

Cancer, fertility and pregnancy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

G. Pentheroudakis¹, R. Orecchia², H. J. Hoekstra³ & N. Pavlidis¹
On behalf of the ESMO Guidelines Working Group*

¹Department of Medical Oncology, Ioannina University Hospital, Ioannina, Greece; ²Department of Radiation Oncology, European Institute of Oncology and University of Milan, Milan, Italy; ³Division of Surgical Oncology, Department of Surgery, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

incidence

The estimated incidence of cancer diagnosed in pregnant women in developed societies is 1:1000 pregnancies and is predicted to rise as childbearing is shifted towards later reproductive ages. The most common cancers associated with pregnancy are cervical, breast cancer, melanoma, lymphomas and acute leukemias (Table 1).

diagnosis and staging

The diagnostic work-up should include a thorough physical examination, including the pelvis, breasts, lymph nodes, skin and should limit unnecessary exposure to ionizing radiation. Fine-needle aspiration, core needle or open excisional biopsies are safe to perform. Routine examination of obtained tumour biological material by haematoxylin–eosin and immunohistochemical stains is reliable and should be sought when indicated. Conflicting data exist on underestimation of hormone dependence of pregnancy-associated breast cancer when using immunohistochemical estrogen and progesterone receptor tumour levels. The merit of immunohistochemical determination of cytosolic pS2/Trefoil Factor 1, an estrogen-inducible transcription factor, in identifying hormone receptor-positive breast tumours during pregnancy should be validated.

Chest X-ray and mammography with abdominal shielding and ultrasonic examinations are the cornerstone of a basic staging. Routine use of MRI is discouraged: gadolinium crosses the placenta and induced malformations in animal models. In view of the theoretical risk of fetal heating/cavitation, first trimester MRI scans should be avoided and the potentially teratogenic contrast agent gadolinium should not be

administered, while second and third trimester scans should only be done when detailed anatomical information is required [V, D]. Computerized tomography or radioisotope studies should be avoided.

Minor staging procedures (spinal tap, bone marrow biopsy, endoscopies) are relatively safe to perform [IV, B]. Sentinel lymph node biopsy has been reported in >50 pregnant women with breast cancer and is associated with very low fetal radiation exposure (<2 mGy) when technetium-99m is used, though blue dyes are contraindicated. Accordingly, its sensitivity is still not well validated and its use in pregnant women should be considered experimental.

risk assessment

Ionizing radiation and cytotoxic agents have potential mutagenic, teratogenic and carcinogenic effects for the embryo, depending on dose, nature of compound, treatment field and gestational stage (Table 2).

Fetal exposure to radiation doses in excess of 5–10 cGy should be avoided. Doses below this threshold are associated with a very low risk of stochastic biological effects (mutations) and do not cause non-stochastic effects (malformations, developmental disorders) at a rate higher than observed in the general population (3%–5%). Exposure to antineoplastic agents should be avoided during the first trimester (organogenesis) but can be justified with little excess risk for mother and fetus during the second and third trimesters.

treatment and follow-up

The optimal therapeutic strategy should be jointly chosen by the medical team, patient and family and will depend on gestational age, nature and stage of cancer, treatment options and patient wishes. The medical team should include an obstetrician, a neonatologist, a medical oncologist/radiation oncologist, a surgeon and a psychologist and the patient should be treated at major hospitals with the required expertise and infrastructure.

*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland;
E-mail: clinicalrecommendations@esmo.org

Approved by the ESMO Guidelines Working Group: June 2007, last update October 2009. This publication supersedes the previously published version—Ann Oncol 2009; 20 (Suppl 4): iv178–iv181.

Conflict of interest: The authors have reported no conflicts of interest.

Table 1. Incidence of tumour types in pregnant women

Malignancy	Incidence (per number of gestations)
Malignant melanoma	1:1000–10 000
Breast carcinoma	1:3000–1:10 000
Carcinoma of the cervix	1:2000–10 000
Lymphoma	1:1000–1:6000
Leukaemia	1:75 000–1:100 000
Ovarian carcinoma	1:10 000–1:100 000
Colon cancer	1:13 000

Table 2. Gestational stage and effects of antineoplastic therapy

Gestational stage	Embryonal/fetal development	Impact
Weeks 0–2	Undifferentiated multicellular organism	'All or nothing', spontaneous abortion of normal development
Weeks 3–12	Organogenesis	Spontaneous abortion, major congenital anomalies
Second and third trimester	Intrauterine growth and maturation, continuing development of CNS, gonads, teeth–palate, eyes, ears	Functional defects and minor anomalies of late-forming tissues, stillbirth, intrauterine growth retardation, premature delivery, myelosuppression

Pregnancy termination is advised in the case of chemotherapy or radiotherapy administration during the first trimester, need for radical gynecological surgery, poor maternal life expectancy. There are no data to suggest that pregnancy termination alters the biological behaviour of the tumour or patient prognosis in the presence of appropriate antineoplastic therapy.

surgery

Surgery is the mainstay of treatment of solid tumours and pregnancy is not a contraindication for surgery. With modern surgical and anaesthesia techniques the maternal death rate is negligible. Surgery in the first trimester does not appear to increase major birth defects but the risk of miscarriage is increased. Therefore, when possible, surgery should be deferred until the second trimester, when the risk to the fetus is the lowest.

Surgery for cancer during pregnancy should proceed after multidisciplinary consultation in which, besides the appropriate cancer specialists, an anaesthetist, obstetrician and neonatal specialist should be involved. Informed consent is a critical component of choosing appropriate (surgical) cancer treatment. Since surgery in pregnant women is extremely rare, the majority of information that guides the surgical management of pregnant women with cancer is based on retrospective chart reviews, anecdotal experience and case reports.

breast cancer

Women with pregnancy-associated breast cancer often present with large, high-grade infiltrating ductal carcinomas and advanced stage of disease, both nodal and metastatic, attributable in part to a delay in the diagnosis. A higher frequency of BRCA1/2 germline mutations was observed in pregnant versus non-pregnant women with breast cancer, a fact reflecting the younger age of pregnant patients. In the International BRCA1/2 Carrier Cohort Study ($n = 1601$), no difference in the risk of breast cancer between parous and nulliparous women was seen, providing evidence that pregnancy should not be avoided in BRCA1/2 mutation carriers.

Treatment of a breast cancer should not be unnecessarily delayed because of pregnancy. Since there is no consistent evidence that the prognosis of breast cancer in pregnant women is different from non-pregnant women, the trimester of pregnancy dictates the local and systemic treatment options. Termination of the pregnancy (abortion) is not usually recommended, but may be considered during treatment planning. Approximately 60% of the pregnant women are diagnosed with early stage breast cancer (stage I and II) and should be approached with curative intent.

Mastectomy and axillary staging [axillary lymph node dissection (ALND)] during pregnancy can be safely performed during any trimester of pregnancy. A sentinel lymph node biopsy (SLNB), in the absence of definitive data on the safety and accuracy, can be performed with technetium-99m. The radiation exposure to the fetus is extremely low, especially when the time interval between lymphoscintigraphy and surgery is small. There are still insufficient data to recommend the use of SLNB staging of breast cancer during pregnancy and therefore the indication to perform a SLNB and, if indicated, completion lymph node dissection (CLND) should be discussed with the patient and the partner.

In the first trimester breast-conserving treatment (BCT) is not a treatment option, since adjuvant radiotherapy would be delayed until post-partum (>6 months from BCT). Mastectomy with ALND is the only treatment option. The patient and partner may choose, after extensive consultation with their physician, for a termination of pregnancy (abortion), based on the extent of the disease and/or psychosocial aspects.

In the second and third trimesters of pregnancy the surgical approach applied should not differ significantly from that applied to non-pregnant women. Surgical treatment of the breast tumour and systemic treatment are based on tumour size, tumour grade and stage of disease. Breast cancer treatment may consist of BCT or non-BCT (mastectomy) and ALND with or without adjuvant chemotherapy (SLNB \pm CLND optional).

cervical cancer

Most pregnant patients are diagnosed with an early stage of disease as a result of a pelvic examination, a Pap smear at their first antenatal visit. Based on the Pap smear and colposcopy a diagnostic large loop excision of the transformation zone (LLETZ) or conization is performed. If justified, the conization is postponed until post-partum. If a prepartum conization needs to be performed, the optimal time is in the second trimester between 14 and 20 weeks of gestation. A clone cerclage may be indicated after a true conization.

Complications are less frequently encountered after a diagnostic LLETZ than after conization. Complications of conization during pregnancy are haemorrhage, miscarriage, preterm labour/delivery, infection and even fetal death. Conization may disrupt the pregnancy, especially in the first trimester and is associated with an abortion rate of up to 33%.

The choice of therapeutic modality in pregnant women with cervical cancer should be decided in the same manner as for non-pregnant patients. The treatment is individualized, based on the stage of the disease according to the International Federation of Gynecology (FIGO), the trimester of pregnancy, the desire to continue the pregnancy and the risks of modifying or delaying cancer treatment during the pregnancy. When the pregnancy is terminated, the patient can be treated according to the stage of the disease. In the case of continuation of the pregnancy, the patient is non-invasively staged with MRI without gadolinium contrast or invasively staged with laparoscopic nodal evaluation when indicated.

When the patient is diagnosed with carcinoma *in situ* or stage IA1 disease without LVSI, no further treatment is indicated after LLETZ or conization. For pregnant women with early stage disease (FIGO: IA2, IB1, 2A) diagnosed after 20 weeks of gestation, treatment may be delayed until the fetus has matured. Upon fetal maturation a Caesarean section is performed, followed by radical hysterectomy with bilateral pelvic lymphadenectomy and adjuvant radiation treatment when indicated. For patients with cervical cancer stage IB2 after 20 weeks of gestation delaying treatment for ~8 weeks to allow fetal maturation is acceptable. The treatment options are outlined in Figure 1. In selected patients with stage IA, IB, IIA tumours who have a desire for fertility preservation, radical trachelectomy with lymphadenectomy is an alternative to conventional radical hysterectomy. Antepartum trachelectomy is accompanied by a high rate of fetal loss.

A difficult dilemma arises when fetal immaturity requires prolongation of the pregnancy which could negatively affect the mother's survival. An individualized treatment plan should be determined, in consultation with the patient and partner by the multidisciplinary team, which should include an obstetrician. In such cases women should receive a complete evaluation including MRI and (laparoscopic) lymphadenectomy before considering delayed therapy. For pregnant women with stage IB/IIA and IIB–IVA during gestational weeks 1–20, the standard treatment for cervical cancer is radical hysterectomy and chemoradiation respectively with pregnancy termination or spontaneous abortion. Neoadjuvant cisplatin-based chemotherapy in selected cases beyond the first trimester after careful counselling might be an option to allow for fetal maturation. Cisplatin crosses the placenta but more than 10 cases of fetal exposure to the drug without untoward effects have been published.

melanoma

Pregnant patients may present with thicker melanoma and therefore worse prognosis. The prognosis of pregnant melanoma patients did not differ from non-pregnant melanoma patients when matched for stage and thickness. The surgical margins are well defined (melanoma <2 mm in depth, excision margin 1 cm and melanoma >2 mm in depth,

excision margin 2 cm). SLNB is a staging procedure, affecting disease-free survival (DFS) and not overall survival (OS), that can be offered to the patient. In the absence of definitive data on safety and accuracy, technetium-99m can be used without patent blue dye or Isolsulfan blue for various, previously described reasons (see also SLNB breast cancer). The indication for a CLND after SLNB or therapeutic lymph node dissection (stage III disease) did not differ from non-pregnant patients. Although low to moderate doses of interferon have been safely administered in pregnant patients with chronic myeloid leukaemia, there is no experience with administration of high-dose adjuvant interferon therapy in pregnant women with resected melanoma. The potential for severe toxicity and the marginal survival improvement with this regimen make its administration during pregnancy inadvisable.

cytotoxic chemotherapy and hormonal therapy

Chemotherapy can be administered during the second and third trimesters with reasonable safety, though there is an increased risk of stillbirth, growth retardation and premature delivery [III, B]. Older-generation alkylators (thiotepa, busulfan, chlorambucil, nitrogen mustard) and antimetabolites (aminopterin, methotrexate) have the most pronounced teratogenic and abortive potential, while anthracyclines, 5-fluorouracil, cytarabine and vinca alkaloids (vinblastine, vincristine) the least. Emerging evidence from a small number of case reports suggests that taxanes and platinum compounds are relatively safe to administer beyond the first gestational trimester [IV, C]. There are no or scant data on pemetrexed, gemcitabine, vinorelbine, oxaliplatin. Tamoxifen and aromatase inhibitors should be deferred until after delivery in view of observed teratogenic impact in animals and humans.

targeted agents

Only a few pregnant women have inadvertently been exposed to targeted agents. Trastuzumab caused oligohydramnios in four and abnormal implantation in one out of seven pregnant women, while no data exist on its effects on fetal cardiac development. This agent should be withheld until after delivery or pregnancy termination.

Rituximab only caused transient neonatal lymphopenia in four reported cases. Imatinib was occasionally associated with low birth weight and premature delivery in 29 reported cases, though one case of hypospadias and one of meningocele have been published as well. Though erlotinib was administered in one pregnant woman with advanced lung carcinoma without untoward effects for the fetus, no other data are available and its administration is not advised during gestation.

In view of animal experiments showing occurrence of fetal malformations, and data and past experience with the antiangiogenic agent thalidomide, administration of targeted agents modulating angiogenesis (bevacizumab, sunitinib, sorafenib) should be avoided in pregnant women [V, D].

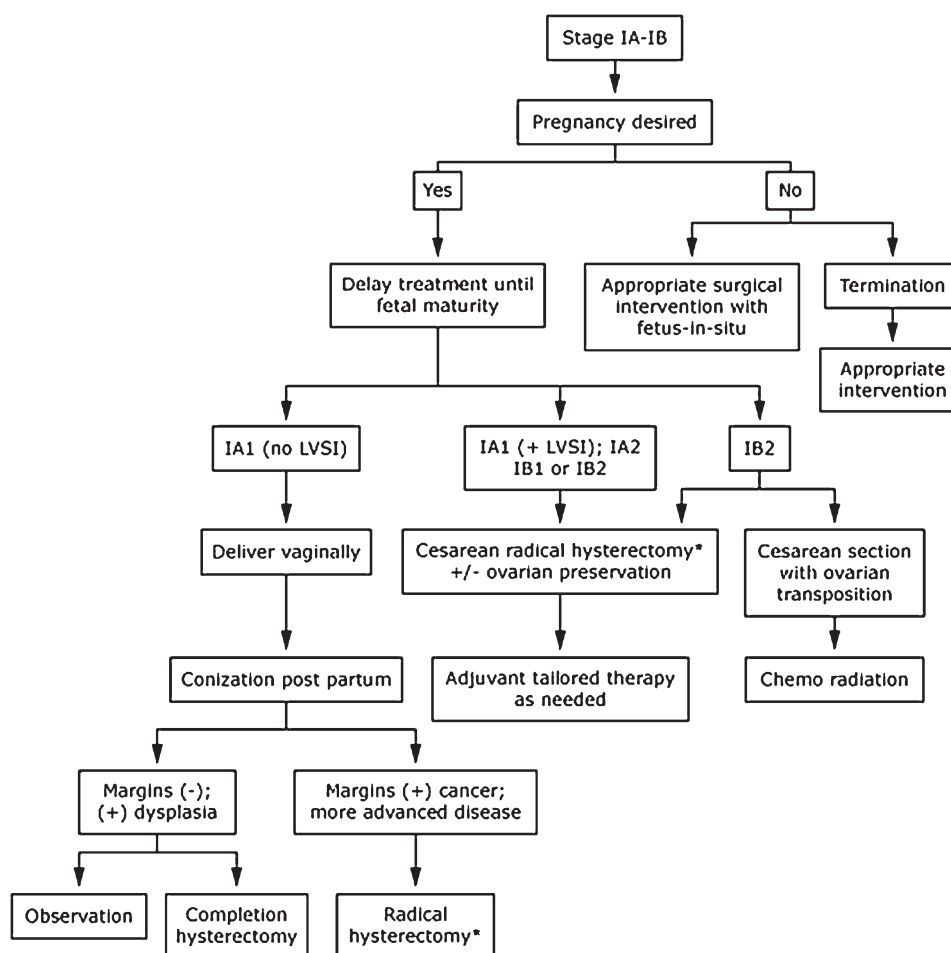


Figure 1. Algorithm for possible treatment options in patients with early stage invasive cervical cancer diagnosed at <20 weeks of gestation. *Consider radical trachelectomy 6 weeks post-partum in very select cases. Reproduced with permission from Muller CY, Smith HO. Cervical neoplasia complicating pregnancy. *Obstet Gynecol Clin North Am* 2005; 32: 533. Copyright ©2005 Elsevier.

radiation therapy

If possible, radiotherapy should be administered post-partum. Care should be taken to limit fetal exposure to ionizing irradiation of any source to <5–10 cGy [IV, C].

Some radiation effects, such as mental and/or growth retardation and organ malformation, only arise above a threshold dose of 100–200 cGy. In the intermediate-dose range, up to 50 cGy, the situation is less clear cut and effects are strongly dependent on the gestational age, the major risk being between the 8th and 15th weeks. For doses in excess of 50 cGy the probability of radiation-induced damage dramatically increases. This is the case for cancers located in the pelvis, when severe or lethal consequences for the fetus are expected. In contrast, radiation therapy to non-pelvic fields can be performed if absolutely indicated and in the absence of alternative therapeutic strategies. Such therapy should be based on careful individual planning, and fetal doses <100 cGy should not be considered a reason for terminating a pregnancy. Because of very special devices to shield and protect the fetus, the treatment should be carried out only in specialized centres.

An advanced consultation between the radiation oncologist, medical oncologist, obstetrician and medical physicist is also

strongly recommended in order to assess on an individual basis the balance between medical needs and potential radiation risks. The severity and frequency of adverse effects increase with total dose, therefore reduction of fetal dose to a level that is as low as reasonably achievable is necessary using proper technical resources. Typical anatomical points utilized for dose estimation are in uterine fundus, symphysis pubis and patient umbilicus. It also should be remembered that fetal orientation changes frequently and no single point can adequately describe the location of organs or part of the body. After radiotherapy careful records of all the treatment parameters should be maintained and strict counselling and follow-up is recommended, for both mother and child.

delivery

Delivery should take place after completion of the 32nd–35th week when fetal maturity and viability are satisfactory and at least 3 weeks after the last chemotherapy cycle to ensure resolution of maternal/fetal myelosuppression. A Caesarean section may be chosen instead of vaginal delivery in the case of invasive cervical cancer. Although placental/fetal metastases are exceedingly rare, histological examination of the placenta after

delivery should take place. The neonate should be thoroughly assessed by means of physical examination, full blood counts and biochemistry at birth, 1 month and 6 months later. Imaging studies of the neonate may be ordered in the case of clinical or laboratory abnormalities.

supportive therapy

Antiemetics (ondansetron, metoclopramide, metoclozine) may be safely administered with omission of corticosteroids in the first trimester [II, B]. Use of tropisetron is discouraged: studies showed teratogenic effects in animals. Granisetron and palonosetron have been rarely used in pregnancy. Analgesics (paracetamol, opioids, anti-inflammatory agents) [IV, B] and growth cytokines [V, D] have been administered in pregnant women beyond the first trimester without untoward effects, though some risk of fetal respiratory depression and ductus arteriosus closure exists. Biphosphonates and somatostatin should be deferred after delivery in view of their observed teratogenic impact in animals and humans. Therapy with anti-infectious agents should follow published principles of avoidance of those drugs with teratogenic effects. Breastfeeding should be avoided during chemotherapy.

follow-up and patient outcome

The follow-up of women diagnosed with cancer during pregnancy and their offspring should adhere to common standards. Most cohort studies showed that the outcome of pregnant cancer patients is not significantly inferior to non-pregnant patients matched for age and stage of cancer, though late diagnosis is frequently seen in pregnant patients. Some series including a large retrospective review of 4974 women with breast cancer reported inferior survival of pregnant women with cancer when compared with non-pregnant patients matched for age, tumour stage. Still, it is currently unknown if the latter finding is due to more aggressive cancer biology during gestation or simply due to undertreatment of

these patients. Recent data on women <35 years showed no outcome difference between pregnancy- and non-pregnancy-associated breast cancer. In the pregnancy-associated group a poor prognosis was observed in women untreated during pregnancy.

There is no evidence to establish that patient outcome is compromised by future pregnancies [III, B]. Most cohort studies have shown that women with a history of breast cancer who later become pregnant are at a reduced risk of malignant relapse/death. This finding should be interpreted with caution, as healthy women are the ones who attempt pregnancy, while those who experience a malignant relapse do not.

To date, there is no evidence supporting that *in utero* exposure to chemotherapy (beyond first trimester) or radiotherapy (doses <10–20 cGy) compromises the long-term physical and mental development of children [IV, B].

Most oncologists would recommend that potentially cured breast cancer patients postpone childbearing for at least 2–3 years, the median time to recurrence for relapsing women.

fertility preservation

The gonadotoxic effects of ionizing radiation, chemotherapy and surgery depend on patient age, treatment fields, total dose and nature of insulating agents (Table 3).

Conservative or modified abdominopelvic/genitourinary surgery should only be implemented if it does not compromise patient outcome. All patients at risk of infertility who have not completed childbearing should discuss germ-cell storage options with the medical team. Women with amenorrhoea should be screened for serum levels of estradiol, follicle-stimulating hormone, luteinizing hormone, in order to examine hormone circulating levels and better assess their reproductive potential.

Available interventions for male fertility preservation are unlikely to delay cancer treatment. Semen cryopreservation of

Table 3. Treatment options in pregnant patients with breast cancer

	First trimester	Second trimester	Third trimester
Stage 0	Diagnostic excision	Diagnostic excision	Diagnostic excision
Stage I–III	Mastectomy and ALND	Mastectomy or BCTa and ALND ± chemotherapy	Mastectomy or BCTa and ALND ± chemotherapy
	SLNB ± CLND experimental or elective termination of pregnancy and appropriate breast cancer therapies	SLNB ± CLND experimental	SLNB ± CLND experimental.
Stage IV	Elective termination of pregnancy followed by systemic ± locoregional treatment ^b	Chemotherapy and induction labour when fetus viable Systemic and locoregional treatment ^b	Induction labour when fetus viable and systemic and locoregional treatment ^b

^aAdjuvant radiation postponed till after delivery.

^bIn all disease stages, hormonal therapy should be deferred until after completion/discontinuation of pregnancy.

Table 4. Treatment options for the pregnant patient with cervical cancer

Stage	First trimester	Second trimester	Third trimester
Carcinoma <i>in situ</i>	Conization post-partum and if indicated further treatment	Conization post-partum and if indicated further treatment	Conization post-partum and if indicated further treatment
Stage IA–IB (<2 cm)	See algorithm	See algorithm	See algorithm
Stage IB (>2 cm), and IIA	Radical hysterectomy	Radical hysterectomy	Caesarean section followed by modified radical hysterectomy with pelvic lymph node dissection
Stage IIB–IV	Chemoradiation treatment	Chemoradiation treatment	Caesarean section followed by chemo-radiation treatment

Table 5. Treatment options for the pregnant patient with melanoma

	First trimester	Second trimester	Third trimester
Stage I–II	Wex ± SLNB ± CLND	Wex ± SLNB ± CLND	Wex ± SLNB ± CLND
Stage III	TLND	TLND	TLND
Stage IV	Elective termination of pregnancy and tailored treatment	Tailored treatment and induction labour when fetus viable	Induction labour when fetus viable Tailored treatment

Wex, wide excision; TLND, therapeutic lymph node dissection.

Table 6. Risk of female gonadotoxicity of various antineoplastic agents

	High risk (>80%) ^a	Intermediate risk	Low risk (<20%)	Unknown risk	
Single agents	Cyclophosphamide	Anthracyclines	Methotrexate	Taxanes	
	Busulfan	Cisplatin	Bleomycin	Oxaliplatin	
	Melphalan	Carboplatin	5-Fluorouracil	Irinotecan	
	Chlorambucil	Ara-C	Actinomycin-D	Monoclonal antibodies	
	Dacarbazine		Vinca alkaloids	Tyrosine kinase inhibitors	
	Procarbazine		Mercaptopurine		
	Ifosfamide		Etoposide		
	Thiotepa		Fludarabine		
	Combinations and radiation therapy	Nitrogen mustard	CMF, CAF, FEC × 6 in women 30–39 years	ABVD	
		High-dose cyclophosphamide/busulfan and haemopoietic stem cell transplantation		CMF, FEC, CAF × 6 in women <30 years	
Ovarian irradiation		AC, EC × 4 in women >40 years	CHOP, CVP		
CMF, CAF, FEC × 6 in women >40 years			Protocols for AML, ALL AC × 4 in women <40 years		

^aIncidence of permanent amenorrhoea in exposed women.

at least three samples with 48-h abstinence intervals is recommended for men [III, A]. For azoospermic men, testicular biopsy and sperm extraction may be an option for fertility preservation [V, D]. Prepubertal males may participate in clinical research of testicular tissue/spermatogonial stem cell storage. No studies support the effectiveness of male gonadal protection by means of hormonal manipulations during chemotherapy or radiotherapy.

Female fertility preservation procedures have requirements for scheduling and ovarian stimulation, resulting in a likely delay of 2–6 weeks of cancer treatment initiation. Embryo cryopreservation and ovary transposition are the only established fertility-preserving options for female patients, live birth rates being inferior to fresh embryo procedures. Menstrual function resumes in ~50% of women undergoing ovarian transposition, due to ischaemia and scatter

radiation [III, A]. Short-term ovarian stimulation with gonadotrophins is necessary for oocyte retrieval and may be associated with a theoretical risk of growth of hormone-sensitive tumours.

Emerging evidence on alternative (letrozole or tamoxifen) stimulation protocols provides hope in these cases but should be performed in the clinical research setting only. Experimental fertility preservation options are as follows.

- Unfertilized oocyte cryopreservation for women without a partner, a procedure that also relies on hormonal stimulation for germ cell harvest. Despite >120 deliveries with oocyte storage, issues with oocyte damage, DNA integrity and low yield of pregnancy urge us to consider oocyte cryopreservation experimental.
- Laparoscopy for removal of one ovary and ovarian tissue storage for those who cannot undergo ovarian stimulation or are prepubertal. Cryopreserved ovarian tissue can later be transplanted to the patient orthotopically or heterotopically or be subjected to *in vitro* maturation for oocyte extraction/*in vitro* fertilization. Ovarian tissue reimplantation carries a low risk of reintroduction of cancer cells if ovarian micrometastases were present.

Female gonadal protection from chemotherapy by means of oral contraceptive or GnRH agonist administration was effective in observational studies but should be considered investigational until mature results of ongoing prospective randomized trials become available [III, B]. Small phase III studies produced conflicting results.

Post-hoc subgroup analyses of prospective trials and three meta-analyses showed that amenorrhoea induced by chemotherapy or GnRH agonists, compared with menses preservation, was associated with improved survival in premenopausal women with resected hormone receptor-positive breast cancer. However, permanent amenorrhoea had no advantage over a temporary one in terms of patient outcome. These facts should be communicated to the patient with hormone-responsive tumour who is considering preservation of menses.

Aside from the risk of cancer relapse which may require avoidance of childbearing for 2–3 years, all male and female patients who remain fertile after cancer treatment should defer childbearing for at least 12 months to ensure germ-cell integrity [IV, C].

Women with a history of cancer/cancer treatment should be considered high risk for perinatal complications (maternal cardiac failure, miscarriage, low birth weight and prematurity of the newborn) and receive specialized, close care. Though poor DNA integrity has been reported in gametes of cancer patients, in the setting of successful fertility preservation/restoration there is no evidence that prior history of cancer or cancer therapy increases the rates of malformations, functional defects or malignancies in the patient's offspring [V, D].

note

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

literature

1. Pentheroudakis G, Pavlidis N. Cancer and pregnancy: poena magna, not anymore. *Eur J Cancer* 2006; 42: 126–140.
2. Loibl S, Minckwitz G, Gwyn K et al. Breast carcinoma during pregnancy. International Recommendations from an Expert Meeting. *Cancer* 2006; 106: 237–246.
3. Mazze R, Kallen B. Reproductive outcome after anesthesia and operation during pregnancy: a registry of 5405 cases. *Am J Obstet Gynecol* 1989; 161: 1178–1185.
4. Mathelin C, Annane K, Treisser A et al. Pregnancy and post-partum breast cancer: a prospective study. *Anticancer Res* 2008; 28: 2447–2452.
5. Nicklas A, Baker M. Imaging strategies in pregnant cancer patients. *Semin Oncol* 2000; 27: 623–632.
6. International Commission on Radiological Protection. Biological Effects after Prenatal Irradiation (Embryo and Fetus). ICRP Publication 90. *Ann ICRP* 2003; 33: 5–206.
7. Cohen-Kerem R, Railton C, Oren D et al. Pregnancy outcome following non-obstetric surgical intervention. *Am J Surg* 2005; 190: 467–473.
8. Woo JC, Yu T, Hurd TC. Breast cancer in pregnancy: a literature review. *Arch Surg* 2003; 138: 91–98.
9. Beadle BM, Woodward WA, Middleton LP et al. The impact of pregnancy on breast cancer outcomes in women ≤35 years. *Cancer* 2009; 115: 1174–1184.
10. Keleher AJ, Theriault RL, Gwyn KM et al. Multidisciplinary management of breast cancer concurrent with pregnancy. *J Am Coll Surg* 2002; 194: 54–64.
11. Andrieu N, Goldgar DE, Easton DF et al. Pregnancies, breast-feeding, and breast cancer risk in the International BRCA1/2 Carrier Cohort Study (IBCCS). *J Natl Cancer Inst* 2006; 98: 535–544.
12. Spanheimer PM, Graham MM, Sugg SL et al. Measurement of uterine radiation exposure from lymphoscintigraphy indicates safety of sentinel lymph node biopsy during pregnancy. *Ann Surg Oncol* 2009; 16: 1143–1147.
13. Hacker NF, Berek JS, Lagasse LD et al. Carcinoma of the cervix associated with pregnancy. *Obstet Gynecol* 198; 59: 735–746.
14. Zemlickis D, Lishner M, Degendorfer P et al. Maternal and fetal outcome after invasive cervical cancer in pregnancy. *J Clin Oncol* 199; 9: 1956–1961.
15. Reznick RH, Sahdev A. MR imaging in cervical cancer: seeing is believing. The 2004 Mackenzie Davidson Memorial Lecture. *Br J Radiol* 2005; 78 (Spec issue 2): S73–S85.
16. Alouini S, Rida K, Mathevet P. Cervical cancer complicating pregnancy: implications of laparoscopic lymphadenectomy. *Gynecol Oncol* 2008; 108: 472–477.
17. Muller CY, Smith HO. Cervical neoplasia complicating pregnancy. *Obstet Gynecol Clin North Am* 2005; 32: 533.
18. Ungar L, Smith JR, Palfalvi L et al. Abdominal radical trachelectomy during pregnancy to preserve pregnancy and fertility. *Obstet Gynecol* 2006; 108: 811–814.
19. van de Nieuwenhof HP, van Ham MA, Lotgering FK, Massuger LF. First case of vaginal radical trachelectomy in a pregnant patient. *Int J Gynecol Cancer* 2008; 18: 1381–1385.
20. Seamon LG, Downey GO, Harrison CR et al. Neoadjuvant chemotherapy followed by post-partum chemoradiotherapy and chemoconsolidation for stage IIIB glassy cell cervical carcinoma during pregnancy. *Gynecol Oncol* 2009; 114: 540–541.
21. Tewari K, Cappuccini F, Gambino A et al. Neoadjuvant chemotherapy in the treatment of locally advanced cervical carcinoma in pregnancy: a report of two cases and review of issues specific to the management of cervical carcinoma in pregnancy including planned delay of therapy. *Cancer* 1998; 82: 1529–1534.
22. Daryanani D, Plukker JT, De Hullu JA et al. Pregnancy and early-stage melanoma. *Cancer* 2003; 97: 2248–2253.
23. Morton DL, Thompson JF, Cochran AJ et al. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med* 2006; 355: 1307–1317.
24. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol* 2004; 5: 283–291.
25. Mir O, Berveiller P, Ropert S et al. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. *Ann Oncol* 2008; 19: 607–613.

26. Robinson AA, Watson WJ, Leslie KK. Targeted treatment using monoclonal antibodies and tyrosine-kinase inhibitors in pregnancy. *Lancet Oncol* 2007; 8: 738–743.
27. Zambelli A, Prada GA, Fregoni V et al. Erlotinib administration for advanced non-small cell lung cancer during the first 2 months of unrecognized pregnancy. *Lung Cancer* 2008; 60: 455–457.
28. Kal HB, Strukmans H. Radiotherapy during pregnancy: fact and fiction. *Lancet Oncol* 2005; 6: 328–333.
29. International Commission on Radiological Protection. Pregnancy and Medical Radiation. *Ann ICRP* 2000; 30 iii–viii, 1–43.
30. Orecchia R, Lucignani G, Tosi G. Prenatal irradiation and pregnancy: the effects of diagnostic imaging and radiation therapy. *Recent Results Cancer Res* 2008; 178: 3–20.
31. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. *Obstet Gynecol* 2006; 107: 1120–1138.
32. Rodriguez AO, Chew H, Rosemary C et al. Evidence of poorer survival in pregnancy-associated breast cancer. *Obstet Gynecol* 2008; 112: 71–78.
33. Petrek JA, Dukoff R, Rogatko A. Prognosis of pregnancy-associated breast cancer. *Cancer* 1991; 67: 869–872.
34. Kroman N, Jensen MB, Wohlfahrt J, Ejlersen B. Pregnancy after treatment of breast cancer—a population-based study on behalf of DBCCG. *Acta Oncologica* 2008; DOI 10.1080/02841860801935491.
35. Ives A, Saunders C, Bulsara M, Semmens J. Pregnancy after breast cancer: a population based study. *BMJ* 2007; 334: 194.
36. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2006; 24: 5769–5779.
37. Borde F, Chapelle-Marcilac IFP, Hery M et al. Role of chemo-induced amenorrhea in premenopausal, node positive, operable breast cancer patients. Nine-year follow up results of FASG database. *Breast Cancer Res Treat* 2003; 82 (Suppl 1): 30.
38. Cuzick J. The impact of LHRH agonists on breast cancer recurrence and mortality: an overview of the randomized trials. *Breast Cancer Res Treat* 2006; 100 (Suppl 1): S10.
39. Aviles A, Neri N. Hematological malignancies and pregnancy: a final report of 84 children who received chemotherapy in utero. *Clin Lymphoma* 2001; 2: 173–177.
40. Lee SJ, Schover LR, Partridge AH et al. ASCO Recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006; 24: 2917–2931.
41. Gerber B, Dieterich M, Muller H, Reimer T. Controversies in preservation of ovary function and fertility in patients with breast cancer. *Breast Cancer Res Treat* 2008; 108: 1–7.
42. Gerber B, Stehle H, Ricardo F et al. ZORO: A prospective randomized multicenter study to prevent chemotherapy-induced ovarian failure with the GnRH-agonist goserelin in young hormone-insensitive breast cancer patients receiving anthracycline containing (neo-) adjuvant chemotherapy (GBG 37). *J Clin Oncol* 2009; 27 (15 Suppl): Abstr 526.
43. Badawy A, Elnashar A, El-Ashry M, Shahat M. Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study. *Fertil Steril* 2009; 91: 694–697.
44. Shin D, Lo KC, Lipshultz LI. Treatment options for the infertile male with cancer. *J Natl Cancer Inst Monogr* 2005; 34: 48–50.
45. Orwig KE, Schlatt S. Cryopreservation and transplantation of spermatogonia and testicular tissue for preservation of male fertility. *J Natl Cancer Inst Monogr* 2005; 34: 51–56.
46. Marhohm E, Cohen I. Fertility preservation options for women with malignancies. *Obstet Gynecol Surv* 2006; 62: 58–72.
47. Donnez J, Martinez-Madrid B, Jadoul P et al. Ovarian tissue cryopreservation and transplantation: a review. *Human Reprod Update* 2006; 12: 519–535.