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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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1 Summary

- The stage of pregnancy and close cooperation in a multidisciplinary team are essential for the therapeutic procedure. The risk-benefit analysis is particularly important for pregnant tumor patients.
- 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 treatment during the second trimester, a slightly increased rate of miscarriage, 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 standard.
- Some substances such as tyrosine kinase inhibitors, (V)EGF antibodies, anti-hormonal substances or immune checkpoint inhibitors are contraindicated throughout the course of pregnancy. This is outlined in the respective special sections of this guideline.
- The substances used for supportive therapy can also be used in the 2nd and 3rd trimesters without any expected late effects on the newborns.
- If possible, an interval of 3 weeks between end of chemotherapy and delivery is recommended if chemotherapy causes severe myelosuppression.
- The goal is normal delivery; early induction of labor and section delivery (except for patients with cervical cancer) are discouraged.
- As a rule, normal development 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, 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 pregnancy among 42,511 women with cancer from 1967-2002. Again, an increase in annual inci-

dence 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 type of malignancies with initial diagnosis in 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 Cancer	13
Lymphomas	10
Ovarian Cancer	6
Leukemias	6
Melanoma	4
Gastrointestinal tumors	4
Thyroid cancer	3
Brain tumors	2
Other	12

These malignancies were also broken down by stage of disease at initial diagnosis during pregnancy, see Table 2:

Table 2: Stages of disease at the time of diagnosis in pregnancy [27]:

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

2.3 Treatment modalities

An overview of the type of cancer care provided to 1170 pregnant women is provided in the 2018 INCIP work, see Table 3.

Table 3: Treatment modalities in 1170 pregnant women with malignancies [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 Cancer	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 cancer	37	7 (19%)	30 (81%)	-	1 (3%)	-	-
Brain tumors	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%)

2.4 Pharmacological particularities

Pharmacological data on the specifics of tumor therapy in pregnant women are scarce. All current approvals of chemotherapeutic agents, immunotherapeutic agents, and molecularly targeted agents for antineoplastic therapy exclude their use in pregnant women, so that there are no systematic studies on this topic. For a review, see [20].

2.4.1 Volume of distribution, metabolization, excretion

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

2.4.2 Placental transfer and penetration into fetal circulation

Most chemotherapeutic agents are penetrating the placental barrier. This has been demonstrated for doxorubicin, daunorubicin, epirubicin, cyclophosphamide, paclitaxel (only minimally), 5-FU, capecitabine, oxaliplatin, irinotecan/SN38 (metabolite), vinblastine, cisplatin, carboplatin, and cytarabine [14, 60, 69]. Penetration into the fetal circulation must be distinguished from placental transfer. From sparse study results in humans and some data collected in monkeys, rabbits, rats, and mice, the following data can be derived (Table 4):

Table 4: Transfer of systemic anticancer agents into fetal circulation [1, 60].

Substance class	Active ingredient	Concentration in fetal compared to maternal circulation (%).
Anthracyclines	Doxorubicin	1.
	Epirubicin	1.
Taxanes	Docetaxel	0
	Paclitaxel	1.
Alkylating agents	Cyclophosphamide	1.
Antimetabolites	Cytarabine	1.
	5-fluorouracil	1.
Vinca alkaloids	Vinblastine	1.
Platinum derivatives	Cisplatin	31-65
	Carboplatin	1.
Monoclonal antibodies	Trastuzumab	85
	Pertuzumab	30-40
	Bevacizumab	2-9
	Rituximab	150-328
Tyrosine kinase inhibitors	Gefitinib	20
	Erlotinib	25
	Imatinib	31
	Nilotinib	32

2.4.3 Dose adjustment of antineoplastic agents in pregnant women

Despite the relevant pharmacological and pharmacokinetic peculiarities in pregnant women, no fundamental changes in dosages are recommended for systemic anticancer agents compared with use in non-pregnant women. Chemotherapy dosing is based on current body weight, and the Area Under the Curve (AUC) for carboplatin dosing is unchanged from non-pregnant patients [16].

6 Therapy

6.1 Tumor entities

6.1.1 Acute leukemia

General symptoms such as fatigue and shortness of breath as well as blood count changes, e.g., 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 special clinical attention, especially since any delay in induction chemotherapy is associated with a reduction in the rate of complete remissions [78].

6.1.1.1 Acute myeloid leukemia (except acute promyelocytic leukemia).

AML accounts for two-thirds of acute leukemias during pregnancy [78]. In addition to some reports from single centers, each with small numbers of patients, two literature reviews are available that compiled data on AML in pregnant women from 1955-2013 [44] and 1969-2014 [23], respectively.

In 138 cases from 1955-2013, a standard combination of anthracycline and cytarabine was generally used for therapy (58%). The rate of complete remissions was reported to be 91%. Long-term maternal survival was 30%, with a low rate of risk-adapted consolidation therapies and allogeneic stem cell transplantation noted in affected patients. The rate of live births was 87%, with complications documented in 16%. Standard AML therapy during pregnancy was found to be safe and effective, and early referral of patients with high-risk AML for allogeneic hematopoietic stem cell transplantation was recommended [44].

In 85 cases of AML in pregnant women from 1969-2014, outcomes were broken down by chemotherapy initiation in the 1st trimester (n = 8), 2nd trimester (n = 61), or 3rd trimester (n = 14). CR rates were 100%, 81%, and 67% in the 1st, 2nd, and 3rd trimesters, respectively. Fetal death and spontaneous abortion occurred in 37.5% vs 9.7% vs 0%, respectively. Of note, the rates of malformations or death after cytarabine + daunorubicin were 8.5%/6.4%, vs 28.6%/12.5% after use of cytarabine + idarubicin [23]. In contrast to daunorubicin, idarubicin is more lipophilic, has a longer half-life, better placental transfer, and higher affinity for DNA, so that daunorubicin is considered the anthracycline of choice in pregnancy. [58].

Therapy of AML in pregnancy should be initiated immediately. Since a successful pregnancy outcome seems unlikely in the first trimester, the reasons for or against termination of pregnancy should be discussed with the patient [4]. From the 2nd trimester, standard therapy with daunorubicin and cytarabine is recommended [4]. If the AML diagnosis was made from the 32nd week of pregnancy, delivery should be attempted prior to initiation of therapy, both to avoid the risk of chemotherapy-induced pancytopenia associated with higher risk of infection and bleeding during the delivery period [4] and to minimize exposure of the fetus to chemotherapeutic agents.

6.1.1.2 Acute promyelocytic leukemia (AML M3/M3v)

In APL diagnosed during pregnancy, there is a chance of cure for the patient. ATRA and ATO have a high teratogenic potential. Options in the first trimester are termination of pregnancy (cave bleeding complications) or mono-chemotherapy with daunorubicin. After abortion, standard therapy with ATRA plus chemotherapy can be started immediately.

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

A systematic literature review [70] of pregnant women with APL showed a complete remission rate of 89% for 92 patients receiving remission induction therapy with ATRA (32%) or ATRA + chemotherapy (43%). Respiratory distress syndrome was present in 12 of 16 neonates with neonatal complications. Therefore, the ELN guideline [71] recommends prophylactic adminis-

tration of glucocorticoids, preferably prednisolone or methylprednisolone, in births before 36 weeks of gestation.

6.1.1.3 Acute lymphoblastic leukemia

Due to the less frequent occurrence of ALL compared to AML, therapeutic experience during pregnancy is limited. The application of methotrexate, usually a component of ALL therapy, is contraindicated due to the high risk of aminopterin syndrome [45, 58]. A prospective study showed a more frequent occurrence 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 levels (38.0 vs. 9.6 x 10^9 /l, p = 0.01) [76]. This study reports a total of 15 pregnant patients and with 12 live births without subsequent impairment of fetal development. Three patients underwent termination of pregnancy in the first trimester and three other patients underwent induction of labor after application of pre-phase in the last trimester, 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 effect on overall survival and recurrence rate [76].

6.1.2 Chronic myeloid leukemia

CML accounts for 10% of leukemias in pregnancy. During pregnancy, the use of tyrosine kinase inhibitors is contraindicated due to the teratogenic risk and an incidence of more than 10% serious adverse events [1]. For male patients of childbearing potential, the possibility of sperm cryopreservation should be discussed at the time of initial diagnosis [64]. For CML patients of childbearing potential, individualized measures are needed to allow for the possibility of remission maintenance during pregnancy without the use of TKIs. Interruption of therapy 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 to achieve a level below this threshold. Thus, in patients on imatinib therapy seeking pregnancy during a treatment break with stable molecular remission, a switch to a second-generation TKI should be considered to allow deeper and longer-lasting molecular remission [43]. If stable for 3-6 months, remission maintenance over a 9-month gestation is likely. If molecular remission is lost during the break in therapy in a pregnant woman, the time to delivery should be bridged without TKI resumption, if necessary with interferon-alpha. The use of PEG-IFN is controversial and should be avoided because of the accumulation of polyethylene glycol in pregnancy. If necessary, bridging cytoreduction with leukapheresis is possible in individual cases of significant leukocytosis. Since relatively low placental permeability has been demonstrated for imatinib and nilotinib, the use of these substances after the 16th week of pregnancy may be considered in selected individual cases under very strict indication and risk-benefit analysis [1]. Dasatinib should generally not be used in pregnancy due to placental permeability and the high teratogenic risk. The use of bosutinib and newer TKIs is also contraindicated. Current data on the outcome of TKI exposure during pregnancy have been compiled [22].

6.1.3 Gliomas

Few reports of pregnant women with primary brain tumors or brain metastases exist in the literature. Reliable epidemiological data are lacking. Among 27 documented cases in the INCIP registry, 13 were diagnosed in the 2nd trimester and 12 in the 3rd trimester. Therapeutic interventions included neurosurgery (n = 8), radiation (n = 7), and chemotherapy (n = 3). All 21 children born were described as healthy with no apparent damage, even at follow-up of up to 25 years [74]. Case series from single centers [76] as well as a systematic literature review [73] indicate that pregnancy may cause a less favorable clinical course of gliomas, but without

a significant impact on prognosis [73]. Evidence-based guidelines on clinical procedures for pregnant women with primary brain tumors or brain metastases are not available.

For pregnant women in the second and third trimesters, the current data suggest that the same standard protocols should be used as for nonpregnant women.

6.1.4 Colorectal cancer

According to the age distribution of patients with colorectal cancer, only few well-documented cases are available in the literature. A 2017 literature search revealed 119 case reports (53% colon, 44% rectal, 3% multiple) with 2nd and 3rd trimester manifestations of 88%. Among 82 patients whose therapy was described, approximately 10% received chemotherapy during pregnancy [67]. Forty-one well-documented cases, including 27 colon and 14 rectal cancers, were published from the INCIP registry [47]. Advanced stages were found in 73% of patients. Surgical intervention was performed in 51% and chemotherapy in 29% of pregnant women. Delivery of healthy infants 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 colorectal cancer compared with nonpregnant women.

No robust data are available on the selection of antineoplastic agents or therapy protocols suitable for drug therapy of pregnant women with colorectal carcinoma. Fluoropyrimidines such as 5-FU and capecitabine as well as irinotecan and oxaliplatin, predominantly administered in the standard FOLFOX and FOLFIRI protocols, seem to be applicable in the second and third trimesters without specific toxicities being found in the newborns [69]. EGFR antibodies such as cetuximab and panitumumab as well as agents directed against VEGF(R) such as bevacizumab, aflibercept, or ramucirumab are contraindicated, as are multikinase inhibitors that also target VEGFR (e.g., regorafenib).

6.1.5 Lung Cancer

The largest collection of all cases of non-small cell lung carcinoma in pregnant women documented in the literature and in a single institution published to date includes 77 patients [75]. It is estimated that 85% of all lung carcinomas in pregnant women are non-small-cell lung cancers [59]. Only 9 cases of lung carcinoma 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 has been reported to be as high as 26% of 44 cases evaluated [12].

Evidence-based treatment recommendations for pregnant women with lung cancer are not available. Curative intended primary resections are not very promising in view of the usually advanced disease stages. 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], the use of molecularly targeted tumor therapies seems obvious. For this, as well as for therapy with immune checkpoint inhibitors, individual case reports are available [17], from which the justification for individual therapy decisions can be derived. Reliable study data are not available.

6.1.6 Malignant lymphomas

Malignant lymphoma represents the fourth most common cancer diagnosis in pregnancy. Hodgkin and non-Hodgkin lymphomas (NHL) account for 5% and 6%, respectively, of all pregnancy-related cancers [30].

6.1.6.1 Non-Hodgkin's Lymphoma

The most comprehensive data on NHL in pregnant women to date were published from the INCIP registry in 2021 [56]. Of a total of 80 patients, 57 had diffuse large cell lymphoma. One patient had her pregnancy terminated, and 46 women received systemic lymphoma therapy (usually R-CHOP). All 46 patients with as well as all 10 patients without systemic lymphoma therapy during pregnancy had a live birth. One of the newborn children in utero exposed to chemotherapy was found to have a malformation. Also, among the 23 women with other NHL, 20 of whom carried their pregnancy to term, 19 had a live birth. The treatment outcome, followed up for more than 10 years, in patients with NHL who received systemic lymphoma therapy during their pregnancy was comparable to that of nonpregnant patients. As a conclusion, it is recommended that pregnant women with NHL should generally be treated in the same manner as nonpregnant women [56]. This was also published as a recommendation in a consensus guideline [52].

As a special feature, it was pointed out that due to a low placental receptivity and a pronounced placental metabolization, prednisolone and methyprednisolone should be given preference over the other glucorticoids in case glucocorticoid therapy is needed.

A review on the use of new substances in lymphoma therapy [54] shows that only for the application of rituximab in the 2nd and 3rd trimester data are available that may justify its use. Close blood count monitoring in the newborn should be considered after therapy with rituximab until 6 months of age. The Onkopedia guideline on diffuse large cell non-Hodgkin's lymphoma (DLBCL), updated in 2022, includes specific recommendations for the therapy of pregnant patients with DLBCL [65]:

- In case of occurrence of aggressive lymphoma in the first trimester, termination of pregnancy is recommended, since chemotherapy administered in the phase of organogenesis carries a high risk of malformations. In the second and third trimesters, the risk is low.
- The R-CHOP protocol is suitable as a standard therapy regimen. Antimetabolites (e.g., MTX) are contraindicated because of the risk of fetal CNS damage.
- If the lymphoma occurs in late pregnancy and is not very aggressive, treatment can be postponed until after delivery.

6.1.6.2 Hodgkin's Lymphoma

In 24 patients with Hodgkin lymphoma treated with systemic chemotherapy during pregnancy (usually ABVD), pregnancy outcome was documented in 20 cases. Here, 2 premature births were found. However, 2 of 11 patients who did not receive lymphoma treatment during pregnancy also had a preterm birth [34].

While the use of ABVD for the therapy of Hodgkin lymphoma in the first trimester is controversial, its use in the 2nd and 3rd trimesters can be considered an appropriate and safe therapeutic option [36]. Accordingly, ABVD is the most commonly used regimen for Hodgkin therapy during pregnancy [30]. Only one case report is available on the use of nivolumab during pregnancy in the relapse situation of refractory Hodgkin's disease with subsequent engraftment syndrome. The concentration of nivolumab in the mother's blood was higher than in the cord blood and could not be detected in the placenta [35]. The use of brentuximab vedotin is contraindicated during pregnancy.

6.1.7 Breast Cancer

Breast cancer accounts for 39% of all malignancies in pregnant women, see Chapter 2.2. Accordingly, the literature available is extensive, providing detailed data on diagnosis and treatment, specified for surgical, radiotherapeutic, chemotherapeutic, endocrine and immunotherapeutic treatment procedures, compared to other cancers in pregnant women.

A comparison of the prognosis of pregnant (n = 662) vs. non-pregnant (n = 2081) patients with breast cancer has been published from the INCIP registry, showing no significant differences in disease-free (78% vs. 85%) and overall survival (90% vs. 94%) at 3 years [8]. These registry data also suggest that surgical interventions, chemotherapies, and local radiation were administered in almost comparable proportions. Both endocrine and HER2-targeted therapies are not recommended in pregnancy based on current knowledge [10, 61].

While surgical procedures are also permitted in the 1st trimester, although possibly associated with a higher risk of miscarriage, (only technetium is recommended for sentinel node diagnosis, due to allergic reactions described), systemic chemotherapy may only be administered from the 2nd trimester (from week 13) [38, 42]. Anthracyclines (doxorubicin and epirubicin, in combination with cyclophosphamide) and taxanes (paclitaxel and docetaxel, but not nab-paclitaxel) are indicated as for other chemotherapies in pregnancy *(see above),* as in nonpregnant women. Carboplatin is recommended as a case-by-case decision according to the current AGO recommendation [2]. Thus, from the 2nd trimester, standard regimens such as AC/EC followed by paclitaxel, or the additional use of carboplatin in triple-negative carcinomas, are available in the same way as in non-pregnant patients. Dose-dense administration of AC/EC (q2w) followed by weekly paclitaxel is also possible when indicated under 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, PI3kinase 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). The same applies to rarely used substances such as capecitabine, eribulin or vinorelbine, for which no reliable data on their use in pregnant women are available.

6.1.8 Melanoma

Melanoma is relatively common in pregnant women worldwide. For example, the incidence in Australia (New South Wales) was 52 cases per 100,000 pregnancies in 2008 [13], but is far lower, in line with the epidemiology of malignant melanoma, in other regions of the world, for example 3-5/100,000 pregnancies in Europe [68]. From the INCIP registry, there is a report of 60 documented cases, including 14 in stage III, 16 in stage IV (27% in recurrence) [28]. Therapeutically, mainly locoregional surgery and in single cases local radiotherapy were used, while systemic therapeutics such as BRAF/MEK-targeted tyrosine kinase inhibitors or immune checkpoint inhibitors should usually be avoided due to their incalculable risks for the fetuses despite single case reports on favorable outcome [9].

Localized melanomas 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 approach in pregnant women with melanoma [24].

As a special feature of melanoma, it is recommended to carefully search 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 in the order of 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 malignant neoplasia [37].

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

Radiotherapy of malignant ovarian tumors is obsolete in pregnant women.

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

Currently, the following recommendations result:

Surgical intervention in the early stage of 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 in 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].

6.1.10 Sarcomas

The largest data collection to date includes 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 cycles of therapy were administered beginning 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%) 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 neonates required intensive care. Abortion occurred in 4 patients. These patients had received prior therapy with doxo- and idarubicin beginning at 15.5 gestational weeks, whereas initiation of therapy in all other patients was significantly later (median at 21.3 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 Cancer

A cohort study of the INCIP registry analyzed 132 pregnant and 256 non-pregnant women with cervical cancer and well-balanced patient characteristics from 1990-2012 [41]. 14.4% of pregnant women were in stage IA, 47.0% in stage IB1, 18.9% in stage IB2, and 19.7% in stages II-IV. Tumor therapy could be deferred until delivery in 26.5%, 17.4% received primary surgery, 16.7% received neoadjuvant chemotherapy, and 12.9% had early delivery. Progression-free survival did not differ between pregnant and nonpregnant women. A long-term study of 21 pregnant women with cervical cancer from 1985-2000 described a 5-year survival rate of 82%, again with no significant difference from comparable nonpregnant patients [39].

An international consensus conference has developed detailed treatment recommendations in 2019 [5]. For pregnant women with cervical carcinoma in stages IA2-IB3 beyond 22 gestational weeks, in whom therapy cannot be deferred until delivery, neoadjuvant chemotherapy using carboplatin and paclitaxel is recommended.

The AWMF S3 guideline on cervical carcinoma 2022 recommends that treatment of pregnant women with cervical carcinoma should be the same as for non-pregnant women, with neoadjuvant platinum-based chemotherapy recommended from the 2nd trimester [11]. Sectional delivery preferred as the method of choice in all present recommendations. There are no randomized studies regarding maternal outcome depending on the mode of delivery. For microinvasive carcinomas, case-control studies and retrospective analyses show no worsening of prognosis by spontaneous partus. In the S3 guideline, spontaneous parturition is only recommended for microinvasive carcinomas if an R0 resection was previously performed as part of a conization. Spontaneous parturition is not recommended in the presence of microinvasive carcinoma with R1 resection or without conization due to the risk of bleeding and lymphovascular dissemination (S3-LL).

6.1.12 Other solid tumors

No conclusive data on pregnant patients are available for numerous other solid tumor diseases such as head and neck carcinomas, pancreatic carcinomas, neuroendocrine tumors, urothelial carcinomas, renal cell carcinomas or hepatobiliary carcinomas.

A collection of 13 pregnant women with gastric carcinoma published from the INCIP registry [55] does not allow derivation of recommendations for the oncologic care of these patients.

Thyroid carcinomas represent 3% of malignant neoplasms in pregnant women (see above), but they are almost exclusively treated without systemic agents and have no worse prognosis as compared with non-pregnant patients [62].

6.2 Drug for supportive therapy in pregnancy

According to the recommendations of an international consensus conference with INCIP participation [52], both metoclopramide and 5-HT3 antagonists can be safely used for antiemetic therapy in pregnant women receiving 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 under chemotherapy, many common substances are non-critical according to current knowledge, however, aminoglycosides, sulfonamides, trimethoprim, fluoroquinolones, amoxicillin-clavulanic acid and tetracyclines should be avoided [4]. If systemic antifungal therapy is required, preference should be given to amphotericin B preparations.

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

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

If glucocorticoid treatment is required, prednisolone and methylprednisolone are preferred, see Chapter 6.1.6.1.

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

6.3 Other non-drug supportive measures

6.3.1 Fertility Protection

In the case of an existing desire to have children, options for fertility preservation in oncological patients should be discussed with the patient in the same way as for the diagnosis of the oncological disease outside the time of pregnancy. In addition to surgical conservative treatment of cervical carcinoma, possibilities include cryopreservation of ovarian tissue, which can be harvested, for example, in the course of a section.

6.4 Neonatal outcomes in patients and newborns.

According to a 2016 meta-analysis, chemotherapy administered in the 2nd or 3rd trimester (after 14 weeks gestation) (according to the premises stated in this guideline) is not associated with significant problems in fetal development, so early termination of pregnancy is not necessary [32]. In a long-term follow-up of the INCIP registry, 129 infants born after maternal chemotherapy during pregnancy were not found to have impaired cognitive, cardiac, or general development compared with a matched control group. It is emphasized that regardless of the presence of cancer or the delivery of cancer treatment, preterm birth shows unfavorable effects, so that a normal delivery should be sought in pregnant cancer patients [7].

7 Register

It is recommended that data on treatment and outcome of malignancies in pregnant women be documented in established registries. For breast carcinoma: BCP Register of the German Breast Group (www.gbg.de), for all other carcinomas: INCIP Register (www.incipregistration.be).

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16 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.