

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

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introduction

Over the past four decades, there has been a rising trend of delaying childbearing [1]. Given that cancer incidence increases with age, more women are either diagnosed with cancer during the course of gestation or inquire into the feasibility and safety of pregnancy following cancer diagnosis. Here, we provide the ESMO Clinical Practice Guidelines for managing patients diagnosed with cancer during pregnancy. Also, we provide guidance on fertility considerations for women desiring pregnancy following cancer diagnosis. Given the relative rarity of the topic, we lack data from large randomised trials. Hence, the recommendations provided here are mainly based on well-conducted prospective and retrospective cohort studies along with systematic reviews and meta-analyses.

cancer during pregnancy: incidence

The diagnosis of cancer during pregnancy is uncommon. It is estimated that 1 in every 1000 pregnant women is diagnosed with cancer. Breast, melanoma and cervical cancers are those most commonly diagnosed during pregnancy, followed by haematological malignancies [2–4].

diagnosis and biological features

Obstetricians and general practitioners should be well informed of the possibility that a breast lump, an atypical vaginal discharge, a changing mole or an enlarging lymph node may be associated with a cancer diagnosis [V, A]. When indicated, pathological examination of suspected lesions

should follow standard procedures as in the non-pregnant setting, including immunohistochemical or molecular analysis [5] [V, B]. No clear evidence exists regarding the presence of different pathological features in patients diagnosed with cancer during pregnancy. Pathological features and prognosis of patients diagnosed during pregnancy are usually comparable with age- and stage-matched non-pregnant patients [3] [IV, B]. The discussion remains open for breast cancer during pregnancy; while few studies have pointed to poor prognosis of patients diagnosed during pregnancy, others did not reproduce the same results [6].

Once the diagnosis of cancer during pregnancy is confirmed, we recommend referring the patient to an institution with expertise in dealing with such cases and possibly involving her partner and family in the decision-making process. Patients should be managed within a multidisciplinary team which includes an obstetrician and a neonatologist in addition to the oncology team in order to adequately evaluate potential maternal benefits and possible fetal risks [V, A].

staging and risk assessment

Imaging procedures should aim to limit the exposure to ionizing radiation, whenever possible. Ultrasound is the preferred imaging modality for breast, abdomen and pelvis. Chest X-ray and mammography with abdominal shielding can be safely carried out during pregnancy [IV, B]. Magnetic resonance imaging (MRI) without gadolinium can be used if any of the previously mentioned modalities were inconclusive or in cases of suspicious bone or brain metastases [IV, C]. Computed tomography (CT), bone and positron emission tomography (PET) scans should be avoided throughout the course of pregnancy [7].

Considerable variations are observed in evaluating serum tumour markers during pregnancy, particularly for CA125 and CA15.3 [8], hence they should not be considered in the management of pregnant cancer patients [IV, C].

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obstetric care and fetal follow-up

Systemic treatment with chemotherapy during the first trimester is associated with a high risk of miscarriage and in some cases congenital malformations, this being the period of organogenesis. The situation is less problematic when treatments are initiated in the second trimester. However, an increased number of obstetric and fetal complications are still observed even when chemotherapy is used in the second or third trimesters (Table 1) [9–11]. This includes a relatively higher risk of intrauterine growth restriction, premature rupture of membranes and premature labour. Thus, while current recommendations advocate standard chemotherapy regimens in pregnant cancer patients after the first trimester, this might not be feasible in all cases and hence tailored approaches may sometimes be needed.

Available clinical data suggest that fetuses exposed to chemotherapy starting in the second trimester do not experience significant long-term complications [12, 13]. Nevertheless, these pregnancies should be regarded as high risk, and it is therefore reasonable to consider regular fetal monitoring during gestation [V, C]. We recommend targeting full-term delivery (i.e. ≥ 37 weeks) whenever possible [III, A], since subtle but significant cognitive impairment has been described in preterm babies who have been exposed to chemotherapy *in-utero* [12]. Early or very early delivery (i.e. between 34–37 weeks and <34 weeks, respectively) should be discouraged, unless maternal and/or fetal health are endangered by the postponement of delivery until term.

Placental metastases remain a rare event. However, whenever possible, we recommend subjecting the placenta to histological examination, particularly in patients diagnosed with melanoma, which remains the most common tumour associated with placental metastasis [14].

local treatments

general concepts

surgery. Surgery can be safely carried out at any time during the course of the pregnancy. However, a slightly higher risk of miscarriage has been reported during the first trimester [IV, B]. Major abdominal and pelvic surgery might be associated with increased morbidity, and pregnancy complications during the whole pregnancy and their indications should follow a thorough discussion with the patient and the multidisciplinary team.

Nevertheless, surgery should never be postponed if deemed to be crucial in the management plan [IV, B], with careful monitoring of maternal and fetal conditions, particularly after the 25th week of gestation.

radiotherapy. Several fetal adverse effects, including the risk of childhood cancer, intrauterine growth restriction, mental retardation or even fetal death have been described after gestational radiotherapy. The critical factors are fetal dosage, radiation field extension and gestational age [15]. An increased risk of fetal malformation and mental retardation occurs with radiation doses >100 – 200 mGy [16]. This dose is generally not reached with curative radiotherapy during pregnancy, provided that tumours are located sufficiently far from the uterus with adequate shielding. Nevertheless, even lower dosages might be causal in the development of childhood cancer or sterility. Hence, it is preferable to postpone radiation therapy to the postpartum period irrespective of the treated site, unless there is an urgent clinical need and provided that the site is located sufficiently far from the uterus [IV, C].

breast cancer

The decision to proceed to mastectomy or breast conservative surgery should follow the standard practice as in the non-pregnant setting [IV, B]. Either can be safely carried out at any time during the course of gestation [5].

Relatively limited data are available on sentinel lymph node biopsy (SLNB) in breast cancer patients diagnosed during pregnancy. Several simulation studies pointed out to the safety of lymphoscintigraphy using Technetium-99 [15, 17]. Only one clinical series involving 12 pregnant breast cancer patients has been reported to date [18]. No fetal defects secondary to SLNB were observed and no evidence of axillary relapse was encountered at a median follow-up of 32 months. It is clear that more data on SLNB are needed in the pregnancy setting; however, we would not discourage SLNB in pregnant breast cancer patients in centres in which SLNB is routine practice in the non-pregnant setting [IV, C]. We discourage the use of vital blue dye in pregnant patients [V, D], which is associated with a 2% risk of allergic reactions which could be life-threatening [19].

The fetal exposure secondary to adjuvant breast irradiation is expected to be low and below the threshold for deterministic effects, if radiation is during the first or second trimesters. However, adjuvant radiotherapy is never an urgent procedure

Table 1. Obstetric complications, fetal weight and complications at birth secondary to exposure to chemotherapy during the second and third trimesters in three large cohort studies

	Cancer type	Obstetric complications		Fetal weight below 10th percentile		Fetal complications at birth	
		Chemo ^a	No chemo	Chemo	No chemo	Chemo	No chemo
Van Calsteren et al. [9]	All	17/62 (27%)	11/118 (9%)	14/62 (22%)	12/113 (11%)	7/62 (11%)	6/113 (5%)
Cardonick et al. [10]	Breast Cancer	22/104 (22%)	NR	8/104 (7.5%)	0/12 (0%)	12/104 (11%)	2/12 (16%)
Loibl et al. [11]	Breast Cancer	31/179 (17%)	15/149 (9%)	15/175 (9%)	5/139 (4%)	31/203 (15%)	7/170 (4%)

^aAll treatments were given during the second or third trimesters; 85%–90% of chemotherapy was anthracycline-based

and hence it is advisable to postpone it until delivery [V, D]. Careful planning of the local management strategy should be made in breast cancer patients diagnosed during the first trimester. When breast-conserving surgery is planned, it should be acknowledged that postponement of radiotherapy until delivery could result in delay of radiotherapy for >6 months, which could increase the risk of local recurrence [20]. Hence, thorough discussion should take place between the patient and the multidisciplinary team to discuss the risks and benefits of the different surgical modalities and the timing of radiotherapy in such cases.

cervical cancer

Radical hysterectomy and/or pelvic radiotherapy with or without cisplatin are the main modalities used in managing cervical cancer. Radical surgery and pelvic radiation would result in pregnancy termination and fetal death. Therefore, patients who wish to preserve their pregnancy should be informed that management would require modification of standard local treatment. Whether this could potentially have detrimental effects on patient outcome remains unknown.

Treatment depends on stage and gestational age. In early-stage cervical cancer, definitive treatment can be postponed until after delivery, with close monitoring during pregnancy [V, B].

For more advanced cases (stage IB1, IB2, IIA), in patients who wish to preserve the pregnancy, thorough radiological and surgical staging is used to discriminate between immediate treatment and watchful waiting [V, C].

Pelvic MRI during pregnancy has shown a good positive predictive value for nodal metastases [21], but the gold standard remains lymphadenectomy. This procedure can be safely carried out laparoscopically during pregnancy, even if the risk of bleeding or complications may be higher, compared with non-pregnant cases [22].

If the patient needs treatment for a locally advanced or high-risk tumour, platinum-based chemotherapy with or without paclitaxel can be proposed [23, 24], with a local response rate similar to non-pregnant cases.

Radical surgery can be offered concomitantly to Caesarean section in qualified centres [V, B].

Table 2 summarises the ESMO Clinical Practice Guidelines for managing cervical cancer during pregnancy [V, C]. Active treatment with modified strategies has been advocated also by other groups [23, 25].

systemic treatments

general concepts on the use of chemotherapy during pregnancy

Chemotherapy should not be administered during the first trimester of gestation [IV, D] since it is associated with a high risk of fetal congenital malformations reaching as high as 20% [26]. In patients requiring chemotherapy initiation during the first trimester, pregnancy termination would be considered [IV, B]. Administration of chemotherapy during the second and third trimesters has not been associated with significant fetal defects in the short or long term. However, it is important to note that not all chemotherapeutic agents should be regarded as ‘equally safe’ even when administered after the first trimester [26, 27]. This will be further discussed in subsequent sections.

Dose calculation should follow the standard procedures outside the pregnancy setting [IV, B], acknowledging that the pharmacokinetics of some cytotoxic drugs might be altered during pregnancy [28].

A 3-week period should be allowed between the last chemotherapy dose and the expected date of delivery to avoid delivery during the nadir period [IV, B]. However, spontaneous delivery could occur any time after week 34 of gestation and hence chemotherapy should not be administered beyond week 33 of gestation. This risk is relatively lower when weekly schedules

Table 2. ESMO Clinical Practice Guidelines in patients diagnosed with cervical cancer during pregnancy

Time of diagnosis	Recommendations	
First trimester	Discuss pregnancy termination and standard treatment as outside pregnancy. If the patient wishes to preserve the pregnancy, discuss close monitoring up to second trimester (see below).	
Second trimester	Stage IB1	Lymphadenectomy (i) Node-negative: watchful waiting or chemotherapy ^a during pregnancy, followed by hysterectomy or large cone after delivery. (ii) Node-positive: chemotherapy ^a during pregnancy followed by radical hysterectomy at delivery or chemo-radiotherapy following delivery. Discuss pregnancy termination and standard treatment as outside pregnancy.
	Stage IB2-IVA	Chemotherapy ^a during pregnancy. Manage the case by surgery and/or chemoradiotherapy according to the stage and level of nodal involvement after delivery. Discuss pregnancy termination and standard treatment as outside pregnancy.
	Distant metastasis	Chemotherapy during pregnancy. Discuss pregnancy termination and standard treatment as outside pregnancy.
Third trimester	Delay treatment until delivery and consider early induction of labour.	

^aCisplatin (75 mg/m² q 3 weeks) or carboplatin-based regimens ± paclitaxel regimens q 3 weeks or weekly.

are used, particularly with doxorubicin, epirubicin and paclitaxel. Their weekly application has been shown to be associated with lower risk of haematological toxic effects and shorter nadir periods [29, 30], warranting the consideration of this approach in pregnant cancer patients [IV, C].

breast cancer

The indications for systemic therapy should follow those for the non-pregnant setting, taking into consideration the gestational age at diagnosis and the expected date of delivery. Table 3 summarises the ESMO Clinical Practice Guidelines for the management of breast cancer during pregnancy according to the gestational age and breast cancer subtype [IV, B].

Anthracycline-based regimens are the most studied during pregnancy and remain the first choice [10, 11, 31, 32] [III, A]. There is no particular preference given for one regimen over another (e.g. AC, FAC, FEC, EC), hence the choice should be made based on the local practice in the non-pregnant setting. To date, none of the studies has shown an increased risk of fetal cardiotoxicity secondary to in-utero exposure to an anthracycline-based regimen [10, 11, 31, 32].

Data from animal models have shown that transplacental transfer of both paclitaxel and docetaxel is minimal, probably as a result of high expression of p-glycoprotein in the placenta [33]. A recent systemic overview of 50 breast cancer patients treated with taxanes has shown adequate pregnancy outcomes [34]. The same data were shown in 15 and 12 patients reported within European- and American-based registries, respectively [11, 35]. Hence, we endorse the use of taxanes during pregnancy in cases where they are clinically indicated or the use of anthracyclines is contraindicated [IV, C]. Outside the pregnancy setting, weekly paclitaxel (80 mg/m²) or 3-weekly docetaxel (100 mg/m²) are the most effective schedules. During pregnancy, the former would allow close pregnancy monitoring since it is a weekly schedule; it is also associated with a better overall toxicity profile [30], with no need for high dose steroid premedication or prophylactic use of granulocyte colony stimulating factor (G-CSF). Very limited data are available on the safety of the docetaxel schedule, and thus its use should be restricted to situations in which it is clinically urgent [V, C]. Weekly paclitaxel would therefore be the preferred option if taxanes were to be considered in pregnant breast cancer patients [V, C].

The use of tamoxifen during pregnancy is contraindicated at any time during the course of pregnancy as it has been shown to be associated with fetal malformation [36] [V, E].

Trastuzumab is a monoclonal antibody that crosses the placenta at increased levels starting in the second trimester [37]. Consistent observations have been made of an apparent high risk of oligo-anhydramnios secondary to exposure to trastuzumab during the second and third trimesters [38, 39]. Hence, in patients with HER2-positive disease, trastuzumab or any other HER2-targeted agent should be postponed until after delivery [IV, D].

lymphoma

Low-grade non-Hodgkin's lymphoma (NHL) is a disease of the elderly and is rarely diagnosed in young women and during pregnancy. In case a diagnosis is made, these patients are often

Table 3. ESMO Clinical Practice Guidelines for systemic management of patients diagnosed with breast cancer during pregnancy according to gestational age at diagnosis and breast cancer subtype

Breast cancer subtype	Recommendations
Endocrine-sensitive	<p>Hormonal agents (LHRH, tamoxifen) are contraindicated during pregnancy.</p> <p>Early (i.e. adjuvant, neoadjuvant)</p> <p>(i) If node-positive, and/or signs of aggressive disease (i.e. luminal-B), wait until second trimester and start anthracycline-based chemotherapy. Patients diagnosed in the third trimester could be counselled on a case-by-case basis and in some of them treatment could be deferred until delivery.</p> <p>(ii) If node-negative, low proliferative disease (i.e. luminal-A), observe until delivery, then start hormonal therapy.</p> <p>Metastatic</p> <p>(i) Wait until the second trimester and start an anthracycline-based regimen.</p>
HER2-positive	<p>HER2-targeted agents are contraindicated during pregnancy.</p> <p>Early (i.e. adjuvant, neoadjuvant)</p> <p>(i) Wait until second trimester and start anthracycline-based chemotherapy until delivery. Taxanes could be added in sequence during pregnancy if needed,</p> <p>(ii) Trastuzumab to be added following delivery.</p> <p>(iii) Patients diagnosed in the third trimester could start chemotherapy until W34 and aim to deliver at term.</p> <p>Metastatic</p> <p>(i) If chemotherapy and/or trastuzumab need to be urgently started during the first trimester, discuss pregnancy termination. Otherwise, follow the procedure as in the early setting.</p>
Triple negative	<p>Early (i.e. adjuvant, neoadjuvant)</p> <p>(i) Wait until the second trimester and start an anthracycline-based chemotherapy until delivery. Taxanes could be added in sequence during pregnancy if needed.</p> <p>(ii) Patients diagnosed in the third trimester could start chemotherapy until W34 and aim to deliver at term.</p> <p>Metastatic</p> <p>(i) If chemotherapy needs to be urgently started during the first trimester, discuss pregnancy termination. Otherwise, follow the procedure as in the early setting.</p>

asymptomatic and do not require immediate therapy. Hence, they should be kept under close observation until delivery [V, B].

Immediate therapy should be initiated in patients with aggressive NHL. If diagnosis is made early during the first trimester, pregnancy termination should be considered since

initiation of chemotherapy is associated with a high risk of fetal malformations [IV, B]. CHOP is the standard chemotherapy regimen used in managing NHL [V, B], and it remains the first choice in patients diagnosed during pregnancy. Several reports have shown favourable pregnancy outcomes when administration is started in the second trimester [40].

Administration of rituximab during pregnancy in patients with B-cell lymphoma has been shown to increase the risk of B-cell depletion in the new-born [38]. Patients starting rituximab during pregnancy should be informed that this approach may influence fetal immunity for some time even if spontaneous recovery of the neonatal B cell count has been observed in all reported cases. Thus, we do not discourage the administration of rituximab during pregnancy in patients in which postponement of rituximab would significantly compromise maternal prognosis [V, C].

Patients diagnosed with Hodgkin's lymphoma who need prompt treatment with chemotherapy may receive ABVD starting from the second trimester of gestation [V, B], without significant fetal impairment described [27].

leukaemia

Table 4 summarises the ESMO Clinical Practice Guidelines for managing leukaemia during pregnancy [IV, B].

Daunorubicin or idarubicin are classically used in combination with cytarabine in managing patients with acute myeloid leukaemia. However, their administration in pregnancy has been associated with considerable fetal morbidity and

mortality, possibly due to their high placental crossing [V, D] [27]. Therefore, we propose instead the use of cytarabine in combination with doxorubicin. The latter has been used in managing acute leukaemia in the past with acceptable results.

More than 200 pregnant women with chronic myeloid leukaemia (CML) have been reported in the literature. Interferon-alpha can be used safely even during the first trimester [32]. No data are available on the use of targeted agents except for imatinib, which seems to be safe only when administered during the second and third trimesters [27, 41].

other tumours

Melanoma is one of the common tumours diagnosed during pregnancy. Surgical management should follow standard procedures outside pregnancy [42]. While a recent study pointed to the potential safety of SLNB using vital blue dye [43], we would rather restrict the SLNB procedure using Technetium-99 until more data are available. In patients with metastatic melanoma, we lack any safety data on the use of ipilimumab or vemurafenib during gestation and hence they should not be used during pregnancy [V, D]. If clinically appropriate, an alternative could be interferon-alpha, which could be safely administered during pregnancy.

Treatment recommendations for other solid tumours commonly presenting with advanced and/or metastatic disease requiring systemic treatment are summarised in Table 5 [V, C]. These include soft tissue sarcoma, ovarian and lung cancers.

Table 4. ESMO Clinical Practice Guidelines for systemic management of patients diagnosed with leukaemia during pregnancy according to gestational age at diagnosis

	First trimester	Second trimester	Third trimester
Acute leukaemia (myeloid or lymphocytic leukaemia)	Discuss pregnancy termination	Induction therapy with doxorubicin and cytarabine	Induction of labour and initiation of therapy after delivery
Acute promyelocytic leukaemia	Discuss pregnancy termination	Doxorubicin and All Trans-Retinoic Acid (ATRA)	Induction of labour and initiation of therapy after delivery
Chronic myeloid leukaemia	Interferon-alpha	Interferon-alpha or imatinib	Interferon-alpha or imatinib

Table 5. ESMO Clinical Practice Guidelines for systemic management of patients diagnosed with soft tissue sarcoma, ovarian and lung cancer during pregnancy according to gestational age at diagnosis

	First trimester	Second trimester	Third trimester
Soft tissue sarcoma	Observe until second trimester. If urgent treatment is required, discuss pregnancy termination.	Single agent doxorubicin (60–75 mg/m ²)	
Epithelial ovarian cancer	Observe until second trimester. If urgent treatment is required, discuss pregnancy termination.	Carboplatin (AUC5 or 6) + weekly paclitaxel (80 mg/m ²)	
Germ cell ovarian tumours	Observe until second trimester. If urgent treatment is required, discuss pregnancy termination.	Cisplatin (75 mg/m ²) and weekly paclitaxel (80 mg/m ²)	
Non-small-cell lung cancer	Observe until second trimester. If urgent treatment is required, discuss pregnancy termination.	Carboplatin (AUC5 or 6) + weekly paclitaxel (60–80 mg/m ²)	Carboplatin + weekly paclitaxel. If diagnosed later in the third trimester, consider pre-term delivery and initiation of therapy afterwards

These recommendations are based on small case series and case reports.

In patients with soft tissue sarcoma, we recommend single-agent doxorubicin in patients with metastatic disease. This is based on the overall safety of using doxorubicin during pregnancy in other cancer types. A case series of nine patients using the combination of doxorubicin and ifosfamide during pregnancy has been reported [44]. However, the limited safety information on ifosfamide during pregnancy, its toxicity profile, and the lack of survival advantage of the combination over single-agent doxorubicin [45] would favour single agent regimens in these patients [V, C]. Switching to a combination therapy could be done after delivery, if necessary.

Germ cell ovarian tumours are classically treated with an etoposide-platinum based combination (BEP or EP). While some reports have been published on the potential safety of this regimen [46], it remains relatively toxic, particularly etoposide, which has been shown to be associated with relatively high risk of fetal growth restriction and new-born complications including myelosuppression [46–49]. The latter has been reported in at least 6 infants of around 40 reported pregnancies in the literature. Hence, an alternative regimen that can be considered during pregnancy is the combination of cisplatin with paclitaxel [IV, C]. Paclitaxel has been shown to be effective as single agent in relapsed germ cell tumours [50] and is currently incorporated in combination with other agents including cisplatin in the management of relapsed germ cell tumours outside the pregnancy setting [51].

Around 50 patients with lung cancer during pregnancy have been reported in the literature [52]. However, incidence is believed to be on the rise given the rising trend of cigarette smoking in the young population. Anti-metabolites (e.g. gemcitabine and pemetrexed) should be avoided during pregnancy. The preferred combination is carboplatin and weekly paclitaxel [V, C], which has been reported both in ovarian and lung cancer during pregnancy with acceptable toxicity. Very limited data are available on the use of epidermal growth factor receptor inhibitors and hence we discourage their use during pregnancy.

managing pregnancies diagnosed while undergoing anti-cancer therapy

All pre-menopausal patients undergoing any form of systemic anti-cancer therapy (i.e. chemotherapy, hormonal therapy, immunotherapy or targeted therapy) should be advised to use active contraception [IV, A]. The same applies for male cancer patients as some of these agents could be partially excreted in semen and influence sperm DNA integrity. It is generally advised to continue using active contraception up to 3–6 months following the last administered dose.

If pregnancy occurs while on tamoxifen, the patients should be informed of the possible increased risk of fetal malformations secondary to the first trimester exposure [36] and hence pregnancy termination could be considered [V, D]. The same applies to patients accidentally becoming pregnant while on chemotherapy [V, D].

The situation is somewhat different with monoclonal antibodies, which do not cross the placenta early in gestation [37]. Data from the HERA trial on patients who became accidentally pregnant while receiving trastuzumab ($n = 16$) as well as sporadic case reports ($n = 5$) did not show fetal malformations secondary to brief first trimester exposure [53]. Hence, we would not encourage pregnancy termination in patients willing to preserve their pregnancy [IV, C], provided that trastuzumab is stopped and the patient is informed that this recommendation is based on data from a limited number of patients. The same applies for patients becoming pregnant while receiving rituximab.

Tyrosine kinase inhibitors cross the placenta during the first trimester and hence high fetal exposure could be of concern. Data on imatinib in patients with CML suggest a high risk of fetal malformation and miscarriage following first trimester exposure [27].

pregnancy in cancer survivors

In general, cancer survivors have reduced rates of subsequent pregnancy compared with the general population, although the rates are higher in males compared with female cancer survivors [54]. On average, pregnancy rates are 40% lower among female cancer survivors compared with the general population adjusting for women's age, education level and previous parity. This observation is highly dependent on the cancer type, in which women diagnosed with melanoma or thyroid cancer have pregnancy rates highly comparable with the general population (Figure 1). On the contrary, women diagnosed with breast cancer have the lowest chance of subsequent pregnancy, which is nearly 70% lower compared to the general population. This is believed to be secondary to frequent treatment with gonadotoxic chemotherapy, prolonged treatment periods with tamoxifen in patients with endocrine-sensitive disease and also a general misconception that pregnancy could stimulate cancer recurrence being a hormonally driven disease.

Apart from breast cancer, no reservations were made regarding the safety of pregnancy following cancer. Neonatal outcomes in men or women with prior history of cancer were highly comparable with those of the general population [55, 56]. However, concerns were raised in women with history of breast cancer. Despite several studies and a meta-analysis having shown that pregnancy after breast cancer is safe [57–59], if not associated with better outcomes, selection bias and lack of information on the outcome according to the ER status resulted in a lack of confidence in the reliability of these data. A recent large-matched multicentre retrospective study including more than 1000 patients confirmed that pregnancy after ER-positive breast cancer is not detrimental, at least during the first 5 years following pregnancy [60]. Hence, we do not discourage pregnancy following breast cancer diagnosis irrespective of the ER status [III, A]. Importantly, once pregnancy has occurred, induction of abortion has no impact on maternal prognosis and hence is strongly discouraged for such purposes [IV, A].

There is no particular time-point when it is considered optimal to allow patients to become pregnant following cancer diagnosis. The timing should consider the time of completion of therapy, risk of relapse, and the age and ovarian function of the

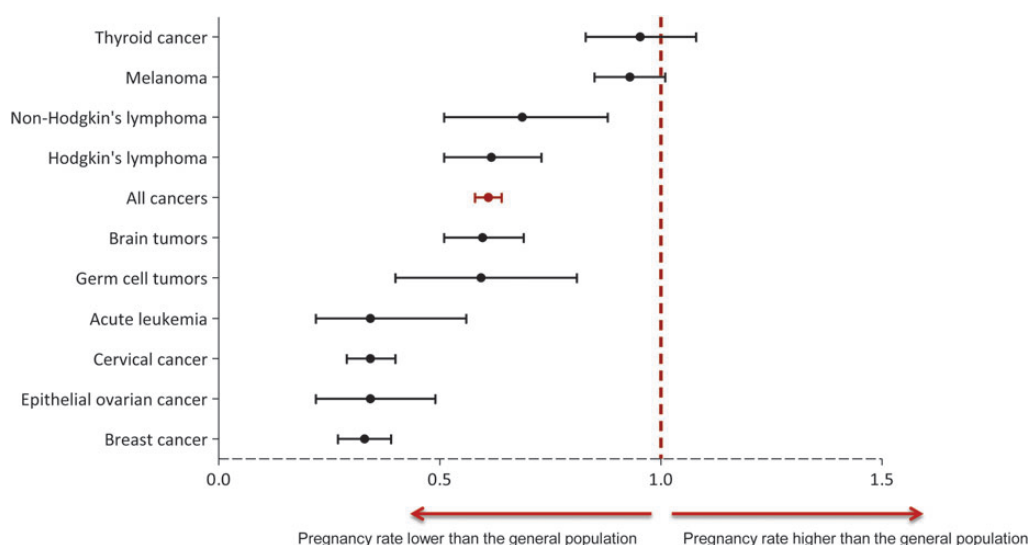


Figure 1. Female cancer survivors have 40% less chance of becoming pregnant compared with the general population. Chances of subsequent pregnancy depend on the type of cancer. Analysis adjusted for age, previous parity and level of education. Data adopted from a population-based study from Norway, which included 16 105 female cancer survivors and 85 500 controls [54].

patient. Hence, in breast cancer patients, it is reasonable to postpone pregnancy for 2 years following diagnosis [IV, C] to allow resumption of adequate ovarian function, and to overcome the time frame associated with a relatively high risk of recurrence. In patients considered for 5 years of adjuvant tamoxifen, we lack data to support the safety of early interruption of tamoxifen. Hence, in patients in whom the completion of the full course of tamoxifen would hinder their chances of future pregnancy, it should be made clear that early interruption could have potential detrimental effects on their breast cancer outcome. In women willing to consider this risk, interruption after 2 to 3 years of tamoxifen could be considered to allow pregnancy [V, C]. We strongly encourage the resumption of tamoxifen following delivery in these patients.

fertility preservation methods in cancer patients

For males who are scheduled for treatments that may affect their chance of future fertility, sperm banking should be planned before treatment initiation. Semen cryopreservation with one to three samples collection is recommended [III, A]. With the advent of intra-cytoplasmic sperm injection, collection of one sample could suffice in case more samples cannot be obtained. Sperm banking can be proposed independently of patients' age, according to their wishes of future paternity. There is no role for gonadal protection by any form of hormonal or pharmacological means.

Young women desiring future fertility should be counselled on available fertility preserving options before starting anticancer treatments. Counselling should be implemented soon after diagnosis, to allow prompt referral to fertility specialists [IV, B]. Age is the most important determinant of chemotherapy or radiotherapy-induced ovarian dysfunction [61]. The younger the patient's age, the lower her risk of ovarian dysfunction [62]. The other factors that influence ovarian

toxicity are the use of alkylating agents and the total dose of chemotherapy delivered [61]. If pelvic radiotherapy is used, fields and dosage are strictly related to subsequent ovarian dysfunction as well. In most studies, persistence of regular menstruation after treatment has been used to assess the residual ovarian function. Yet women who resume menses after treatment have compromised ovarian reserve [63] and hence, may have reduced fertility. Thus, better markers of ovarian function are needed for counselling patients before and after treatment. Probably, the best available markers of ovarian reserve are anti-Müllerian hormone and antral follicle count carried out in the first part of the menstrual cycle [64].

The concomitant use of gonadotropin-releasing hormone (GnRH) agonists during the course of chemotherapy as a mean of preserving fertility has been addressed in several phase III trials with conflicting results [65–69]. Some studies have shown higher rates of menses recovery in the GnRH arms, but others failed to reproduce the same results. These studies did not have the same patient population, and their primary end points were defined differently across the different studies. In addition, most of these studies reported on menstrual rather than on ovarian function, with no increase in pregnancy rates. Hence, the use of GnRH analogues concomitantly with chemotherapy should not be regarded as a reliable means of preserving fertility. Data on long-term ovarian function and pregnancy rates in these cohorts are warranted.

Embryo or oocyte cryopreservation is the main method to preserve female fertility [II, B]. Ovarian stimulation should be carried out before commencing chemotherapy [IV, A]. This may result in relative delay in oncological treatment and in increased serum estradiol levels, which could be of concern in hormone-driven tumours like breast cancer.

The use of gonadotropins and letrozole or tamoxifen has been shown to be associated with adequate yield of oocytes with a lower increase in serum estradiol levels compared with standard stimulation regimens [70, 71] and is generally

Table 6. Summary of recommendations**Cancer during pregnancy**

Diagnosis and biological features

- (i) When indicated, pathological examination of suspected lesions should follow standard procedures as in the non-pregnant setting, including immunohistochemical or molecular analysis.
- (ii) Once diagnosis is confirmed, the patient should be referred to an institution with expertise in dealing with such cases.
- (iii) Patients should be managed within a multidisciplinary team which includes an obstetrician and a neonatologist in addition to the oncology team.

Staging and risk assessment

- (i) Imaging procedures should aim to limit the exposure to ionizing radiation.
- (ii) Ultrasound is the preferred imaging modality for breast, abdomen and pelvis.
- (iii) Chest X-ray and mammography with abdominal shielding can be safely carried out during pregnancy.
- (iv) MRI without gadolinium can be used if any of the above modalities was inconclusive or in cases of suspicious bone or brain metastases.
- (v) CT, bone and PET scans should be avoided throughout the course of pregnancy.

Obstetric care and fetal follow-up

- (i) Chemotherapy is generally safe beyond the first trimester of gestation. However, increased rates of premature delivery, growth retardation and stillbirth have been reported.
- (ii) Standard chemotherapy regimens in pregnant cancer patients after the first trimester might not be feasible in all cases and hence tailored approaches may be needed.
- (iii) Pregnancies where the fetus has been exposed to chemotherapy starting in the second trimester should be regarded as high-risk and regular fetal monitoring during gestation should be considered.
- (iv) Full-term delivery (i.e. ≥ 37 weeks) should be targeted whenever possible.
- (v) Early or very early delivery should be discouraged, unless maternal and/or fetal health are endangered by the postponement of delivery until term.
- (vi) The placenta should be subjected to histological examination whenever possible, and particularly in patients diagnosed with melanoma or leukaemias.

Local treatments:

General concepts—surgery

- (i) Surgery can be carried out with relative safety at any time during the course of the pregnancy.
- (ii) Major abdominal and pelvic surgery should only be indicated following a thorough discussion with the patient and the multidisciplinary team.
- (iii) Surgery should never be postponed if deemed crucial in the management plan and careful monitoring of the maternal and fetal conditions particularly after the 25th week of gestation is recommended.

General concepts—radiotherapy

- (i) It is preferable to postpone radiation therapy to the postpartum period irrespective of the treated site, unless there is an urgent clinical need and provided that the site is located sufficiently far from the uterus.

Breast cancer

- (i) The decision to proceed to mastectomy or breast conservative surgery should follow the standard practice as in the non-pregnant setting.
- (ii) SLNB in pregnant breast cancer patients in centres in which SLNB is routine practice in the non-pregnant setting is not discouraged.
- (iii) The use of vital blue dye is discouraged in pregnant patients.
- (iv) Adjuvant radiotherapy is never an urgent procedure and hence it is advisable to postpone it until after delivery.
- (v) Careful planning of the local management strategy should be made in breast cancer patients diagnosed during the first trimester.
- (vi) If breast-conserving surgery is planned, radiotherapy may be delayed for more than 6 months increasing the risk of local recurrence—thorough discussion with the patient and the multidisciplinary team to review the risks and benefits of the different surgical modalities and the timing of radiotherapy is advised.

Cervical cancer

- (i) Radical surgery and pelvic radiation would result in pregnancy termination and fetal death—patients who wish to preserve their pregnancy should be informed that management would require modification of standard local treatment.
- (ii) In early-stage cervical cancer, definitive treatment can be postponed until after delivery, with close monitoring during pregnancy.
- (iii) For more advanced cases (stage IB1, IB2 and IIA), in patients who wish to preserve the pregnancy, thorough radiological and surgical staging is used to discriminate between the need for immediate treatment and watchful waiting. For assessment of nodal metastases, the gold standard is lymphadenectomy, which can be safely carried out laparoscopically during pregnancy.
- (iv) If the patient needs treatment for a locally advanced or high-risk tumour, platinum-based chemotherapy with or without paclitaxel can be proposed.
- (v) Radical surgery can be offered concomitantly to Caesarean section in qualified centres.

Continued

Table 6. Continued

Systemic treatments:
(i) Chemotherapy should not be administered during the first trimester of gestation. In patients requiring chemotherapy initiation during the first trimester, pregnancy termination would be considered.
(ii) Dose calculation should follow the standard procedures outside the pregnancy setting, acknowledging that the pharmacokinetics of some cytotoxic drugs might be altered during pregnancy.
(iii) A 3-week period should be allowed between the last chemotherapy dose and the expected date of delivery.
(iv) Weekly schedules of chemotherapy allow close pregnancy monitoring and are associated with shorter nadir periods warranting consideration of this approach in pregnant cancer patients.
Managing pregnancies diagnosed while undergoing anticancer therapy
(i) All pre-menopausal patients undergoing any form of systemic anti-cancer therapy (i.e. chemotherapy, hormonal therapy, immunotherapy or targeted therapy) should be advised to use active contraception. This applies also to male patients. It is advised to continue active contraception up to 3–6 months following the last dose of anticancer therapy.
(ii) If pregnancy occurs during tamoxifen treatment, the patient should be informed of the possible increased risk of fetal malformations secondary to first trimester exposure and pregnancy termination could be considered. The same applies to patients accidentally becoming pregnant while on chemotherapy.
(iii) In patients receiving trastuzumab or rituximab treatment, pregnancy could be allowed to continue, provided that treatment is stopped and the patient is informed that this recommendation is based on data from a limited number of patients.
Pregnancy in cancer survivors
(i) Timing of pregnancy following cancer diagnosis should take into consideration the time of completion of therapy, risk of relapse, age and ovarian function of the patient.
(ii) After this period, pregnancy is not discouraged, even in women with history of an endocrine-sensitive breast cancer. Once pregnancy has occurred, induction of abortion has no impact on maternal prognosis and is strongly discouraged for such purposes.
(iii) In patients considered for 5 years of adjuvant tamoxifen in whom the completion of the course would hinder their chances of future pregnancy, it should be made clear that it is unknown whether early interruption could have detrimental effects on their breast cancer outcome. We strongly encourage the resumption of tamoxifen following delivery in these patients.
Fertility preservation methods in cancer patients
Males:
(i) For males scheduled to receive treatment which could affect their future fertility, sperm banking should be planned before treatment initiation. Semen cryopreservation with one to three samples collection is recommended.
(ii) There is no role for gonadal protection by any form of hormonal or pharmacological means.
Females:
(i) Young women desiring future fertility should be counselled on available fertility preserving options before starting anti-cancer treatment. Counselling should be implemented soon after diagnosis to allow prompt referral to fertility specialists.
(ii) The use of GnRH analogues concomitantly with chemotherapy should not be regarded as a reliable means of preserving fertility.
(iii) Embryo or oocyte cryopreservation is the main method to preserve female fertility.
(iv) Ovarian stimulation should be carried out before commencing chemotherapy.
(v) The use of gonadotropins and letrozole or tamoxifen for ovarian stimulation is suggested for cancer patients. Consideration of such an approach in patients with ER-positive breast cancer should be made during a discussion with the patient and requires intensive interdisciplinary discussion including oncologists, radiotherapists and reproductive medicine specialists.
(vi) Chemotherapy and radiotherapy-induced sterility can be prevented also by freezing ovarian tissue before treatment. This is still experimental.

recommended for cancer patients [III, B]. In endocrine-sensitive breast cancer, this regimen has been used and was not associated with a higher risk of recurrence, at least during the first 2 years [72]. Long-term follow-up is needed to confirm its safety. Until then, consideration of such an approach in patients with endocrine-receptor-positive breast cancer should be made during a personal discussion with the patient and requires intensive interdisciplinary discussion, including oncologists, radiotherapists and reproductive medicine specialists [III, B].

Chemotherapy- and radiotherapy-induced sterility can be prevented also by freezing ovarian tissue before treatment. The tissue is harvested with laparoscopy, and re-implanted—after

thawing—in the pelvis, when needed. The procedure implies two surgical interventions and around 28 pregnancies have been reported so far [73]. It is still considered experimental, but remains a unique option for young girls with cancer.

note

A summary of recommendations is given in Table 6. Levels of evidence and grades of recommendation have been applied using the system shown in Table 7. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

Table 7. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System^a)

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

^aDykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

conflict of interest

The authors have declared no potential conflicts of interest.

references

- Matthews TJ, Hamilton BE. Delayed childbearing: more women are having their first child later in life. *NCHS Data Brief* 2009; 1–8.
- Pentheroudakis G, Pavlidis N. Cancer and pregnancy: poena magna, not anymore. *Eur J Cancer* 2006; 42: 126–140.
- Stensheim H, Møller B, van Dijk T, Fosså SD. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. *J Clin Oncol* 2009; 27: 45–51.
- Mieog JS, van der Hage JA, van de Velde CJ. Neoadjuvant chemotherapy for operable breast cancer. *Br J Surg* 2007; 94: 1189–1200.
- Amant F, Deckers S, Van Calsteren K et al. Breast cancer in pregnancy: Recommendations of an international consensus meeting. *Eur J Cancer* 2010; 46: 3158–3168.
- Azim HA Jr, Santoro L, Russell-Edu W et al. Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies. *Cancer Treat Rev* 2012; 38: 834–842.
- Wang PI, Chong ST, Kiehl AZ et al. Imaging of pregnant and lactating patients: part 2, evidence-based review and recommendations. *AJR Am J Roentgenol* 2012; 198: 785–792.
- Han SN, Lotgerink A, Gziri MM et al. Physiologic variations of serum tumor markers in gynecological malignancies during pregnancy: a systematic review. *BMC Med* 2012; 10: 86.
- Van Calsteren K, Heyns L, De Smet F et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. *J Clin Oncol* 2010; 28: 683–689.
- Cardonick E, Dougherty R, Grana G et al. Breast cancer during pregnancy: maternal and fetal outcomes. *Cancer J* 2010; 16: 76–82.
- Loibl S, Han SN, von Minckwitz G et al. Treatment of breast cancer during pregnancy: an observational study. *Lancet Oncol* 2012; 13: 887–896.
- Amant F, Van Calsteren K, Halaska MJ et al. Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. *Lancet Oncol* 2012; 13: 256–264.
- Litton JK, Hodge S, Mattair D et al. Outcomes of children exposed to chemotherapy in utero for breast cancer. *J Clin Oncol* 2011; 29 Abstr # 1099.
- Perret-Court A, Fernandez C, Monestier S et al. [Placental metastasis of melanoma: a new case and literature review]. *Ann Pathol* 2010; 30: 143–146.
- Gentilini O, Cremonesi M, Trifirò G et al. Safety of sentinel node biopsy in pregnant patients with breast cancer. *Ann Oncol* 2004; 15: 1348–1351.
- Kal HB, Struikmans H. Radiotherapy during pregnancy: fact and fiction. *Lancet Oncol* 2005; 6: 328–333.
- 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.
- Gentilini O, Cremonesi M, Toesca A et al. Sentinel lymph node biopsy in pregnant patients with breast cancer. *Eur J Nucl Med Mol Imaging* 2010; 37: 78–83.
- Cimmino VM, Brown AC, Szocik JF et al. Allergic reactions to isosulfan blue during sentinel node biopsy—a common event. *Surgery* 2001; 130: 439–442.
- Chen Z, King W, Pearcey R et al. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. *Radiother Oncol* 2008; 87: 3–16.
- Balléguier C, Fournet C, Ben Hassen W et al. Management of cervical cancer detected during pregnancy: role of magnetic resonance imaging. *Clin Imaging* 2013; 37: 70–76.
- Shepherd JH. Cervical cancer. *Best Pract Res Clin Obstet Gynaecol* 2012; 26: 293–309.
- Morice P, Uzan C, Gouy S et al. Gynaecological cancers in pregnancy. *Lancet* 2012; 379: 558–569.
- Fruscio R, Villa A, Chiari S et al. Delivery delay with neoadjuvant chemotherapy for cervical cancer patients during pregnancy: a series of nine cases and literature review. *Gynecol Oncol* 2012; 126: 192–197.
- Amant F, Van Calsteren K, Halaska MJ et al. Gynecologic cancers in pregnancy: guidelines of an international consensus meeting. *Int J Gynecol Cancer* 2009; 19 (Suppl 1): S1–12.
- Azim HA Jr, Peccatori FA, Pavlidis N. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part I: solid tumors. *Cancer Treat Rev* 2010; 36: 101–109.
- Azim HA Jr, Pavlidis N, Peccatori FA. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part II: hematological tumors. *Cancer Treat Rev* 2010; 36: 110–121.
- Van Calsteren K, Verbesselt R, Ottevanger N et al. Pharmacokinetics of chemotherapeutic agents in pregnancy: a preclinical and clinical study. *Acta Obstet Gynecol Scand* 2010; 89: 1338–1345.
- Ellis GK, Barlow WE, Gralow JR et al. Phase III comparison of standard doxorubicin and cyclophosphamide versus weekly doxorubicin and daily oral cyclophosphamide plus granulocyte colony-stimulating factor as neoadjuvant therapy for inflammatory and locally advanced breast cancer: SWOG 0012. *J Clin Oncol* 2011; 29: 1014–1021.
- Sparano JA, Wang M, Martino S et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med* 2008; 358: 1663–1671.
- Hahn KM, Johnson PH, Gordon N et al. Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. *Cancer* 2006; 107: 1219–1226.
- Peccatori FA, Azim HA Jr, Scarfone G et al. Weekly epirubicin in the treatment of gestational breast cancer (GBC). *Breast Cancer Res Treat* 2009; 115: 591–594.
- Van Calsteren K, Verbesselt R, Van Bree R et al. Substantial variation in transplacental transfer of chemotherapeutic agents in a mouse model. *Reprod Sci* 2011; 18: 57–63.

34. Zagouri F, Sergentanis TN, Chrysikos D et al. Taxanes for breast cancer during pregnancy: a systematic review. *Clin Breast Cancer* 2013; 13: 16–23.
35. Cardonick E, Bhat A, Gilmandyar D, Somer R. Maternal and fetal outcomes of taxane chemotherapy in breast and ovarian cancer during pregnancy: case series and review of the literature. *Ann Oncol* 2012; 23: 3016–3023.
36. Braems G, Denys H, De Wever O et al. Use of tamoxifen before and during pregnancy. *Oncologist* 2011; 16: 1547–1551.
37. Pentsuk N, van der Laan JW. An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal antibodies. *Birth Defects Res Part B Dev Reprod Toxicol* 2009; 86: 328–344.
38. Azim HA Jr, Azim H, Peccatori FA. Treatment of cancer during pregnancy with monoclonal antibodies: a real challenge. *Expert Rev Clin Immunol* 2010; 6: 821–826.
39. Zagouri F, Sergentanis TN, Chrysikos D et al. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2013; 137: 349–357.
40. Brenner B, Avivi I, Lishner M. Haematological cancers in pregnancy. *Lancet* 2012; 379: 580–587.
41. Pye SM, Cortes J, Ault P et al. The effects of imatinib on pregnancy outcome. *Blood* 2008; 111: 5505–5508.
42. Hoekstra HJ. Melanoma during pregnancy: therapeutic management and outcome. Recent results in cancer research. *Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer* 2008; 178: 175–181.
43. Andtbacka RH, Donaldson MR, Bowles TL et al. Sentinel lymph node biopsy for melanoma in pregnant women. *Ann Surg Oncol* 2013; 20: 689–696.
44. Mir O, Berrada N, Domont J et al. Doxorubicin and ifosfamide for high-grade sarcoma during pregnancy. *Cancer Chemother Pharmacol* 2012; 69: 357–367.
45. Judson I, Verweij J, Gelderblom H et al. Results of a randomised phase III trial (EORTC 62012) of single agent doxorubicin versus doxorubicin plus ifosfamide as first line chemotherapy for patients with advanced or metastatic soft tissue sarcoma. A survival study by the EORTC soft tissue and bone sarcoma group. *Ann Oncol* 2012; 23 (Suppl 9): LBA7.
46. Ghaemmaghami F, Abbasi F, Abadi AG. A favorable maternal and neonatal outcome following chemotherapy with etoposide, bleomycin, and cisplatin for management of grade 3 immature teratoma of the ovary. *J Gynecol Oncol* 2009; 20: 257–259.
47. Cardonick E, Usmani A, Ghaffar S. Perinatal outcomes of a pregnancy complicated by cancer, including neonatal follow-up after in utero exposure to chemotherapy: results of an international registry. *Am J Clin Oncol* 2010; 33: 221–228.
48. Han JY, Nava-Ocampo AA, Kim TJ et al. Pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for malignant ovarian germ cell tumors: report of 2 cases. *Reprod Toxicol* 2005; 19: 557–561.
49. Peterson C, Lester DR, Jr, Sanger W. Burkitt's lymphoma in early pregnancy. *J Clin Oncol* 2010; 28: e136–138.
50. Bokemeyer C, Beyer J, Metzner B et al. Phase II study of paclitaxel in patients with relapsed or cisplatin-refractory testicular cancer. *Ann Oncol* 1996; 7: 31–34.
51. Kondagunta GV, Bacik J, Donadio A et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. *J Clin Oncol* 2005; 23: 6549–6555.
52. Azim HA Jr, Peccatori FA, Pavlidis N. Lung cancer in the pregnant woman: to treat or not to treat, that is the question. *Lung Cancer* 2010; 67: 251–256.
53. Azim HA Jr, Metzger-Filho O, de Azambuja E et al. Pregnancy occurring during or following adjuvant trastuzumab in patients enrolled in the HERA trial (BIG 01–01). *Breast Cancer Res Treat* 2012; 133: 387–391.
54. Stensheim H, Cvancarova M, Møller B, Fosså SD. Pregnancy after adolescent and adult cancer: a population-based matched cohort study. *Int J Cancer* 2011; 129: 1225–1236.
55. Langagergaard V, Gislum M, Skriver MV et al. Birth outcome in women with breast cancer. *Br J Cancer* 2006; 94: 142–146.
56. De Sanctis V, Filippone FR, Alfo M et al. Impact of different treatment approaches on pregnancy outcomes in 99 women treated for Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys* 2012; 84: 755–761.
57. Ives A, Saunders C, Bulsara M, Semmens J. Pregnancy after breast cancer: population based study. *BMJ* 2007; 334: 194.
58. Kroman N, Jensen MB, Wohlfahrt J, Ejertsen B. Pregnancy after treatment of breast cancer—a population-based study on behalf of Danish Breast Cancer Cooperative Group. *Acta Oncol* 2008; 47: 545–549.
59. Azim HA Jr, Santoro L, Pavlidis N et al. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. *Eur J Cancer* 2011; 47: 74–83.
60. Azim HA Jr, Kroman N, Paesmans M et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. *J Clin Oncol* 2013; 31: 73–79.
61. Abusief ME, Missmer SA, Ginsburg ES et al. The effects of paclitaxel, dose density, and trastuzumab on treatment-related amenorrhea in premenopausal women with breast cancer. *Cancer* 2010; 116: 791–798.
62. Partridge A, Gelber S, Gelber RD et al. Age of menopause among women who remain premenopausal following treatment for early breast cancer: long-term results from International Breast Cancer Study Group Trials V and VI. *Eur J Cancer* 2007; 43: 1646–1653.
63. Partridge AH, Ruddy KJ, Gelber S et al. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. *Fertil Steril* 2010; 94: 638–644.
64. Peccatori FA, Pup LD, Salvagno F et al. Fertility Preservation Methods in Breast Cancer. *Breast care* 2012; 7: 197–202.
65. Badawy A, Elnashar A, El-Ashry M, Shahat M. Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomised study. *Fertil Steril* 2009; 91: 694–697.
66. Gerber B, von Minckwitz G, Stehle H et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. *J Clin Oncol* 2011; 29: 2334–2341.
67. Munster PN, Moore AP, Ismail-Khan R et al. Randomized trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo)adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2012; 30: 533–538.
68. Del Mastro L, Boni L, Michelotti A et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomised trial. *JAMA* 2011; 306: 269–276.
69. Demeestere I, Brice P, Peccatori FA et al. Gonadotropin-releasing hormone agonist for the prevention of chemotherapy-induced ovarian failure in patients with lymphoma: 1-year follow-up of a prospective randomised trial. *J Clin Oncol* 2013; 31: 903–909.
70. Oktay K, Buyuk E, Libertella N et al. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. *J Clin Oncol* 2005; 23: 4347–4353.
71. Oktay K, Hourvitz A, Sahin G et al. Letrozole reduces estrogen and gonadotropin exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy. *J Clin Endocrinol Metab* 2006; 91: 3885–3890.
72. Azim AA, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. *J Clin Oncol* 2008; 26: 2630–2635.
73. Donnez J, Silber S, Andersen CY et al. Children born after autotransplantation of cryopreserved ovarian tissue: a review of 13 live births. *Ann Med* 2011; 43: 437–450.