP + etoposide) regimens, earlier menopause and lower AMH levels were found [33]. Azoospermia, sometimes causing permanent infertility, has been observed in more than 90% of patients treated with procarbazine [34]. ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) is less gonadotoxic [35].

In patients with hematological malignancies undergoing hematopoietic stem cell transplantation (HSCT), conditioning regimens containing high doses of alkylating drugs are used. This leads to premature gonadal failure in most women and men. The main predictors of ovarian function return include the patient's age at transplantation, AMH level, and the number of chemotherapy cycles [36].

Data on the impact of chemotherapy on fertility in patients with ovarian cancer are limited. In a small group of patients receiving mostly platinum derivatives in monotherapy, no ovarian dysfunction was observed [37]. On the other hand, in patients with non-epithelial ovarian cancer receiving BEP (etoposide, cisplatin, and bleomycin) or EP (etoposide, cisplatin) regimens, amenorrhea, and earlier menopause were more frequent [37].

Chemotherapy regimens used for colorectal cancer have an insignificant effect on fertility. There are no data on the risk of gonadotoxicity of taxanes or fluorouracil in men [25].

Table 2 presents the risk of gonadotoxicity disorders in women depending on the chemotherapy regimen.

Table 3 presents groups at risk of infertility after anticancer treatment in childhood.

Recommendations

1. Due to the gonadotoxicity of chemotherapy, it is recommended to use one of the methods of fertility protection before starting chemotherapy (III, A).
2. Fertility preservation methods with proven effectiveness include freezing of eggs, embryos, or ovarian tissue (II, A).
3. Non-hormonal or barrier contraception is recommended during chemotherapy (II, A).

Hormone therapy

Hormone therapy is routinely used in patients with early and advanced breast cancer, prostate cancer, and some gynecological cancers.

In patients with hormone-sensitive breast cancer postoperative hormone therapy is used for 5–10 years, depending on the cancer stage. In patients in the reproductive period, tamoxifen or aromatase inhibitors in combination with gonadoliberin analogs or tamoxifen alone are most often used. Tamoxifen often leads to menstrual disorders but does not affect AMH levels [38–40]. Data on the effect of this drug on the course of pregnancy and the health of children conceived during therapy are contradictory. Since tamoxifen may increase the risk of miscarriage and developmental defects (e.g., craniofacial malformations, genital defects), non-hormonal or barrier contraception is recommended during therapy and 3 months after its completion [41–43]. Gonadoliberin analogs cause temporary inhibition of ovarian function in approximately 85% of patients [44]. Menstruation returns in 90% of patients up to the age of 40 and much less often in older women [45].

So far, no gonadotoxic effects of tamoxifen and aromatase inhibitors in combination with a gonadoliberin analog have been reported. However, long-term hormone therapy postpones pregnancy; therefore, it is recommended to seek advice on securing fertility before starting treatment. There are two ways to increase the chances of getting pregnant: preserve eggs, embryos, or ovarian tissue before starting treatment, or temporarily stopping hormone therapy and trying to get pregnant in the meantime. The safety of this procedure was assessed in a study involving 518 patients with hormone-dependent breast cancer aged up to 42 years [46]. After 18–30 months of post-operative hormone therapy, it was interrupted for up to 2 years for patients to try to conceive, after which the treatment was continued for the originally planned duration. Preliminary results of the study indicate that a break in hormone therapy does not increase the risk of cancer recurrence; however, further observation is indicated.

Pregnancy after treatment of breast cancer, also expressing hormone receptors, does not worsen the prognosis or affect the health of the child [46].

Recommendations

1. Hormone therapy does not have a gonadotoxic effect, but due to its long duration, it delays conception. For this reason, patients should be advised to seek counseling and take measures to preserve fertility before starting treatment (II, C).
2. Fertility preservation methods with proven effectiveness include eggs, embryos, or ovarian tissue cryopreservation (II, A).
3. During adjuvant hormone therapy, non-hormonal or barrier contraception is recommended (II, A).
4. It is safe to become pregnant during a planned interruption of hormone therapy (II, C).

Molecularly targeted therapy

There are few data on gonadotoxicity induced by molecularly targeted drugs [25]. In patients with HER2-positive breast cancer, no effect of trastuzumab, lapatinib, and T-DM1 (trastuzumab emtansine) on gonadal function was found [47–49]. Less is known about the gonadotoxic effects of poly-(ADP-ribose) polymerase (PARP) inhibitors, cyclin-dependent kinase (CDK 4/6) inhibitors, and targeted drugs used in melanoma patients. In animal studies, testicular degeneration was observed in male rats receiving BRAF inhibitors — dabrafenib, encorafenib, cobimetinib, and a reduced number of oocytes in female rats receiving dabrafenib, trametinib, and cobimetinib [50].

There is some evidence that tyrosine kinase inhibitors (TKIs) may adversely affect oocyte and sperm maturation, gonadal function, and fertility. Treatment with imatinib impairs ovarian function; however, spontaneous pregnancies are observed during treatment with this drug; therefore, the use of effective contraception is recommended. Data on the effect of imatinib on male fertility are inconclusive. Over 90% of patients using this drug experienced a transient decrease in testosterone levels, and 20% developed gynecomastia [51].

In women receiving radioiodine (^{131}I) after surgical treatment for thyroid cancer with high risk of recurrence within a year, decreased AMH levels were observed [52, 53].

Recommendations

1. Most targeted therapies are not gonadotoxic, but data on this are sparse. Therefore, patients should be informed about the potential risk of fertility disorders and recommended methods of fertility preservation (IV, B).
2. During targeted therapy and several months after its completion, contraception is recommended (IV, A).

Immunotherapy

In the ovaries and testes, the physiological expression of programmed death receptor type 1 (PD-1) protein

Table 2. Gonadotoxicity risk of anti-cancer treatment in women (based on the European Society of Human Reproduction and Embryolog recommendations)

Degree of risk of amenorrhea after oncological treatment	Therapy
High risk (> 80%)	Regimens containing cyclophosphamide [with anthracyclines and/or taxanes: (F)EC/(F)AC alone or followed by T or P; TC] in breast cancer patients ≥ 40 years of age
	Conditioning regimens for HSCT with cyclophosphamide and/or TBI in patients with hematological malignancies
	Abdominal and pelvic radiotherapy with ovarian coverage
Intermediate risk (40–60%)	Regimens containing cyclophosphamide [with anthracyclines and/or taxanes: (F)EC/(F)AC alone or followed by T or P; TC] in breast cancer patients aged 30–39 years
	Regimens based on alkylating agents (e.g., MOPP, BEACOPP, CHOP, CHOPE) in patients with lymphoma
Low risk (< 20%)	Regimens containing cyclophosphamide [with anthracyclines and/or taxanes: (F)EC/(F)AC only or followed by T or P; TC] in breast cancer patients ≤ 30 years of age
	Non-alkylating regimens (e.g., ABVD or EBVP) in lymphoma patients ≥ 32 years of age
	BEP/EP in patients with non-epithelial ovarian cancer
	FOLFOX, XELOX, or capecitabine in colorectal cancer patients
	Multi-drug chemotherapy (EMA-CO and platinum-based regimens) for gestational trophoblastic disease
	Radioactive iodine (^{131}I) in thyroid cancer patients
Very low or no risk	*Vinca* alkaloids
	Targeted drugs (trastuzumab, lapatinib, and rituximab)
	Tamoxifen, GnRH analogs, aromatase inhibitors, medroxyprogesterone acetate, megestrol
	Non-alkylating chemotherapy regimens (e.g., ABVD or EBVP) in lymphoma patients < 32 years of age
	Methotrexate monotherapy
Unknown risk	Chemotherapy containing platinum derivatives and taxoids in patients with gynecological and lung cancer
	Most targeted therapies (monoclonal antibodies, PARP inhibitors, CDK4/6 inhibitors, tyrosine kinase inhibitors) and immunotherapy

(F)EC/(F)AC — 5-fluorouracil, epirubicin/doxorubicin, cyclophosphamide; ABVD — doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP — cyclophosphamide, doxorubicin, vincristine, bleomycin, etoposide, procarbazine, prednisone; BEP — etoposide, cisplatin, bleomycin; CHOP — cyclophosphamide, doxorubicin, vincristine, prednisone; CHOPE — CHOP, etoposide; EBVP — epirubicin, bleomycin, vinblastine, prednisone; EMA-CO — etoposide, actinomycin D, methotrexate, followed by cyclophosphamide and vincristine; EP — etoposide, cisplatin; FOLFOX — 5-fluorouracil, oxaliplatin; GnRH analog — analog of gonadotropin-relea sing hormone; HSC — hematopoietic stem cells; MOPP — mechlorethamine, vincristine, procarbazine, prednisone; P — paclitaxel; PARP — poly-(ADP-ribose) polymerase T — docetaxel; TBI — total body irradiation; XELOX — capecitabine, oxaliplatin

and its ligand (PD-L1, programmed death ligand 1) is low. The use of immune checkpoint inhibitors (ICIs) may lead to various hormonal disorders, including primary and secondary hypogonadism, secondary sexual disorders, and decreased libido [54]. So far, the direct impact of ICIs on the ovarian reserve and reproductive potential of men has not been determined, but a few reports indicate autoimmune testicular damage leading to azoospermia [55].

PD-L1 is strongly expressed in the placenta, but no direct teratogenic effect of ICIs on the fetus has been demonstrated. The activated immune response may lead to miscarriage, inhibit fetal growth, or cause immune-mediated adverse reactions in the fetus or mother. For this reason, the use of ICIs in pregnant women is not recommended [55]. In pregnant patients with metastatic cancer (e.g., melanoma), decisions should be made individually, taking into account the dynamics of the disease and available treatment options.

Stimulation of a woman's immune system, even for many months after therapy completion, may reduce the immune tolerance of the developing fetus or cause reproductive failure in the future. For this reason, contraception is recommended during therapy and for 5 months after its completion [56].

Recommendations

1. Fertility counseling is recommended before starting immunotherapy (IV, C).
2. Immunotherapy is not recommended in pregnant women (IV, C).

Table 3. The risk of infertility depending on the type of cancer and treatment in children

Low risk (< 20%)	Intermediate risk	High risk (> 80%)
Acute lymphoblastic leukemia	Acute myeloid leukemia	Total body irradiation
Stage I soft tissue sarcomas	hepatoblastoma	Pelvic or testicular radiotherapy
Germinal tumors (without radiotherapy and with gonad preservation)	Ewing's sarcoma without metastasis	Conditioning chemotherapy prior to bone marrow/stem cell transplantation
Retinoblastoma	Osteosarcoma	Hodgkin's lymphoma (with use of alkylating agents)
Brain tumors (surgery +/– radiotherapy < 24 Gy)	Brain tumors, spinal radiotherapy, brain > 24 Gy	Stage IV soft tissue sarcomas
	Stage II–III soft tissue sarcomas	Ewing's sarcoma with metastases
	Non-Hodgkin's lymphomas	
	Hodgkin lymphoma	

3. Contraception is recommended during immunotherapy and for 5 months after its completion (IV, C).

Fertility protection in women

Along with the growing incidence of cancer, also among women of reproductive age, and the delayed delivery of the first child, the number of women diagnosed with cancer who plan to start or enlarge a family is growing. Fertility preservation should be an integral part of oncological care.

When choosing a method of fertility protection, the patient's reproductive potential and expectations, clinical situation, and having a partner should be taken into account. The decision should be made by the patient, possibly in consultation with his/her partner, after obtaining full information on this subject from a team consisting of an oncologist, a reproductive medicine doctor, a psychologist, and, if necessary, a geneticist. The decision-making algorithm regarding the choice of the method or methods of fertility preservation is presented in Figure 1.

Pharmacological ovarian suppression

Ovarian suppression using GnRH analogs can be used in any case of risk of fertility loss due to chemotherapy. Although the protective mechanism of action of these drugs has not been fully elucidated, their efficacy and safety have been confirmed in several randomized clinical trials [57, 58].

Most of the studies involved patients with breast cancer. A meta-analysis published in 2018 showed that the use of GnRH analogs during chemotherapy increased the chance of getting pregnant almost two-fold [59]. The percentage of pregnancies in the range of 5–10% indicates, however, that this method is rather complementary in patients with breast cancer but is insufficient to preserve fertility. The protective effect of GnRH has not been found in patients with lymphomas [60]. On the other hand, in patients with ovarian cancer, GnRH analogs used together with chemotherapy reduced the risk of ovarian failure [61].

Ovarian transposition before radiotherapy

The evidence for the effectiveness of ovarian transposition is based on small retrospective studies. Ovarian transposition before planned radiotherapy should be performed in a minimally invasive manner. In selected situations, an alternative may be to shield the ovaries during irradiation.

Ovarian tissue cryopreservation

Ovarian tissue freezing (cryopreservation) is still an experimental procedure in Poland. The advantage of autotransplantation of ovarian tissue is the restoration of its natural functions and proper hormonal balance and the possibility for patients to get pregnant naturally. In addition, this method can be used in patients who have already started chemotherapy. However, in such a situation, stimulation and collection of mature oocytes is not recommended due to the risk of damaging their genetic material during chemotherapy. Since the activity of the ovarian tissue has to be maintained for a long time, it is not recommended to freeze it by vitrification, but rather slowly [62].

Oocyte (or embryos) cryopreservation — stimulation of ovulation and eggs retrieval

The most commonly used and most effective method of fertility protection is stimulation of ovulation and the collection of oocytes and their freezing or *in vitro* fertilization and freezing of embryos. In the case

of hormone-dependent tumors, stimulation with an aromatase inhibitor or progesterone may be used. The effectiveness of this method depends to a large extent on the patient's age and her ovarian reserve (number and quality of available oocytes), assessed based on the serum AMH level and the number of antral follicles in the sonographically visualized ovaries.

Oocyte *in vitro* maturation (IVM)

When preparing ovarian tissue for freezing, immature oocytes can be harvested and then prepared for *in vitro* maturation (IVM); however, this method is still experimental.

Recommendations

1. Before gonadotoxic oncological treatment, it is recommended to assess the AMH level (preferably after discontinuation of any drugs affecting the concentration of sex hormones or contraceptives) (III, A).
2. In patients with breast cancer, regardless of its subtype, GnRH analogs are recommended during chemotherapy. These drugs should not be used routinely in patients with cancers other than breast cancer (I, A).
3. In women with sufficient ovarian reserve and no risk of ovarian metastases, ovarian transposition may be used before pelvic radiotherapy, and gonadal shielding may be used in selected patients (IV, C).
4. In women at risk of gonadotoxic effects, ovarian tissue freezing (II, A) may be additionally considered. Relative contraindications include limited ovarian reserve, age > 36 years (III, B), and hematological, pelvic, and other cancers with high risk of gonadal metastasis (III, A). Freezing of ovarian tissue is the most effective method of protecting fertility in women who have already started chemotherapy or who had started chemotherapy up to 6 months earlier (IV, A).
5. If the start of oncological treatment can be postponed by about 2 weeks, the basic method of fertility protection is the collecting and freezing of oocytes (II, A).
6. A patient with a partner may be offered embryo freezing with possible simultaneous oocyte and embryo freezing (IV, A).
7. If rapid initiation of oncological treatment is necessary, stimulation should be started regardless of the phase of the menstrual cycle. Multiple stimulations result in more eggs in less time (III, A). In hormone-dependent tumors, stimulation with an aromatase inhibitor or progesterone may be used (III, A).

Fertility protection in men

The consequence of cancer, radiotherapy, systemic treatment, or surgical treatment may cause temporary or permanent male infertility [63–64]. The resumption of spermatogenesis depends on the type of treatment, its intensity, and individual sensitivity. It is important that before starting treatment, preferably after diagnosis, the medical team, with the participation of a reproductive medicine specialist, presents the patient with options for preserving fertility [65].

The most effective method of reducing the risk of infertility in men is freezing semen obtained by masturbation. It is important to secure more than one sample [66]. Before freezing, a semen sample should be collected for testing to exclude carriers of infectious diseases and to assess its quality. In many patients, the semen quality deviates from the normal values before starting oncological treatment [67]. A chance for fertilization, even with a small number of male reproductive cells, is given by intracytoplasmic sperm injection (ICSI) [66–68].

Sperm collection may be supported by phosphodiesterase type 5 inhibitors used in the treatment of erectile dysfunction [69]. If neurological disorders or psychogenic anejaculation are the cause that makes sperm donation difficult, penile vibratory stimulation (PVS) can be used, while in the case of damage to the ejaculatory reflex arc, electrostimulation may be indispensable (both procedures are rarely performed in Poland) [70, 71]. In men with retrograde ejaculation, semen collection attempts begin with oral administration of sympathomimetic drugs, anticholinergics, or a combination thereof. If these methods are ineffective, sperm can be obtained after masturbation and prior alkalization of the urine [72].

If sperm cannot be obtained by masturbation (e.g. as a result of azoospermia or cryptozoospermia), a fragment of the testicle can be surgically removed [73]. Once selected, the sperm are frozen and used for *in vitro* fertilization (IVF/ICSI).

Gonadoliberin analogs have not been demonstrated to protect fertility in males; therefore, the use of this method is unjustified [74].

A special group includes patients with hematological or testicular cancers, in whom autologous transplantation of frozen testicular cells or tissues carries the risk of cancer dissemination. Research is currently underway on the transplantation of allogeneic testicular cells or tissues and the *ex vivo* culture of mature spermatozoa derived from stem cells [68].

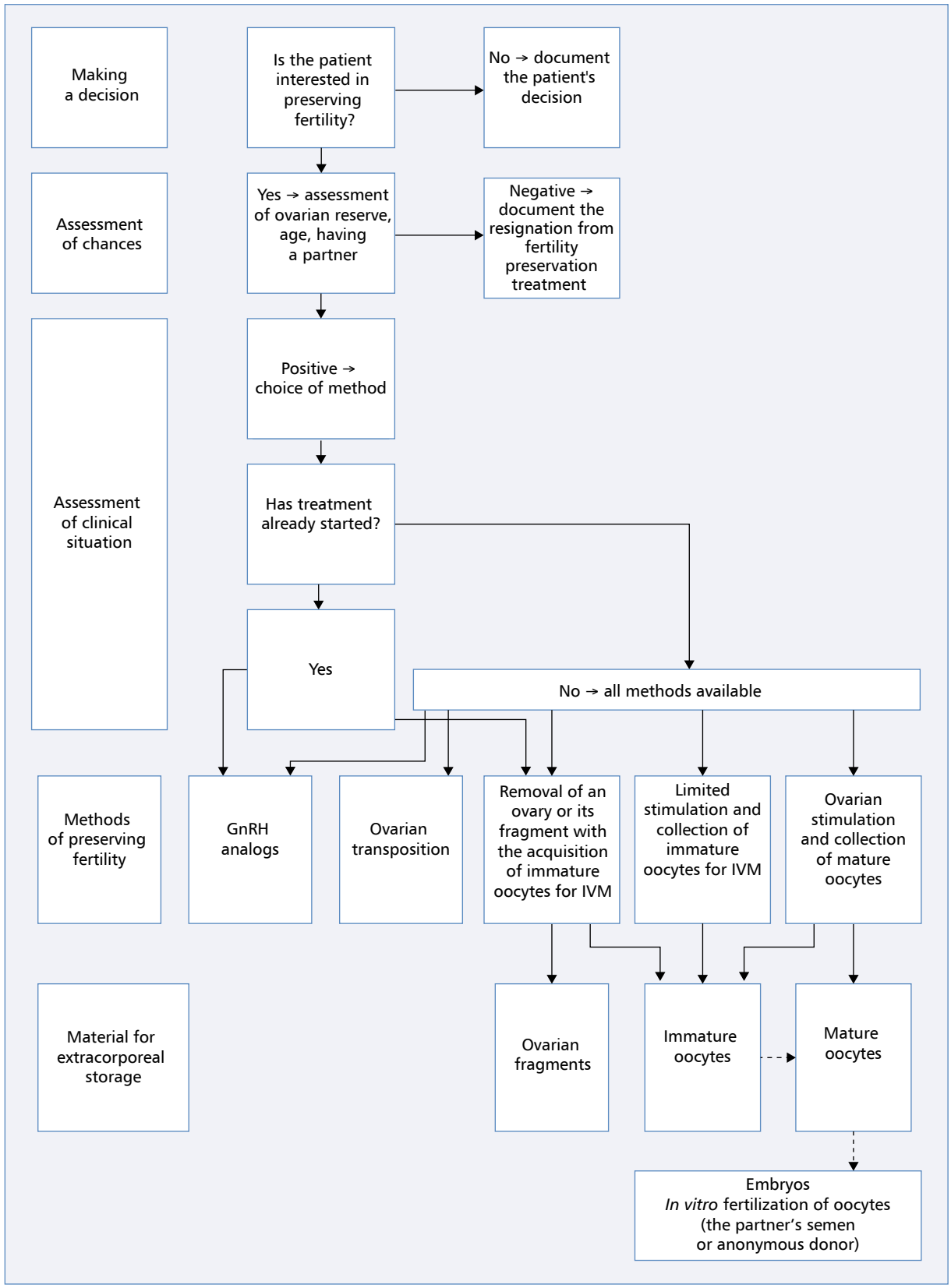

Figure 1. Algorithm for management of fertility preservation in women; GnRH — gonadotropin-releasing hormone; IVM — *in vitro* maturation

Recommendations

1. Semen freezing should be offered to every man of childbearing age before starting oncological treatment. The most effective form is obtaining sperm from the ejaculate (II, A).
2. In exceptional cases, an attempt can be made to surgically obtain sperm from the testicles (IV, C).
3. The use of hormonal protection of spermatogenesis is not recommended (III, B).

Fertility protection in children

In developed countries, over 80% of children with cancer are cured or achieve long-term remission. However, 60–85% of convalescents experience adverse effects of chemo- and/or radiotherapy, including damage to the gonads or infertility. Fertility disorders may result from radio- and/or chemotherapy and surgical treatment [75].

Ovarian and testicular tissue freezing is used to preserve fertility in children receiving chemotherapy, and sperm and egg cells are frozen when they reach maturity. In children receiving radiotherapy, gonadal shields, and ovarian transposition are used.

Testicular tissue freezing is an experimental method and is only used when a semen sample cannot be obtained. The whole or part of the removed testicle may be frozen. An open biopsy of the testis is usually preferred.

In prepubertal girls, the ovaries cannot be stimulated to produce mature eggs. On the other hand, there is no unequivocal evidence confirming the possibilities for pregnancy and delivery as a result of cryopreservation of ovarian tissue collected in the prepubertal period. Such information should be provided to patients and their legal guardians. This is especially true for tumors that may metastasize to the ovaries or, as in the case of leukemia, frozen tissue can contain tumor cells [76].

Once they are mature enough to produce eggs or sperm, the treatment of children is the same as that of adults, except that embryo production is excluded.

The age of spermarche in boys ranges from 10 to 16 years old — usually around 12 years old. Semen for freezing is obtained by masturbation, after obtaining consent of the legal guardian. If obtaining a semen sample in sexually mature boys is not possible, sperm extraction from the testicle and their future use for *in vitro* fertilization using micromanipulation may be considered.

Recommendations

1. It is necessary to inform parents, guardians, and patients — depending on their age — about the possibility of fertility disorders resulting from anticancer treatment, as well as about the possibility of fertility preservation (IV, A).
2. Multidisciplinary cooperation is required, i.e., the establishment of an oncofertility team with the participation of a pediatric oncohematologist, pediatric endocrinologist, reproductive medicine physician, urologist, psychologist, and a specialized nurse. The management plan for patients at prepubertal age is shown in Figure 2 (IV, A).
3. Oocyte or sperm freezing should be offered to any patient at risk of infertility who is eligible for these methods (II, A).
4. Prepubertal children and their legal guardians should be informed that available methods of fertility protection are experimental and may have limited effectiveness (IV, A).
5. In sexually mature individuals in whom sperm cannot be obtained from the ejaculate, freezing of testicular tissue should be considered (IV, C).

Preimplantation genetic diagnostics

Preimplantation diagnostics include genetic testing of embryos before they are transferred to the uterine cavity. Depending on the purpose, it can be used to detect single gene disorders (e.g., point mutations), structural chromosome abnormalities (e.g., translocations), quantitative chromosome disorders (aneuploidies), and predisposition to genetic diseases of polygenic etiology. Patients should be informed that a "normal" or negative preimplantation genetic test result does not guarantee the absence of genetic disorders in the newborn. Performing a preimplantation test does not exclude the need to perform prenatal tests when indicated.

Biopsy of polar bodies (small fragments of cells separated from the oocyte during meiotic division) or embryos (both on the 3rd and 5th–6th day of development), and even performing them sequentially on a single embryo, does not pose a threat to the embryo and the child born from it [77].

Preimplantation testing for monogenic diseases occurring in adults is ethically justified if diseases are serious, the methods of their prevention and treatment are unknown, or when the available methods are ineffective or perceived as very burdensome [78].

It is recommended that before starting preimplantation diagnostics, each patient should have the opportunity to consult a clinical geneticist and, if necessary, an oncologist and a psychologist, and that they should jointly decide on the scope of the planned diagnosis.

Being a carrier of a mutation that increases cancer risk does not exclude the presence of other genetic diseases, such as some rare diseases. As part of the screening, it is recommended to perform a basic test for mutations occurring in all ethnic groups, including in the *CFTR*, *SMA,* and *FMR1* genes, and to extend

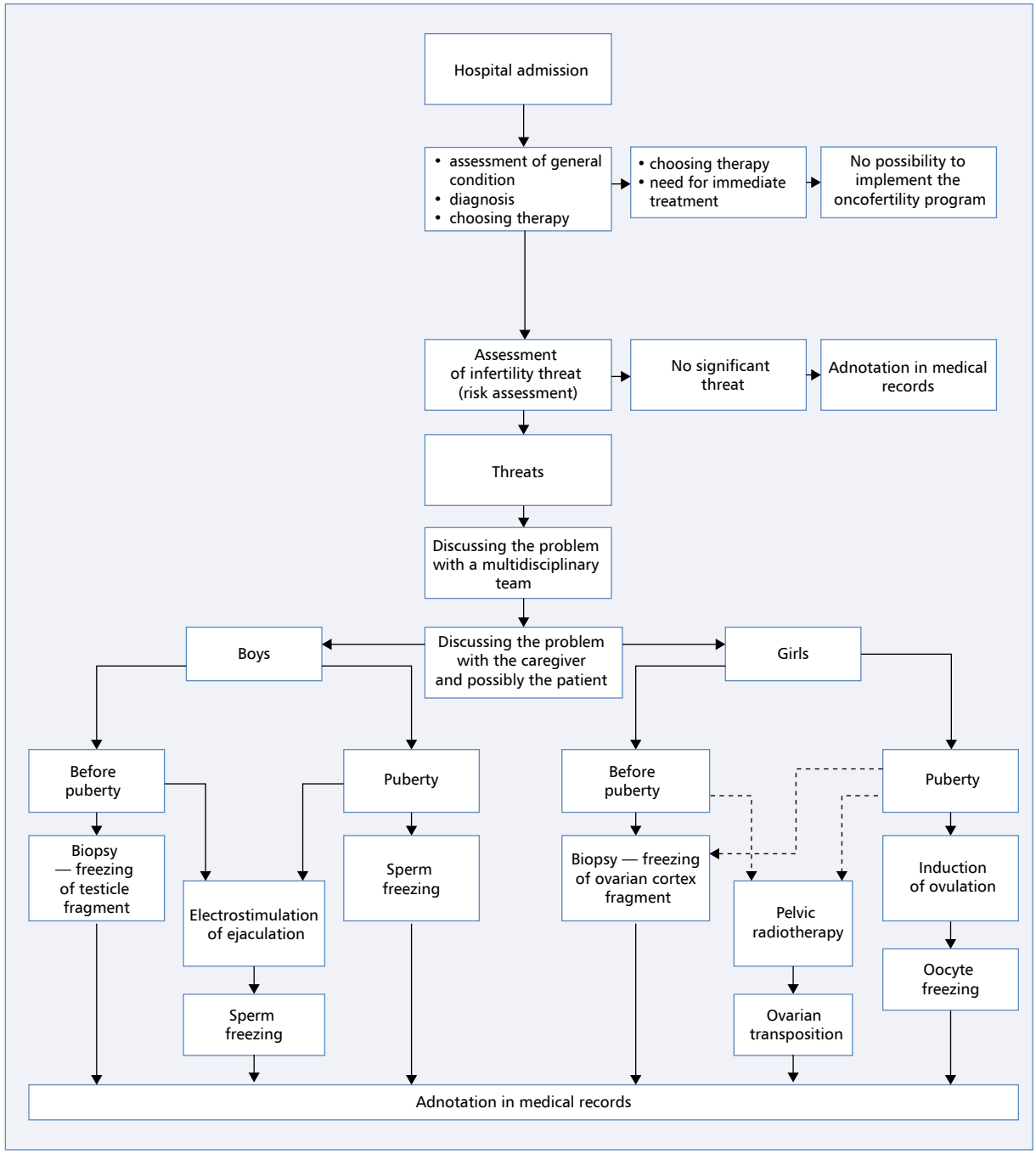

Figure 2. Algorithm for fertility management protection in prepubertal patients

the diagnostics depending on ethnic origin. The second group of disorders that require additional tests as part of preimplantation diagnostics are aneuploidies, i.e., an abnormal number of chromosomes in a cell. The risk of these disorders increases with the mother's age, so it is of particular importance in women with a history of cancer, which usually postpones motherhood for several years.

Preimplantation diagnostics, by removing the genetic etiology of cancer diseases, breaks the chain of their familial occurrence, minimizes the risk of rare diseases, and prevents genetic diseases related to the mother's age (e.g., Down syndrome, Edwards syndrome, or Patau syndrome).

It should be remembered that as a result of the diagnostics, only a part of the examined embryos will meet the criteria for transfer. Embryos with genetic abnormalities

are not transferred and remain frozen. It should also be remembered that only some of the healthy embryos are implanted in the uterus, which limits the effectiveness of attempts to conceive [79].

Recommendations

1. Carriers of pathogenic gene variants with high risk of cancer should receive detailed information on preimplantation genetic testing (IV, C).
2. Each woman who decides to undergo preimplantation diagnostics has to consult a clinical geneticist, and if necessary, an oncologist and a psychologist to jointly decide on the scope of diagnostics (IV, C).
3. Patients should be advised that a "normal" preimplantation genetic test result does not guarantee the absence of genetic abnormalities in the child (IV, C).

Legal aspects of fertility protection in cancer patients

The possibility of impaired fertility related to oncological treatment imposes certain information obligations on the doctor. The Act on Infertility Treatment defines, among others, the principles of protection of the embryo and reproductive cells in this clinical situation, as well as methods of infertility treatment, including medically assisted procreation [80]. The Act allows *in vitro* fertilization of no more than six female reproductive cells. If the recipient reaches the age of 35 or has a disease coexisting with infertility or has failed *in vitro* fertilization twice, it is possible to fertilize more female reproductive cells, but this information should be recorded in the medical documentation. The Act prohibits the use of male and female reproductive cells from a deceased donor in assisted procreation [81].

The patient's consent is a prerequisite for providing a health service, including the procedure of assisted procreation. A minor patient who is over 16 years of age has the right not to consent to an examination or other health services despite the consent of his legal representative or actual guardian. In this case, the law specifies that guardianship court authorization is required.

The Act on the Professions of Physician and Dentist imposes an obligation on the physician to provide the patient or his/her statutory representative with accessible information about the patient's health condition, diagnosis, proposed and possible diagnostic and treatment methods, foreseeable consequences of their use or omission, treatment results, and prognosis. The Act also requires the doctor to provide the patient with full information about the risks associated with fertility, including in particular difficulties in getting pregnant. This information should be documented in medical records. Violation of this obligation may result in the unlawfulness of therapies implemented with regard to the patient and result in the physician's liability [82].

Eggs cryopreservation is legally permissible. The Act on Infertility Treatment formulates the donor's right to dispose of oocytes, including the right to demand their destruction.

Embryos capable of proper development resulting from reproductive cells collected for partner or non-partner donation, which have not been used in the assisted procreation procedure, must be stored in conditions ensuring their proper protection until transferred to the recipient's body.

If both donors die, the embryos are transferred to an anonymous donation program. It is inadmissible to destroy embryos capable of normal development and not transferred to the recipient's body, and it does not have to be the person in whom the implantation of the embryo was originally supposed to take place [83].

Recommendations

1. The patient has the right to consent to the provision of health services, including assisted procreation techniques (IV, A).
2. No more than six female reproductive cells may be fertilized. If the recipient reaches the age of 35, is diagnosed with a disease coexisting with infertility, or has had two ineffective *in vitro* fertilization treatments, it is possible to fertilize more female reproductive cells, in which case the reason should be documented in the patient's medical records (IV, A).
3. The semen of the deceased must not be used in the procedure of insemination and the procedure of medically assisted procreation (IV, A).
4. Embryos incapable of normal development must not be used (IV, A).

Psychological aspects of fertility protection in cancer patients

The risk of losing fertility associated with oncological treatment and making decisions about its protection cause stress and anxiety, and, in the case of abandoning the attempt to preserve fertility, long-term regret. The adverse effects of this situation can be reduced by supporting teams involving doctors, psychologists, and other healthcare professionals. Communication with the patient should be adapted to his/her age and life situation and should also include his/her family [84]. The information provided should cover medical procedures, risks, benefits, chances of success, and costs. The participation of the patient's partner and family may be useful in discussing all aspects related to fertility [85, 86].

Recommendations

1. A clinical psychologist should be part of the multidisciplinary team dealing with fertility preservation in cancer patients (IV, C).
2. Depending on the patient's situation, the cancer patient's partner and other family members should be involved in the decision-making process about fertility preservation (IV, C).

Pregnancy after cancer

The increasing age of mothers giving birth to children is accompanied by a growing desire to have children after being cured of cancer [25]. Most data on pregnancy after cancer treatment concerns patients with breast cancer. They indicate that pregnancy is possible and safe in this group. This also applies to women diagnosed with hormone-dependent breast cancer. Cured patients should be informed that pregnancy, time from cancer diagnosis to pregnancy, or breastfeeding do not affect the risk of recurrence and that in breast cancer it is safe to interrupt postoperative hormonal therapy to become pregnant.

However, there is an increased risk of obstetric and childbirth complications in women after oncological treatment, including prematurity, low birth weight, delivery by cesarean section (elective or emergency), assisted delivery, or postpartum hemorrhage. The risk of complications seems to be higher if the interval between oncological treatment completion and pregnancy is short [87]. For this reason, close monitoring of pregnancies after cancer treatment is recommended. In addition, at least a one-year break from chemotherapy cessation is recommended before trying to get pregnant. In patients using other anticancer drugs, a break should be considered, taking into account the type of therapy (e.g. 3 months in the case of tamoxifen, 5 months in the case of immunotherapy, and BRAF/MEK inhibitors, 7 months in the case of trastuzumab) [47, 50, 88].

Assisted reproductive technology after cancer treatment may be considered with caution if there is difficulty in conceiving. An increase in oncological risk in patients after breast cancer treatment cannot be ruled out by current data [89, 90].

There were no differences in the course of pregnancy in female partners of men after oncological treatment.

Recommendations

1. Consultation on the safety of pregnancy after oncological treatment should take into account the type of cancer, previous treatment, and the patient's situation (IV, A).
2. Patients who have undergone successful cancer treatment should not be discouraged from becoming pregnant (IV, A).
3. An adequate interval between the end of cancer therapy and attempts to get pregnant is recommended (III, B).
4. In patients with breast cancer, especially those with low risk of recurrence, interruption of postoperative hormone therapy may be considered to get pregnant (II, C).
5. Pregnancies of women after cancer treatment should be carefully monitored due to the potential increased risk of obstetric and childbirth complications (IV, B).
6. There are no contraindications to breastfeeding in patients who have completed oncological treatment (IV, B).

Health of children of mothers who received oncological treatment during pregnancy

Cancer affects about 1 in 1000 pregnant women. Treatment of pregnant women should not differ significantly from standard therapy but should be adapted to the gestational age and state of the mother's health. The teratogenic effect of some drugs (e.g., chemotherapy, targeted drugs, or hormone therapy) should be taken into account. Termination of pregnancy does not improve the prognosis of affected women [91].

The effects of chemotherapy depend on the gestational age at the start of treatment. Therapy initiated within the first 10 days after fertilization is associated with high risk of damage to totipotent or pluripotent cells, which may lead to miscarriage [92]. The use of chemotherapy in the first trimester of pregnancy, especially during organogenesis (5–8 weeks), is also associated with increased risk of congenital malformations (7.5–17% compared with a population risk of 4.1–6.9%). The risk of birth defects associated with the initiation of chemotherapy in the second and third trimesters is 3–7.5%, which corresponds to the population risk [93].

In children born within 2 weeks of chemotherapy completion, abnormalities in peripheral blood counts may occur due to transient myelosuppression (leukopenia, anemia, and thrombocytopenia). Therefore, it is recommended to administer the last course of chemotherapy at least 3 weeks before the planned delivery [92]. The offspring of mothers treated with rituximab may have a selective transient B-cells deficiency. No increased susceptibility to infection was observed, and response to vaccination was normal. Oligohydramnios and pulmonary hypoplasia have been observed in children of mothers treated with trastuzumab during

pregnancy; therefore, the use of this drug during pregnancy is not recommended. Data on the use of tamoxifen in pregnancy are conflicting, cases of miscarriage or abnormal pregnancy have been reported; therefore, its use in pregnant women is not recommended.

Chemotherapy administered during pregnancy increases the risk of premature birth and low birth weight in newborns; however, these deficiencies are usually compensated for in further development. However, chemotherapy can adversely affect the child's physical and neurological development. In some studies, attention was paid to the occurrence of problems with concentration, emotional disorders, especially attacks of aggression, and somatic complaints at school age [94]. However, no cardiac complications have been observed in children of mothers who received anthracyclines during pregnancy, although this risk cannot be completely excluded. Hearing loss has been reported in children of mothers who received cisplatin during pregnancy [94]. An increased risk of secondary cancers has not been observed in children of mothers who received chemotherapy during pregnancy, but data on this are scarce [94].

Recommendations

1. Due to the risk of congenital defects in children, chemotherapy should not be used in the first trimester of pregnancy (III, A).
2. Prematurity may be associated with impaired neuropsychological development; therefore, apart from absolute obstetric and gynecological indications or the mother's health status, in women receiving oncological treatment, induction of premature labor is not recommended (I, A).
3. In order to reduce the risk of transient hematological complications in neonates, the last course of chemotherapy should be scheduled at least 3 weeks before the expected delivery date (III, A).
4. Children of mothers receiving oncological treatment during pregnancy should be provided with multidisciplinary care (neonatological and pediatric, cardiological, neurological, ophthalmological, laryngological, and psychological) (IV, A).

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