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Systemic Cancer Treatment in Pregnancy

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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Compliance rules:

- Guideline
- Conflict of interests

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1 Summary

- The stage of pregnancy and close cooperation in a multidisciplinary team are decisive for the therapeutic procedure. The risk-benefit analysis is particularly important for pregnant tumor patients.
- Ultrasound and magnetic resonance imaging are preferably used for diagnostic imaging.
- In the first trimester, an increased rate of subsequent malformations and miscarriages is to be expected as a consequence of systemic tumor therapy, so that systemic tumor therapy is not recommended.
- After systemic cancer therapy in the second trimester, a slightly increased rate of miscarriages, growth retardation, mental and physical underdevelopment has been documented. Systemic tumor therapy is possible here if indicated.
- With systemic tumor therapy in the third trimester, a largely comparable outcome with a normal course of pregnancy and development can be expected; if a premature birth should occur here, the corresponding problems arise as in pregnancies without malignant disease.
- Systemically administered tumor therapeutics are dosed according to the standard.
- Some agents such as tyrosine kinase inhibitors, *(V)EGF* antibodies, anti-hormonal substances or immune checkpoint inhibitors are contraindicated throughout the course of pregnancy. This has been addressed in the respective special sections of this guideline.
- The agents used for supportive therapy can also be used predominantly in the 2nd and 3rd trimester without any expected late effects for the newborn.
- If possible, an interval of 3 weeks between systemic therapy and delivery is recommended if drugs cause substantial myelosuppression.
- The goal is a normal delivery as for non-cancer patients; early induction of labor and section delivery (except for patients with cervical cancer) are discouraged.
- As a rule, normal early and late development of the children can be expected if the treatment recommendations are followed.
- Patient data should be entered into established registries.

2 Basics, epidemiology and pharmacological aspects

2.1 Incidence rates

According to currently available registry data, particularly from the International Network on Cancer, Infertility and Pregnancy (INCIP), 1-2 cases of cancer occur per 1,000 pregnancies [16, 26]. A report from Denmark includes 2426 cases from 1977-2006, with a significant increase from 1977-1986 to 1997-2006 [31]. A report from Norway includes 516 cases of preg-

nancy among 42,511 women with cancer from 1967-2002. Again, an increase in annual incidence was described [72]. Australian registry data of 1798 cases from 1994-2007 describe an increase in annual incidence from 1.12 to 1.91 per 1,000 pregnancies [48]. The increase in the number of cases is associated with the increasing mean age of pregnant women.

2.2 Tumor entities and stages at diagnosis

Reports from 2012-2018 are available from the International Network on Cancer, Infertility and Pregnancy (INCIP), which present the epidemiology of initial diagnoses of malignancies in pregnant women [6, 16, 27, 72].

The types of malignancies first diagnosed during pregnancy in 1170 women from 1996-2016 was reported as follows, see Table 1.

Table 1: Relative frequency of initial diagnoses of malignancies in pregnancy [27]

Malignant disease	Relative frequency (%)
Breast cancer	39
Cervical carcinoma	13
Lymphomas	10
Ovarian cancer	6
Leukemias	6
Melanoma	4
Gastrointestinal tumors	4
Thyroid carcinoma	3
Brain tumors	2
Other	12

These malignancies were also broken down according to the stage of disease at first diagnosis during pregnancy, see Table 2.

Table 2: Disease stages at the time of diagnosis during pregnancy [27]:

Stage	I	II	III	IV	Unknown
Breast cancer	15-20%	50%	20%	5-10%	3-5%
Cervical carcinoma	80%	10%	3%	4%	3%
Lymphoma	15%	50%	10%	10-12%	3-4%
Ovarian cancer	75%	5%	7%	3%	10%
Gastrointestinal tumors	3%	17%	20-25%	55%	2%
Melanoma	45%	10-15%	20-25%	5%	3%
Thyroid carcinoma	90-95%	3%	5%	-	-
Other	25-30%	5-6%	10-15%	30-35%	15%

A report from France that exclusively covers the occurrence of hematologic neoplasms with first diagnosis in pregnancy in 413 women in a total cohort of around 10 million pregnancies in the period from 2012-2022 [91] describes the frequencies shown in the following Table:

Table 3: Relative frequency of initial diagnoses of hematologic malignancies during pregnancy

Hematologic malignancy	Relative frequency (%)
Hodgkin's lymphoma	39.5
Acute leukemia	21.6
Aggressive B-cell non-Hodgkin's lymphoma	11.6
Myeloproliferative neoplasia	8.7
Myelodysplastic neoplasia or chronic myelomonocytic leukemia	5.1
Indolent non-Hodgkin's lymphoma	3.4
Other lymphomas	7.7
Other hematologic neoplasms	2.4

According to this study, there was no difference in the 5-year overall survival of women in whom the hematologic neoplasia was diagnosed during or after pregnancy.

2.3 Imaging diagnostics in women

In pregnancy, ultrasound and magnetic resonance imaging (MRI) without contrast enhancement are preferred imaging procedures due to their lack of ionizing radiation. However, concerns about possible harms to the fetus and mother may complicate decisions for both patients and clinicians. Based on two reviews [86, 96] that comprehensively discuss the use of imaging in pregnancy, the following assessments emerge.

Ultrasound: Ultrasound diagnostics have been used in pregnancy for decades and can be considered safe based on the results of a meta-analysis [93]. However, the theoretical risk of tissue heating and movement effects must be considered. The use of contrast sonography should be avoided unless the benefits clearly outweigh the possible risks of contrast agent administration.

MRI: A feared damage to the fetus in the first trimester due to MRI-induced tissue heating or clinically detectable hearing damage due to the noise in the 3 Tesla MRI could not be proven. Nevertheless, fetal exposure to loudness should be limited to 90 decibel. The use of gadolinium should be avoided, as it crosses the placental barrier, is excreted via the fetal kidneys into the amniotic fluid and can accumulate there. Gadolinium use during pregnancy has been reported to be associated with an increased risk of infiltrative skin diseases, rheumatologic and inflammatory diseases and early mortality of the child [92].

X-ray/computed tomography (CT): X-ray or CT imaging should only be ordered after a thorough risk-benefit assessment and in compliance with the fetal threshold dose of 50-100 mGy. In life-threatening situations or if an MRI is contraindicated, the benefit of a low dose CT may outweigh the risk. Fetal malformation, growth restriction, mental retardation or death are not expected with radiation levels used in diagnostic imaging, but the theoretical carcinogenic potential of ionizing radiation must be considered.

Mammography and sentinel lymph node staging: Mammography is considered safe in pregnancy, however, sensitivity may be reduced due to physiologically increased breast density. Sentinel lymph node staging with ^{99}technetium can also be performed during pregnancy. The radiation dose absorbed in the breast is less than 0.1-0.2 Gy.

2.4 Treatment modalities

An overview of the type of cancer treatment in 1170 pregnant women is provided by INCIP's work from 2018, see Table 4.

Table 4: Treatment modalities in 1170 pregnant women with malignant diseases [27]

	n	No treatment	Surgery	Chemotherapy	Radiotherapy	Targeted or anti-hormonal therapy	Other
Breast cancer	462	116 (25%)	225 (49%)	248 (54%)	12 (3%)	7 (2%)	-
Cervical carcinoma	147	83 (56%)	32 (22%)	66 (58%)	2 (1%)	-	-
Lymphoma	113	41 (36%)	8 (7%)	66 (58%)	4 (4%)	18 (16%)	-
Ovarian cancer	88	23 (26%)	64 (73%)	21 (24%)	-	-	-
Leukemia	68	22 (32%)	-	23 (34%)	1 (1%)	7 (10%)	15 (22%)
Gastrointestinal tumor	49	19 (39%)	21 (43%)	16 (33%)	-	-	-
Melanoma	46	12 (26%)	33 (72%)	-	2 (4%)	-	-
Thyroid carcinoma	37	7 (19%)	30 (81%)	-	1 (3%)	-	-
Brain tumor	21	11 (52%)	10 (48%)	1 (5%)	1 (5%)	-	-
Other	139	57 (41%)	31 (22%)	17 (12%)	6 (4%)	1 (1%)	37 (27%)
Total	1170	391 (33%)	454 (39%)	429 (37%)	29 (2%)	33 (3%)	51 (4%)

2.5 Pharmacological features

Pharmacological data on the special features of systemic tumor therapy in pregnant women are naturally scarce. The approvals of chemotherapeutic agents, immunotherapeutic agents and molecularly targeted agents for antineoplastic therapy exclude their use in pregnant women, so that no systematic studies have been carried out on this topic. An overview can be found in [20]

2.5.1 Volume of distribution, metabolization, excretion

In the 6th-34th week of pregnancy, a volume expansion of 3-4 liters develops. The plasma volume increases by 1200 ml, the total erythrocyte volume by 300 ml, the placenta and the fetal circulation require an additional 2000 ml or more. The dilution effect reduces the albumin concentration in the blood [33]. Another consequence is increased renal clearance [51]. The activation of relevant enzymes of the cytochrome p450 system (*CYP 3A4, CYP 2C9, CYP 2A6*) and uridine diphosphate glucuronosyltransferase (*UGT*) results in faster hepatic metabolization, for example of taxanes and anthracyclines [15].

2.5.2 Placental penetration

Most chemotherapeutic agents are penetrating the placental barrier. This has been demonstrated for doxorubicin, daunorubicin, epirubicin, cyclophosphamide, paclitaxel (only minimally), 5-fluorouracil, capecitabine, oxaliplatin, irinotecan/SN38 (metabolite), vinblastine, cisplatin, carboplatin and cytarabine [14, 60, 69]. Transfer into the fetal circulation must be distinguished from placental transfer. Some of the information presented in Table 5 can be derived from sparse test results in humans and some data collected in monkeys, rabbits, rats and mice. An updated review was published in 2022 on the placental permeability of numerous systemically administered antineoplastic drugs [94].

Table 5: Placental permeability of chemotherapeutic agents [1, 60]

Substance class	Agent	Concentration in fetal compared to maternal circulation (%)
Anthracyclines	Doxorubicin	7.5
	Epirubicin	4.0
Taxanes	Docetaxel	0
	Paclitaxel	1.5
Alkylating agents	Cyclophosphamide	25.1
Antimetabolites	Cytarabine	56.7
	5-Fluorouracil	28.7
Vinca alkaloids	Vinblastine	18.5
Platinum derivatives	Cisplatin	31-65
	Carboplatin	57.5
Monoclonal antibodies	Trastuzumab	85
	Pertuzumab	30-40
	Bevacizumab	2-9
	Rituximab	150-328
Tyrosine kinase inhibitors	Gefitinib	20
	Erlotinib	25
	Imatinib	31
	Nilotinib	32

2.5.3 Dose adjustment of antineoplastic agents in pregnant women

Despite the relevant pharmacological and pharmacokinetic peculiarities in pregnant women, no substantial changes in dosage are recommended for systemic anticancer agents compared to their use in non-pregnant women. Chemotherapy dosing is based on current body weight or surface, and the area under the curve (AUC) for carboplatin dosing is unchanged compared to non-pregnant patients [16].

6 Therapy

6.1 Tumor entities

6.1.1 Acute leukemias

General symptoms such as fatigue and shortness of breath as well as blood count changes in the form of mild anemia or thrombocytopenia can occur both pregnancy-associated and in the early phase of acute leukemia. This carries the risk of delayed diagnosis and therefore requires particular clinical attention, especially as any delay in induction chemotherapy is associated with a reduction in the rate of complete remissions [78]. A treatment algorithm is shown in Figure 1.

6.1.1.1 Acute myeloid leukemia (except acute promyelocytic leukemia)

Acute myeloid leukemia (AML) accounts for two-thirds of acute leukemias during pregnancy [78]. In addition to several reports from individual centers, each with a small number of patients, there are two literature reviews that have compiled data on AML in pregnant women from 1955-2013 [44] and 1969-2014 [23].

In 138 cases from the years 1955-2013, a standard combination of anthracycline and cytarabine was generally used for AML induction treatment (58%). The rate of complete remissions was 91%. The long-term survival of the mothers was 30%, with a low rate of risk-adapted consolidation therapies and allogeneic stem cell transplants in the affected patients. The rate of live births was 87%, with complications documented in 16%. Standard AML therapy during pregnancy was assessed as safe and effective, and early presentation of patients with high-risk AML for allogeneic stem cell transplantation is recommended [44].

In 85 cases of AML in pregnant women from 1969-2014, the results were broken down according to the start of chemotherapy in the 1st trimester (n = 8), 2nd trimester (n = 61) or 3rd trimester (n = 14). The CR rates were 100%, 81% and 67% in the 1st, 2nd and 3rd trimester, respectively. Fetal death and spontaneous abortion occurred in 37.5% vs 9.7% vs 0%. Remarkable were the rates of malformations or death after cytarabine + daunorubicin of 8.5%/6.4%, compared to 28.6%/12.5% after cytarabine + idarubicin [23]. In contrast to daunorubicin, idarubicin is more lipophilic, has a longer half-life, better placental permeability and a higher affinity for DNA, so that daunorubicin is considered the anthracycline of choice in pregnancy due to most extensive clinical experience and lower fetal toxicity [58].

Treatment of AML during pregnancy should be initiated immediately. As a successful pregnancy outcome seems unlikely after treatment start in the first trimester, reasons for or against termination of pregnancy should be discussed with the patient [4]. From the 2nd trimester, standard treatment with daunorubicin and cytarabine is recommended [4]. If AML has been diagnosed after the 32nd week of pregnancy, delivery should be attempted before initiating treatment in order to avoid the risk of chemotherapy-induced pancytopenia with a higher risk of infection and bleeding during the delivery phase [4] and to minimize fetal exposure to chemotherapeutic agents.

6.1.1.2 Acute promyelocytic leukemia (AML M3/M3v)

In acute promyelocytic leukemia (APL) diagnosed during pregnancy, there is a good chance of cure for the patient. All-trans retinoic acid (ATRA) and arsenic trioxide (ATO) have a high teratogenic potential. Options in the first trimester are a termination of pregnancy (attention to bleeding complications) or mono-chemotherapy with daunorubicin. After a termination of pregnancy, standard therapy with ATRA plus chemotherapy can be started immediately.

In the second and third trimester, there are no contraindications to combined treatment with ATRA and anthracyclines. A summary of all published cases of pregnant AML patients shows no increased maternal risk and no increased risk of malformations in the child. However, the rate of miscarriages, premature births and low birth weight newborns is increased. As these complications are associated with chemotherapy, the time to post-partum can be bridged by monotherapy with ATRA in pregnant women with APL at low or intermediate risk. For patients in the high-risk group, combination therapy with ATRA and anthracyclines (preferably daunorubicin) is indicated despite the associated risks [63]. The current guideline of the European LeukemiaNet [71] makes the same recommendations.

A systemic literature review [70] on pregnant women with APL shows a complete remission rate of 89% for 92 patients undergoing remission induction therapy with ATRA (32%) or ATRA +

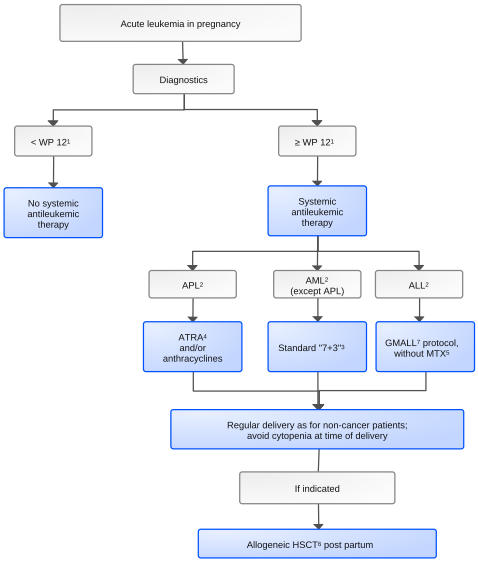
chemotherapy (43%). Respiratory distress syndrome was present in 12 of 16 newborns with neonatal complications. In this regard, the ELN guideline [71] recommends the prophylactic administration of glucocorticoids, preferably prednisolone or methylprednisolone, in births before 36 weeks of gestation.

6.1.1.3 Acute lymphoblastic leukemia

Due to the rarer occurrence of acute lymphoblastic leukemia (ALL) compared to AML, treatment experience during pregnancy is limited. The application of methotrexate, which is usually given as part of ALL therapy, is contraindicated due to the high risk of the aminopterin syndrome [45, 58]. A prospective study showed a higher incidence of T-ALL in pregnant women compared to a control group of non-pregnant ALL patients (53.3% vs. 26.6%, p = 0.034) and also initially higher leukocyte counts (38.0 vs. 9.6 x 10^9/l, p = 0.01) [66]. This study reports on a total of 15 pregnant patients and 12 live births without subsequent impairment of the child development. Three patients underwent a termination of pregnancy in the first trimester and in three other patients the birth was induced in the last trimester after application of the pre-phase and induction therapy was started 3-4 days later. In addition, nine patients received pre-phase and induction therapy, five additionally received induction II and one patient also received two consolidations. In this study, pregnancy had no influence on overall survival and the recurrence rate [66]

The bispecific anti-CD3xCD19 antibody blinatumumab crosses the placenta in the mouse model [89] and should not be used during pregnancy.

Figure 1: Treatment algorithm for acute leukemias in pregnancy



Legend:
= curative intended therapy
[1] *WP = Week of pregnancy*
[2] *AML = Acute myeloid leukemia; APL = Acute promyelocytic leukemia; ALL = Acute lymphoblastic leukemia*
[3] *"7 + 3" = Cytarabine + Daunorubicin*
[4] *ATRA = All-trans-retinoic acid*
[5] *MTX = Methotrexate*
[6] *HSCT = Hematopoietic stem cell transplantation*
[7] *GMALL = German Multicenter ALL study group*

6.1.2 Chronic myeloid leukemia

Chronic myeloid leukemia (CML) accounts for 10% of all leukemias during pregnancy. During pregnancy, the use of tyrosine kinase inhibitors (TKIs) is contraindicated due to the teratogenic risk and an incidence of over 10% for serious events [1]. In patients with desire to have chil-

dren, the possibility of sperm cryopreservation should be discussed at the time of initial diagnosis [64]. For female CML patients desire to have children, individualized measures are required to allow the possibility of maintaining remission during pregnancy without the use of TKIs. Treatment interruption is only recommended in cases of stable molecular remission with a *BCR-ABL1* transcript level < 0.01%. In cases with a *BCR-ABL1* transcript level of 0.01-0.1%, therapy should initially be intensified in order to achieve a level below this threshold. Thus, patients undergoing imatinib therapy who are seeking pregnancy during a treatment break with a stable molecular remission should consider switching to a second-generation TKI in order to achieve a deeper and longer-lasting molecular remission [43]. If stable over 3-6 months, maintenance of remission over the course of pregnancy is likely. If molecular remission is lost during the treatment break in a pregnant woman, the time until delivery should be bridged without TKI resumption - if indicated, with interferon-alpha (IFN). The use of pegylated (PEG-)IFN is controversial and should be avoided, if possible, due to the accumulation of polyethylene glycol during pregnancy. If necessary, bridging cytoreduction with leukapheresis is an option in individual cases of significant leukocytosis. As imatinib and nilotinib have only been shown to have minimal placental permeability, the use of these substances after the 16th week of pregnancy can be considered in selected individual cases under very strict indications and risk-benefit analysis [1]. Dasatinib should generally not be used during pregnancy due to its placental permeability and high teratogenic risk. The use of bosutinib and newer TKIs is also contraindicated. Data on the outcome of different treatment regimens for CML during pregnancy have recently been compiled [22, 80].

6.1.3 Gliomas

There are only a few reports of pregnant women with primary brain tumors or brain metastases in the literature. Reliable epidemiologic data are lacking. Among 27 documented cases in the INCIP registry, 13 were diagnosed in the 2nd and 12 in the 3rd trimester. Neurosurgical interventions (n = 8), radiotherapy (n = 7) and chemotherapy (n = 3) were used therapeutically. All 21 children born were described as healthy with no apparent impairment, also after a follow-up of up to 25 years [74]. Case series from individual centers [76] as well as a systematic literature review [73] indicate that pregnancy can lead to a poorer clinical course of gliomas, without, however, having a significant impact on the prognosis [73]. Evidence-based guidelines on the clinical procedure for pregnant women with primary brain tumors or brain metastases are not available.

For pregnant women in the second and third trimester, current data support the recommendation to use the same standard treatment protocols as for non-pregnant women.

6.1.4 Colorectal cancer

In accordance with the age distribution of patients with colorectal cancer (CRC), only a few properly documented cases of CRC in pregnant women are available in the literature. A literature search from 2017 revealed 119 case reports (53% colon, 44% rectum, 3% multiple), with first diagnosis in the 2nd and 3rd trimester in 88%. Of 82 patients whose treatment was described, around 10% received chemotherapy during pregnancy [67]. The INCIP registry published 41 well-documented cases, including 27 colon and 14 rectal carcinomas [47]. Advanced stages were found in 73% of patients. Surgery was performed in 51% and chemotherapy in 29% of pregnant women. The birth of healthy children was achieved in 33 of the 41 patients (80.5%), with section delivery in 21 cases. According to these registry data and a single center report [40], no significant difference was found in the prognosis of pregnant patients with CRC compared to non-pregnant women.

No reliable data are available on the selection of antineoplastic substances or treatment protocols that are suitable for the drug treatment of pregnant women with CRC. Fluoropyrimidines such as 5-FU and capecitabine, as well as irinotecan and oxaliplatin, mainly administered in the standard protocols FOLFOX and FOLFIRI, appear to be commonly used in the second and third trimester without any specific toxicities being found in the newborns [69]. *EGFR* antibodies such as cetuximab and panitumumab as well as substances directed against *VEGF(R)* such as bevacizumab, aflibercept or ramucirumab are contraindicated, as are multikinase inhibitors directed also against *VEGFR* (e.g., regorafenib).

6.1.5 Lung cancer

The largest published collection to date of all cases of non-small cell lung cancer (NSCLC) in pregnant women documented in the literature and in a single institution includes 77 patients [75]. It is estimated that 85% of all lung cancers in pregnant women are NSCLC [59]. Only 9 cases of lung cancer were reported from the INCIP registry in 2013, all of which were diagnosed at advanced stages [18]. The risk of metastasis to the placenta or fetus is reported to be up to 26% of 44 cases evaluated [12].

There are no evidence-based treatment recommendations for pregnant women with lung cancer. In view of the generally advanced stages of the disease, curative primary resections are not very promising. Chemotherapy using carboplatin and paclitaxel is justified from the beginning of the 2nd trimester, see chapter 6.1.6.1. Since an above-average rate of molecular aberrations such as *ALK* rearrangements and activating *EGFR* mutations is to be expected in pregnant women with NSCLC [25], it is obvious to consider the use of molecularly targeted tumor therapies. Individual case reports are available [17], from which the justification for individual treatment decisions can be derived. Reliable study results are not available. Comprehensive registry data on the use of immune checkpoint inhibitors (ICI) against *PD1*, *PD-L1* or *CTLA4* show no higher overall rates of negative effects on pregnancy, fetuses or newborns than systemically administered chemotherapeutic agents, but an increased rate of premature births after the use of combined checkpoint blockade against *PD1* and *CTLA4* has been reported [84]. Nevertheless, the use of ICI in pregnant women cannot be recommended, especially as no long-term follow-up studies are yet available.

6.1.6 Malignant lymphomas

- Malignant lymphomas are the fourth most common cancer diagnosis in pregnancy. Hodgkin's and non-Hodgkin's lymphomas (NHL) account for 5% and 6% respectively of all pregnancy-related cancers [30]. A treatment algorithm is shown in Fig. 2.

6.1.6.1 Non-Hodgkin's lymphomas

The most comprehensive data by now on NHL in pregnant women was published from the INCIP registry in 2021 [56]. Of a total of 80 patients, 57 had diffuse large B-cell lymphomas. One patient's pregnancy was terminated, 46 women received systemic lymphoma therapy (usually R-CHOP). All 46 patients with and all 10 patients without systemic lymphoma therapy during pregnancy had a live birth. One of the children who had been exposed to chemotherapy *in utero* was found to be malformed. Among the 23 women with other NHL, 20 carried their pregnancy to term, 19 also had a live birth. The treatment outcome of patients with NHL who received systemic lymphoma therapy during their pregnancy, followed up for more than 10 years, was comparable to that of non-pregnant patients. This was also observed in a large registry study from Australia and New Zealand including 41 women with lymphoma during pregnancy [81]. It was concluded that pregnant women with NHL should generally receive the same

systemic treatment as non-pregnant women [56]. This was also published as a recommendation in a consensus guideline [52].

As a special aspect, it was pointed out that prednisolone and methylprednisolone should be given preference over other glucocorticoids, if glucocorticoid therapy is indicated, due to their lower placental permeability and pronounced placental metabolization. A review of the use of new substances in lymphoma therapy [54] shows that data are only available for the application of rituximab in the 2nd and 3rd trimester [79], which can justify its use. Close blood count monitoring of the newborn should be considered after treatment with rituximab up to 6 months of age. The Onkopedia guideline on diffuse large-cell non-Hodgkin's lymphoma (DLBCL), updated in 2022, contains specific recommendations for the treatment of pregnant patients with DLBCL [65] (extract):

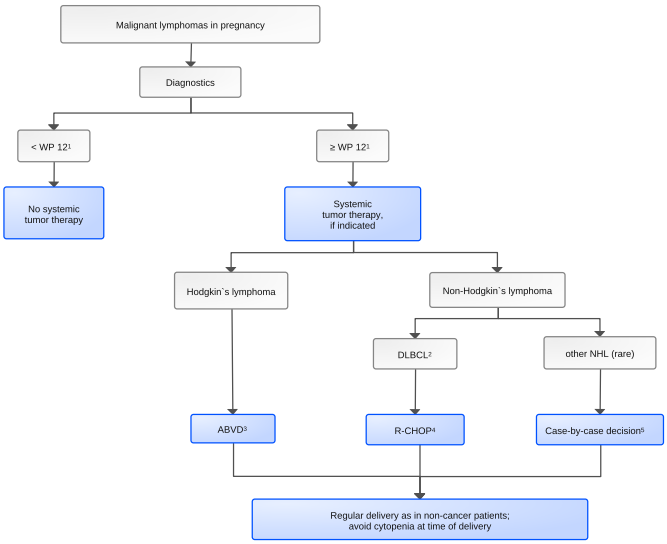
- If an aggressive lymphoma occurs in the first trimester, termination of pregnancy is recommended, as chemotherapy carried out during the organogenesis phase carries a high risk of malformations. The risk is low in the second and third trimester.
- The R-CHOP protocol is suitable as a standard treatment regimen. Antimetabolites (e.g., MTX) must not be used due to the risk of fetal CNS damage.
- If the lymphoma occurs in late pregnancy and is not very aggressive, treatment can be postponed to post delivery.

6.1.6.2 Hodgkin's lymphoma

In 24 patients with Hodgkin's lymphoma (HL) who were treated with systemic chemotherapy during pregnancy (usually ABVD), the outcome of the pregnancy was documented in 20 cases. There were 2 premature births, however, 2 of 11 patients who did not receive lymphoma therapy during pregnancy also had a premature birth [34].

While the use of ABVD for the treatment of HL in the first trimester is controversial, its use in the 2nd and 3rd trimester can be considered an appropriate and safe treatment option [36]. Accordingly, ABVD is the most commonly used regimen for HL therapy during pregnancy, with 241 cases now reported [30, 89]. There is only one case report on the use of nivolumab during pregnancy in the relapse situation of treatment-refractory HL with subsequent engraftment syndrome after autologous stem cell transplantation post partum. The concentration of nivolumab in the mother's blood was higher than in the umbilical cord blood and could not be detected in the placenta [35]. The use of brentuximab vedotin is contraindicated during pregnancy.

Figure 2: Treatment algorithm for malignant lymphoma in pregnancy



Legend:
= curative intended therapy
[1] WP = Week of pregnancy
[2] DLBCL = Diffuse large B-cell lymphoma
[3] ABVD = Doxorubicin/Bleomycin/Vinblastin/Dacarbazine
[4] R-CHOP = Rituximab/Cyclophosphamide/Doxorubicin/Vincristine/Prednisolone
[5] Wait-and-see approach (if possible), local radiotherapy (head/neck/thorax/extremities), CHOP, rituximab; recommendation by a multidisciplinary tumor conference

6.1.7 Breast cancer

Breast cancer accounts for 39% of all malignancies in pregnant women, see chapter 2.2. Accordingly, specific publications available today are extensive, providing detailed data on diagnostics and therapy, specified for surgical, radiotherapeutic, chemotherapeutic, endocrine and immunotherapeutic treatment procedures, in comparison to other cancers in pregnant women. Long-term studies on children who were exposed to chemotherapy in utero for the treatment of their mother's breast cancer show no negative effects of this therapy on their state of health [85].

A comparison of the prognosis of pregnant (n = 662) vs. non-pregnant (n = 2081) patients with breast cancer was published from the INCIP registry, which shows no significant difference in disease-free (78% vs. 85%) and overall survival (90% vs. 94%) after 3 years [8]. These registry data also indicate that surgical interventions, chemotherapy and local radiotherapy were administered in approximately comparable proportions. Both endocrine and *HER2*-targeted therapies are not recommended during pregnancy according to current knowledge [10, 61].

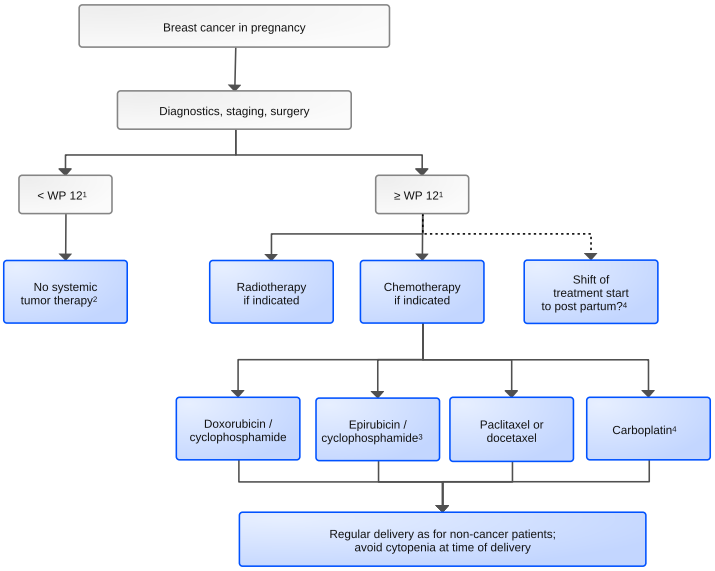
While surgical procedures are also permitted in the 1st trimester, potentially associated with a higher risk of miscarriage (for sentinel node staging, only technetium is recommended due to allergic reactions described), systemic chemotherapy may only be administered from the 2nd trimester (from week 13 of pregnancy) [38, 42]. Anthracyclines (doxorubicin and epirubicin), in combination with cyclophosphamide, and taxanes (paclitaxel and docetaxel, but not nab-paclitaxel) are, as with other chemotherapies in pregnancy *(see above),* indicated as in non-pregnant women [83]. Carboplatin is used on a case-by-case basis according to the current AGO recommendation [2]. Thus, standard regimens such as AC/EC followed by paclitaxel or the additional use of carboplatin in triple-negative carcinomas can be applied from the 2nd trimester onwards in the same way as in non-pregnant patients. Dose-dense administration of AC/EC (q2w), followed by weekly paclitaxel, is also accepted, if indicated, combined with the appropriate supportive measures [53]; 5-fluorouracil or methotrexate should not be used in pregnant women.

Endocrine therapies (tamoxifen, fulvestrant or aromatase inhibitors) should not be administered to pregnant women.

Molecularly targeted therapies such as *PARP* inhibitors, *CDK4/6* inhibitors, lapatinib, neratinib, tucatinib, *PI3 kinase* inhibitors or *mTOR* inhibitors are contraindicated in pregnant women, as are monoclonal antibodies (e.g., bevacizumab, trastuzumab, pertuzumab, *PD1/PD-L1* inhibitors or sacituzumab govitecan). More rarely applied substances such as capecitabine, eribulin or vinorelbine, for which there are no reliable data on their use in pregnant women, should be avoided.

A treatment algorithm is shown in Figure 3.

Figure 3: Treatment algorithm for breast cancer during pregnancy



Legend:
= curative intended therapy
[1] *WP = Week of pregnancy*
[2] *Chemotherapy, immunotherapy/immunoconjugates, anti-hormonal therapy, molecularly targeted therapy*
[3] *Including dose-dense protocols*
[4] *Individual case recommendation by multidisciplinary tumor conference*

6.1.8 Melanoma

Melanoma is relatively common in pregnant women worldwide. For example, the incidence in Australia (New South Wales) in 2008 was 52 cases per 100,000 pregnancies [13], but in line with the epidemiology of malignant melanomas, it is far lower in other regions of the world, for example 3-5/100,000 pregnancies in Europe [68]. The INCIP registry has reported 60 documented cases, including 14 in stage III and 16 in stage IV (27% in relapse) [28]. An analysis of 1406 pregnant melanoma patients from the Californian cancer registry showed no negative impact of pregnancy on overall survival compared to more than 10,000 non-pregnant women in this registry [87]. Therapeutically, mainly locoregional surgery and, in individual cases, local radiotherapy are used, while systemic therapeutics such as *BRAF/MEK*-targeted tyrosine kinase inhibitors or immune checkpoint inhibitors should generally be avoided due to their incalculable risks for the fetus, despite isolated favorable case reports [9]. For further information on immune checkpoint inhibitors, see chapter 6.1.5 (lung cancer).

Localized melanomas in particular do not have a significantly different prognosis in pregnant women, as shown by case-control studies with up to 185 documented patients [49]. The surgical literature contains specific recommendations on the practical surgical procedures for pregnant women with melanoma [24].

As a special feature of malignant melanomas, it is recommended to look carefully for placental metastases after delivery, which have been described as well as fetal metastasis [3, 46].

6.1.9 Malignant ovarian tumors

The incidence of malignant ovarian tumors in pregnant women is reported to be approximately 0.2-3.8 per 100,000 pregnancies [5]. Of the unclear adnexal tumors occurring in 0.2-2% of all pregnancies, 1-6% represent a malignant neoplasm [37].

Standard chemotherapeutic treatment with carboplatin and paclitaxel has proven to be safe for pregnant women in the second and third trimester [21, 77]. As *VEGF* (vascular endothelial growth factor) is of central importance for embryonic and fetal development and for the regulation of amniotic fluid, the use of the *VEGF* inhibitor bevacizumab is contraindicated.

Local radiotherapy of malignant ovarian tumors is obsolete in pregnant women.

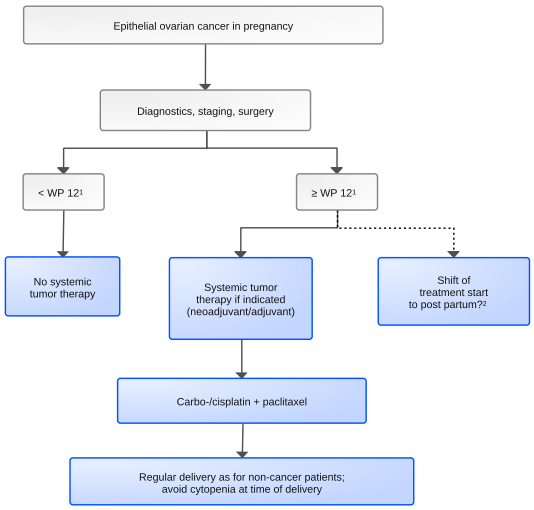
INCIP data indicate that the treatment outcome is similar to that of non-pregnant patients and that the prognosis depends on the tumor stage [37].

The current recommendations are as follows:

Surgical interventions in the early stages of a malignant ovarian tumor should preferably be performed from the 16th week of pregnancy. Chemotherapy can be administered from the 2nd trimester using the same regimens as for non-pregnant women. If neoadjuvant chemotherapy is indicated for locally advanced disease, carboplatin and paclitaxel can be used for epithelial ovarian cancer or cisplatin with etoposide and bleomycin for non-epithelial malignancies [5]. Updated recommendations on the diagnostic, surgical and drug treatment of pregnant women with ovarian cancer were published in 2024 by the European Society of Gynecologic Oncology (ESGO) together with the European Society of Medical Oncology (ESMO) and the European Society of Pathology (ESP) [88].

A treatment algorithm is shown in Figure 4.

Figure 4: Treatment algorithm for ovarian cancer in pregnancy



Legend:
= Curative intended therapy
[1] *WP = Week of pregnancy*
[2] *Recommendation by multidisciplinary tumor conference*

6.1.10 Sarcomas

The largest data collection to date comprises a retrospective analysis of 13 patients (4 with osteosarcoma and 9 with soft tissue sarcoma) who received anthracyclines and / or ifosfamide for sarcoma therapy [57]. A median of 3 treatment cycles were administered starting at a gestational age of 19.5 +/- 4 weeks. Pregnancy complications occurred in 10/13 (76.9%) cases. Fetal growth retardation was described in 6/13 (46.2%) of cases. The median gestational age at the time of preterm delivery, which occurred in all cases, was 30.8 +/- 3.8 weeks. The majority (66.7%) of the newborns required intensive care. Abortion occurred in 4 patients. These patients had previously received treatment with doxorubicin and ifosfamide starting at 15.5 weeks, while all other patients started treatment significantly later (median 21 weeks). The median disease-free survival was 62 months and three patients with soft tissue sarcoma died of the disease within 4 months of diagnosis.

6.1.11 Cervical carcinoma

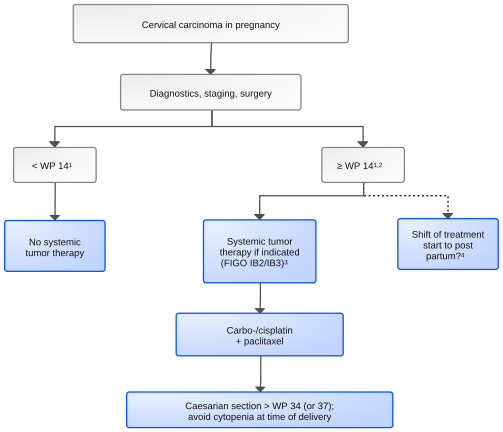
In a cohort study of the INCIP registry, 132 pregnant women and 256 non-pregnant women with cervical cancer and comparable patient characteristics from the years 1990-2012 were analyzed [41]. 14.4% of the pregnant women were in FIGO stage IA, 47.0% in stage IB1, 18.9% in stage IB2 and 19.7% in stages II-IV. In 26.5%, tumor therapy could be postponed until delivery, 17.4% were treated with primary surgery, 16.7% received neoadjuvant chemotherapy and 12.9% had a premature delivery. There was no difference in progression-free survival between pregnant and non-pregnant women. In a long-term study of 21 pregnant women with cervical carcinoma from 1985-2000, a 5-year survival rate of 82% was described, again with no significant difference to comparable non-pregnant patients [39].

An international consensus conference developed detailed treatment recommendations in 2019 [5]. Neoadjuvant chemotherapy using carboplatin and paclitaxel is recommended for pregnant women with cervical carcinoma in stages IA2-IB3 beyond the 22nd week of pregnancy for whom treatment cannot be postponed until delivery.

The AWMF S3 guideline on cervical carcinoma 2022 recommends treating pregnant women with cervical carcinoma similarly to non-pregnant women, with neoadjuvant, platinum-based chemotherapy recommended from the 2nd trimester onwards [11]. All current recommendations support a caesarean section as the delivery method of choice. There are no randomized studies on maternal outcomes depending on the mode of delivery. In the case of microinvasive carcinomas, case-control studies and retrospective analyses show no deterioration in prognosis as a result of spontaneous parturition. In the S3 guideline on cervical carcinoma, spontaneous delivery is only recommended for microinvasive carcinomas if an *in sano* resection was previously performed as part of a conization. Spontaneous delivery is not recommended in the presence of a microinvasive carcinoma with R1 resection or without conization due to the risk of bleeding and the risk of lymphovascular dissemination [11].

A treatment algorithm for cervical cancer in pregnancy is shown in Figure 5.

Figure 5: Treatment algorithm for cervical cancer during pregnancy



Legend:
= curative intended therapy
[1] WP = Week of pregnancy (time limit according to the S3 guideline of the AWMF 2022 [11])
[2] A European consensus conference [5] differentiates again between the 12th and 22nd week of pregnancy
[3] FIGO = International Federation of Gynecology and Obstetrics, version from 2018
[4] Recommendation by multidisciplinary tumor conference

6.1.12 Other solid tumors

No substantial data on pregnant patients is available for numerous other solid malignancies such as head and neck carcinomas, pancreatic carcinomas, neuroendocrine tumors, urothelial carcinomas, renal cell carcinomas or hepatobiliary cancer.

A collection of 13 pregnant women with gastric carcinomas published from the INCIP registry [55] does not allow any recommendations to be derived for the oncological care of these patients.

Although thyroid carcinomas represent 3% of malignant neoplasms in pregnant women (see above), they are almost exclusively treated without systemic antineoplastic agents. Pregnant patients with thyroid cancer do not have a different prognosis compared to non-pregnant patients [62].

6.2 Supportive drug therapy during pregnancy

According to the recommendations of an international consensus conference with INCIP participation [52], both metoclopramide and 5-HT3 antagonists [82] can be used safely for antiemetic therapy in pregnant women undergoing chemotherapy. No data are available on aprepitant and its use in pregnancy is cautioned against (https://www.drugs.com/mtm/aprepitant.html).

For antibiotic therapy in pregnant women undergoing chemotherapy, many of the commonly used antibacterial agents are non-critical according to current knowledge, while aminoglycosides, sulfonamides, trimethoprim, fluoroquinolones, amoxicillin-clavulanic acid and tetracyclines should be avoided [4]. If systemic antifungal therapy is necessary, amphotericin B preparations should be preferred, see ONKOPEDIA Invasive fungal infections - therapy (Guideline in German language).

The use of recombinant G-CSF is not associated with any unusual complications in pregnant patients [19].

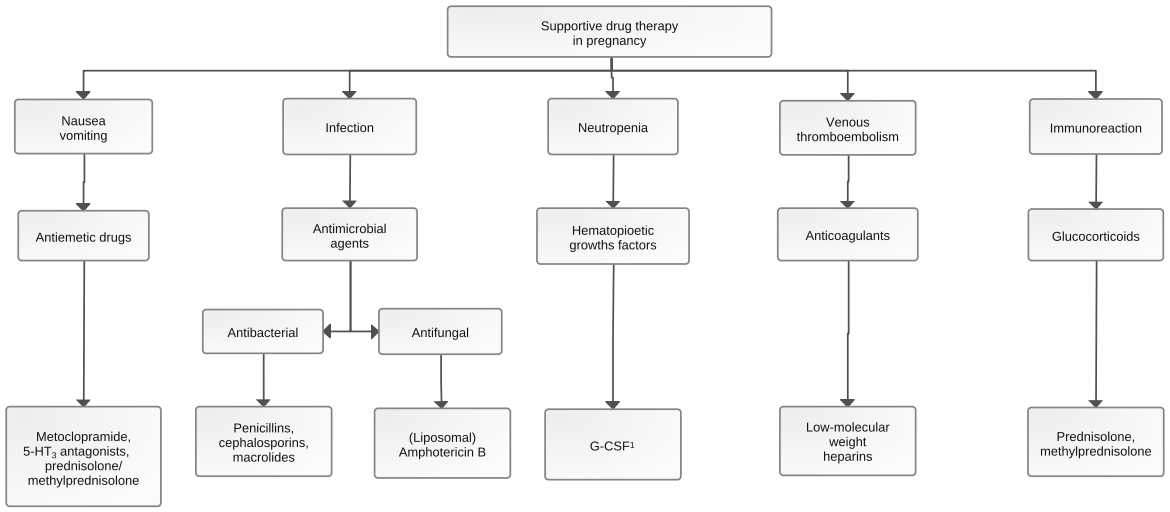
Low-molecular-weight heparins can be used prophylactically and therapeutically [52].

Prednisolone and methylprednisolone are to be preferred for glucocorticoid therapy, see Chapter 6.1.6.1.

Bisphosphonates should not be used in pregnant women. However, there are data from the literature that describe no significant harm to newborns after unknowingly using bisphosphonates during pregnancy [29, 50].

An algorithm for the use of supportive therapy measures in pregnant cancer patients is shown in Figure 6.

Figure 6: Algorithm for the use of supportive drug therapy in pregnant cancer patients



Legend:
[1] G-CSF = granulocyte colony-stimulating factor

6.3 Other, non-pharmacological supportive measures

6.3.1 Fertility protection

In the case of desire to have children, fertility preservation options for oncological patients should be discussed with the patient in the same way as when the oncological disease is diagnosed outside the time of pregnancy. Recommendations for fertility preservation have been published for patients under the age of 25 [90]. In addition to conservative surgical treatment of cervical cancer, other options include cryopreservation of ovarian tissue, which can be removed during a caesarean section, for example, see Onkopedia Fertility Preservation (https://www.onkopedia.com/de/onkopedia/guidelines/fertilitaetserhalt/@@guideline/html/index.html).

6.4 Neonatal outcomes in patients and newborns

According to a meta-analysis from 2016, systemic tumor therapy in the 2nd or 3rd trimester (after the 14th week) of pregnancy (carried out according to the premises stated in this guideline) is not associated with significant problems in fetal development, meaning that early termination of the pregnancy is not necessary [32]. In a long-term follow-up of the INCIP registry, no adverse effects on cognitive, cardiac or general development were observed in 129 children born after maternal chemotherapy during pregnancy compared to a "matched control" group [7]. An analysis of cognitive and behavioral development in a total of 151 nine-year-old children whose mothers had cancer during pregnancy, also published by the INCIP group, showed no deviations from normal findings in the 109 children who were exposed to systemic tumor therapy in utero [95]. It is emphasized that regardless of the presence of cancer or cancer treatment, premature birth has unfavorable effects, so that pregnant cancer patients should aim for a normal duration of pregnancy and normal delivery [7].

7 Registries

It is recommended that data on the treatment and progression of tumors in pregnant women be entered into established registries. For breast cancer: BCP registry of the German Breast Group (www.gbg.de), for all other carcinomas: INCIP registry (https://cancerinpregnancy.org).

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16 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.