

Cancer in pregnancy

National Guideline

Danish Society of Obstetrics and Gynecology (DSOG).

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This final version is based on a draft which was presented and discussed at the obstetrical guideline meeting in 2013. Responsible for this first draft were: Berlac Janne Foss Ersbøll Anne, Grønbeck Lene, Langhoff Roos Jens, Laursen Lone, Nielsen Birgitte Bruun, Schmidt Maria Cathrine, Storgaard Lone (chairman), Sørensen Morten Bek.

In recent years, there has been a change of paradigm in treating pregnant women with newly diagnosed cancer. Recommendations today are less hesitant about the diagnosis of cancer, treatment with chemotherapy and postponement of delivery as long as possible.

This guideline addresses the obstetric care for pregnant women with cancer diagnosed during pregnancy. The guideline does not address the treatment itself, which is handled at centers with specific expertise.

Recommendations:

The literature is sparse and mainly based on case reports. In the guidelines, when possible, this is taken into account.

Guidelines	Recommendations	Evidence
Newly diagnosed cancer in pregnancy should be managed in a multidisciplinary setting, involving obstetrician, oncologist and/or hematologist, pediatrician and family physician as well as the treating department.	II	A
The physician should thoroughly review the situation with the pregnant women and her family.	IV	D
Most chemotherapy is safe to use after the 1 st trimester.	II	B
Postpone chemotherapy to after the 1 st trimester if safe for the mother.	II	B
Timing of delivery should be 2-3 weeks after the last chemotherapeutic regime, allowing for fetal and maternal bone marrow to recover. I-A	I	A
Timing of delivery should be after week 35, if possible, allowing for fetal maturation. II-2 A	II	B
When suspecting cancer and in staging, it is safe to use MRI, Ultra scan, chest x-ray, bone marrow biopsy and surgery. If possible avoid CT and PET.	III	C

The placenta should be histologically examined for placental metastasis. If positive, then pediatricians and oncologist and/or hematologist are informed.	IV	D
Most evidence does not suggest increased maternal survival following therapeutic abortion.	III	C
Surgery during all trimesters is feasible.	III	C
Survival between pregnant and non-pregnant appears to be similar.	III	C

Recommendations: Each cancer type:

Breast cancer

- The obstetric care should be centralized since treatment and the diagnostic examinations could potentially harm the development of the fetus.
- Prior to examinations of the pregnant women for staging and oncological treatment, the fetus must/should have ultrasound scanning for abnormalities.
- The pregnant woman should be managed as a high-risk pregnancy in order to screen for fetal wellbeing, growth and hypertensive disorders.
- Postpone delivery to term (>37 gestational weeks) since prematurity is a known risk factor for cognitive and emotional development in children.
- If breast cancer is diagnosed in the 3rd trimester and only one treatment with chemotherapy can be administered/achieved, then consider delivery at gestational week 35. Chemotherapy treatment should not be postponed in the interest of the fetus.
- After gestational week 35+0, chemotherapy is not an option.
- An interval of 3 weeks between treatment with chemotherapy and delivery is optimal to avoid effects of the suppression of the bone marrow such as bleeding, infections and anemia as well as to avoid accumulation of the medicine in the fetus.
- Normal vaginal delivery is feasible. Caesarean section should be only on obstetric indications.
- Chemotherapy and radiotherapy can restart just after an uncomplicated vaginal delivery, whereas it is advised to wait one week before treatment after an uncomplicated caesarean section.
- Breastfeeding should be avoided during and after chemotherapy. If it is physiologically possible, the woman can breastfeed after radiotherapy.
- In general, chemotherapy, in particular anthracyclines, is associated with chronic and acute cardio toxicity. The newborn child should be referred to neonatal evaluation in order to plan an echocardiographic assessment.
- Thrombosis prophylactic treatment in case of surgery follows normal surgical guidelines.

Hematologic malignancies:

Lymphomas in general:

- For diagnosis, an enlarged lymph node should be achieved with a biopsy, x-ray of the lungs and routine blood work (Evidence: **A**).
- Bone marrow biopsy should be done if B-symptoms (fever, night sweating and weight loss) (Evidence: **A**) are experienced
- Pregnant women with Hodgkin's and Non-Hodgkin's lymphoma can be offered standard treatment. There is no evidence of fetal adverse effect (Evidence: **A**).

Hodgkin's lymphoma (HL)

- For early stage HL diagnosed in the first trimester, it is safe to postpone treatment until the 2nd trimester. However, more than 50% of patients can postpone treatment until delivery. If treatment is required, often a single-agent chemotherapy is enough to control the disease (Evidence: **B**)
- Standard treatment (ABVD) regime is feasible and safe from the 2nd trimester (Evidence: **B**).
- For patients diagnosed early during the first trimester, termination should be considered if waiting until the second trimester is not feasible. Single-agent vinblastine along with steroids is another option (2/4 patient congenital anomalies and spontaneous abortion) (Evidence: **B**).
- For advanced stage or relapsed HL in the first trimester, termination of the pregnancy is recommended. In the second and third trimesters, treatment should not be delayed (Evidence: **B**).

Non-Hodgkin's lymphoma (NHL)

- For indolent (low risk) cases, an initially expectant approach is sensible (Evidence: **B**).
- Use of monoclonal antibodies is contradicted during pregnancy due to possible radiation exposure of the fetus.
- For aggressive NHL, in the 1st trimester therapeutic abortion should be considered. CHOP is the recommended regime during the second and third trimesters (Evidence: **B**).
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- Highly aggressive cases (Burkitts and Burkitt-like lymphomas) are especially aggressive during pregnancy. Termination of pregnancy is recommended in the first trimester. A methotrexate regime contains a risk of teratogenicity during the first trimester and profound myelosuppression during the 2nd and 3rd trimesters (Evidence: **B**).

Leukemias:

- Exposure to chemotherapy in the first trimester is associated with a high incidence of spontaneous abortion and fetal malformations. If treatment is given early, before 2-3 weeks after conception, the risk is low. Then if safe, treatment should be stopped and pregnancy continued. (Evidence: **B**).
- Use of rituximab following the first trimester in treatment of B-cell lymphomas is not associated malformation.
- Acute leukemia in pregnancy has a high risk of complications. Cases diagnosed early in pregnancy should be advised to terminate the pregnancy. Those diagnosed later should be offered systemic chemotherapy (Evidence: **B**).

- Daunorubicin and idarubicin are antracyclines used in AML and ALL. Both have been associated with malformations in all trimesters. Doxorubicin could serve as an alternative (Evidence: **B**).
- With acute leukemia cases, when possible delivery should be planned, preferable after 32 weeks of gestation, when the patient is not cytopenic (Evidence: **B**).

Colorectal cancer:

- Persistent rectal bleeding in pregnancy or discharge of tissue during delivery are serious symptoms of colorectal cancer and should lead to further investigation (Evidence: **D**).
- Sigmoidoscopy is indicated to evaluate rectal bleeding, a suspected mass or stricture (Evidence: **C**).
- To monitor treatment response, Carcinoembryonic antigen (CEA) can be used (Evidence: **C**).

Malignant melanoma (MM)

- Suspicious naevi should be excised in pregnant as well as non-pregnant patients (Evidence: **C**).
- MM in the pregnant patient is treated in the same way as with non-pregnant patients depending on prognostic markers (tumor thickness, mitotic rate, ulcerations) (Evidence: **C**).
- Sentinel node biopsy should be offered following discussion with the patient (Evidence: **B**).
- In case of disseminated disease, placenta should be pathologically examined (Evidence: **B**).

Gynecological cancer:

Cervical cancer:

- The diagnosis is made by colposcopy, biopsy, smear and if necessary, an excisional cone biopsy.
- Stage Ia1 and Ia2 are treated with an excisional cone.
- Stage Ia1 and Ia2 patients who have completed their treatment can be delivered vaginally.
- Consider postponing treatment to a viable fetus, taking into account gestational age, FIGO-stage and histology.
- If the pregnancy is terminated, then radical surgical procedures are done as usual.
- Mode of delivery is caesarean section in cases with cervical cancer where the treatment is not completed

Ovarian cancer

- The ultrasound criteria for malignancy is as in non-pregnant patients.
- Alfa-fetoprotein, hCG and inhibin cannot be used as a biomarker for tumors during pregnancy.
- CA-125 can be used as a biomarker after 1st trimester, but not around delivery.
- Suspicion of malignancy in ovarian cysts should be removed surgically.
- If considered safe, surgery should be postponed until after the 1st trimester because of the function of the corpus luteum.
- In the case of a suspected malignant tumor in the 3rd trimester, surgery should wait until lung maturation of the fetus.
- In the case of borderline tumors and a desire to preserve fertility, conservative surgical intervention can be considered and possible further treatment postponed until after delivery.
- In advanced FIGO-stages of epithelial ovarian cancer, treatment of the pregnant is as for non-pregnant patients with radical surgery. Caesarean section can be done after gestational week 24, after lung maturation.

Thyroid cancer

- Diagnosis:
 - Ultrasound examination of the thyroid.

- Fine needle aspiration biopsy when the tumor is solid and more than 5 mm in diameter.
- Scintigraphy is contradicted in pregnancy and breast feeding.
- Pregnancy can maintain when there is malignancy or suspicion of malignancy .
- Surgery should be offered in case of metastases or substantial growth, preferable in the 2nd trimester
- In well-differentiated tumors without advanced disease, surgery can be delayed under close surveillance until after delivery
- Suppressive doses of levothyroxine should be continued or started in earlier treated, present or suspicion of thyroid cancer with a TSH level of less than 0.05 mIU/L. A high TSH level stimulates tumor growth and thereby increases relapse.
- A supplement of thyroxin, calcium and vitamin D should be given in therapeutic doses in order to ensure proper neurological development and growth of the fetus.
- Radioiodine therapy is contradicted in pregnancy and breastfeeding. It is recommended to postpone pregnancy for at least 4 months after cessation of treatment.
- Placenta metastasis is not seen in thyroid cancer.

Brain Tumors

- The type of tumor and its prognosis should guide preconception advice to women with brain tumors. The patient should be informed of the following:
 - Symptoms related to raised intra cranial pressure (ICP) may increase during pregnancy.
 - Sex hormone dependent tumors (i.e. prolactinomas) can increase in size during pregnancy.
 - Prolactin antagonists are not contraindicated in pregnancy, but they have an inhibitory influence on lactation.
 - Tumor volume treatment and associated symptoms should be started prior to pregnancy.
- A brain tumor should be considered in a pregnancy with unexplained and persistent neurological symptoms.
- Diagnosis of a brain tumor is by magnetic resonance imaging and subsequent histology at surgery.
- Stereotactic surgery and craniotomy is not contradicted in pregnancy.
- Radiotherapy and chemotherapy after the 2nd trimester is safe to use if delay of treatment reduces the maternal prognosis.
- Consider steroids and antiepileptic drugs when unstable neurological symptoms are present. In a situation is unstable, preterm delivery may be indicated.
- Delivery can be vaginal or by caesarean section. Caesarean section is mainly indicated when symptoms are unstable, new or the diagnosis is unclear, and in the case of increased intracranial bleeding.
- Vaginal delivery is safe for patients with chronic tumors, growing tumors and in the presence of symptoms of ICP.
- Assisted vaginal delivery to shorten the 2nd stage of labor may be considered to avoid an increase in ICP, in particular those with unstable symptoms and seizure risk.
- Both the risk of thrombosis and the risk of cerebral hemorrhage should be individually considered by the multidisciplinary team.

Sarcomas

- Rarely occur in pregnancy
- Surgery should be done as soon as possible
- In the case of an intra-abdominally located tumor, gestational age and the progression of the tumor must be taken into account in order to optimize the timing of delivery