CANCERS OCCURRING DURING PREGNANCY

PREFERRED MODELS OF CARE AND CRITERIA FOR REFERENCE CENTRES

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PREFERRED MODELS OF CARE AND CRITERIA FOR REFERENCE CENTRES

A. Type of cancer

All types of malignancy diagnosed in pregnant women, including pre-invasive disease during pregnancy are referred to. The different types of cancer which can be diagnosed in pregnant women are similar to the cancer types in non-pregnant young women. Pregnancy does not predispose to any particular cancer type. Most frequently, breast cancer, hematological cancers and melanoma's are diagnosed during pregnancy. Other rare types of cancer (e.g. sarcoma, thyroid, lung and tongue cancer) can also be diagnosed during pregnancy.

For pre-invasive disease, we mainly refer to ductal carcinoma in situ (DCIS) of the breast, lobular cancer in situ (LCIS of the breast), cervical intraepithelial neoplasia (CIN), vaginal intraepithelial neoplasia (VAIN), and vulvar intraepithelial neoplasia (VIN). The motivation to include pre-invasive disease is that a proper diagnosis and exclusion of a malignancy may request sufficient expertise. Patients diagnosed with cancer postpartum (thus after delivery) are not included in this proposal.

B. Short description of the cancer

Cancer during pregnancy has an estimated incidence of one per 1 000 to 2 000 pregnancies. This means that we estimate approximately 60-120 cases in Belgium on a yearly basis. As women delay the timing of their pregnancies to a later age, there is a higher risk to develop cancer during pregnancy. Treating a pregnant woman with cancer requires a delicate balancing between maternal benefit and foetal risk. Historically, and also intuitively, cancer treatment was not started during pregnancy, because of fear for foetal safety. However, prolonged treatment delay may worsen the mother's chances for survival. On the other hand, iatrogenic induction of preterm labour in an attempt to start treatment postpartum may impair foetal outcome, as prematurity is associated with higher risks of short and long term morbidity and also mortality. Oncologic treatment during pregnancy has been proven feasible in several case series, with maximal consideration for foetal safety and well-being. With adequate staging and treatment during pregnancy, standard treatment should be aimed for, meanwhile awaiting foetal maturity and aiming for term delivery. Optimal treatment during pregnancy requires constant communication between oncologist and perinatologist (and also other specialists) to maintain the balance between mother and unborn child: cancer treatment for the mother, without jeopardizing foetal safety. The maternal prognosis is only described for the most common cancers. It appears that for breast cancer the maternal prognosis is comparable to non pregnant women with breast cancer. We hypothesise that also for other cancer types the prognosis is comparable provided that the same treatment is applied.

C. Model of care pathway suggested for pregnant women with a cancer

Model of care pathway	Preferred model
1. Model 1: Reference Centres exclusively (from diagnosis to follow-up). Once there is a suspicion of a cancer or a cancer has been diagnosed, the patient should be referred to a Reference Centre. A network with other Reference centres or with specific experts working in other centres is encouraged.	For all invasive cancer types during pregnancy.
2. Model 2: Shared care between Reference Centres and peripheral hospitals. Part of the care pathway is performed in the Reference Centre and for another part of the care pathway, the patient is referred (back) to the peripheral hospital.	For all pre-invasive diseases during pregnancy.

D. Phase(s) of the clinical pathway for which Reference Centres are required

D.1. Pre-invasive disease

For pre-invasive disease (ductal carcinoma in situ (DCIS) of the breast, lobular cancer in situ (LCIS of the breast), cervical intraepithelial neoplasia (CIN), vaginal intraepithelial neoplasia (VAIN), and vulvar intraepithelial neoplasia (VIN)), treatment can be postponed until after delivery. Therefore, the discussion on the treatment should be discussed in the COM/MOC of the reference centre. For cervical intraepithelial neoplasia a colposcopy by an expert from the reference centre is mandatory. The subsequent follow-up during pregnancy can in most cases be performed in the peripheral centre. However, the advice of the COM/MOC should be followed in case a closer follow-up is needed. These diseases are not interfering with the pregnancy evolution and a natural term delivery is possible.

D.2. Invasive disease

In the following, we discuss more in detail the proposal for invasive cancer during pregnancy.

Phase of the Clinical Pathway	Reference Centre A and B	Peripheral centre
1. COM/MOC	X	
2. Diagnostic confirmation	X	
3. Comprehensive AP diagnosis	X	
4. Therapeutic modalities	X	
• **Follow-up of pregnancy (US)**	X	(X)
• **Delivery**	X	(X)
5. Follow-up after pregnancy		
• **Oncological, mother**	X	(X)
• **Pediatric**	X	

Multidisciplinary Oncological Consult: Reference Centre

Although precise figures are lacking, we estimate that 60-120 (1 in 1 000-2 000 pregnancies and approximately 120 000 births per year) cases of cancer in pregnancy are diagnosed in Belgium. Given a complex situation, a multidisciplinary discussion with the oncologist (medical, radiation and surgical), obstetrician, neonatologist and psychologist is mandatory. The complexity cannot be underestimated and therefore all steps in the diagnostic procedure and interpretation, therapeutic modalities and follow-up need to take place in centre that is used to deal with the complexity.

Diagnostic confirmation: Reference Centre

In case of doubt and when a biopsy without any particular harm can be taken to make a diagnosis, this can be done in the peripheral centre. However, in any case, an expert organ pathologist should evaluate the slides. This, not only to confirm the diagnosis, but also to exclude pre-invasive disease. So, where possible, the biopsy is best taken in a reference centre. Especially, when the clinical diagnosis is very suspect or when major surgery is needed to make a diagnosis (for example, a laparotomy or laparoscopy for an ovarian cyst/mass), the patient is referred to the reference centre.

It is important to perform a full staging with the lowest possible foetal exposure dose of radiation. Before any staging procedure is performed, a multidisciplinary meeting should define which examinations are needed during pregnancy and which will alter the treatment. Different examinations (and thus cumulation of foetal radiation exposure) that inform on the same organ site should be avoided. This requires a clear view that needs to be established during a first COM/MOC. During these discussions, new approaches in diagnostics can be discussed and applied where possible or needed. A second COM/MOC aims to discuss the treatment modalities.

- Complexity and new approaches: The pregnancy complicates imaging of breast and abdomen, necessitating sufficient expertise from the radiologist. Expertise is mainly defined as working in a large volume radiological unit.
- Facilities and equipment required: ultrasonography, Rx, MRI scan, PET, diffusion MRI
- Professional expertise required both to perform the diagnostic procedure and to interpret the results: breast tissue, haematological parameters, renal and liver metabolism change in pregnancy and levels of tumour markers change during pregnancy. These physiologic changes are likely to disturb the results and the results need to be interpreted taking the pregnancy into consideration. Clinicians need to be aware of the impact of the pregnant state on the results. In some cases, for example magnetic resonance imaging, the influence of pregnancy is unknown and caution is needed. Organ specialists are required to treat these patients. The medical and surgical oncology expertise thus is dependent on the organ that is involved. Per organ one reference specialist per centre is suggested. For example, if 4 specialists treat breast cancer in one centre, one of these 4 should see all pregnant breast cancer patients. In addition, one physicist per centre should calculate the expected foetal radiation exposure. Similarly, among obstetricians, one expert obstetrician should be appointed who is the reference clinician for all cancer types.

Comprehensive pathological diagnosis: Reference Pathology Laboratory

Apart from confirming a diagnosis, the pathologist should make sure the patient does not suffer from pre-invasive disease. The discrimination between invasive and pre-invasive disease is of paramount importance, especially during pregnancy.

Therapeutic modalities: Reference Centre

Cervical cancer is the most challenging situation since the pregnant organ itself is involved. Therefore we suggest that treatment of cervical cancer should be strictly centralised in one of the centres specialised in cancer treatment during pregnancy. Cervical cancer during pregnancy is diagnosed in approximately 6-12 patients per year in Belgium. The same is true for ovarian cancer. Individualisation according to tumour type is therefore of paramount importance and needs to be discussed and decided among reference centres. Referral from one reference centre to another should be possible for all cancers but for cervical and ovarian cancer in particular.

The follow-up of the pregnancy should be organised by one of the reference centres and can be done in collaboration with peripheral centres. The advised place of delivery depends on the gestational age at that time, the timing in the oncological treatment, whether or not complications occurred. The decision on the place of delivery should be taken in the reference centre.

- Expertise required to perform the treatment : As we stated above, individualisation is mandatory since the type of surgery is more standard in some cases (e.g. breast, thyroid, melanoma...) when compared to other situations (e.g. cervical cancer). However, complexity is determined by the different pharmacokinetics in pregnancy, the foetal dose calculation of radiotherapy, high risk obstetrics / foeto-maternal medicine and high care neonatology, and the combination of these suggest that overall, treatment is best planned and performed in a reference centre.
- Para-medical expertise required: a reference centre is more likely to provide a specialised social assistant and psychologist. These are very important when cancer is diagnosed during pregnancy. The complex situation and the uncertainty about the oncological and obstetrical outcome put a large amount of stress on both the patient and her partner. A permanent support is therefore mandatory.

Follow-up: Collaboration between a peripheral centre with a program in oncology and a Reference Centre

- Complexity: Children who were exposed to antenatal chemo and/or radiotherapy need careful follow-up in order to assess the impact of treatment on their health. In particular, their growth, cardiac function (especially after exposure to anthracyclines), neurocognitive outcome, fertility and secondary cancers need to be documented. We propose that all these children are investigated according to the same protocol in order to document these health aspects. The results of these examinations will inform parents and the pooled analysis on the long term will inform future parents and clinicians.
- We do believe that mothers can be followed in the peripheral centre, however in close collaboration with the reference centre. Follow-up data from the reference centre need to be transferred to the reference centre. If a mother wants to become pregnant again later, the safety should be discussed with the reference centre.
- Facilities and equipment required: Pediatricians, psychologists and echocardiographists can examine these children using a clinical examination, sonar and a test battery for the neurocognitive outcome. Especially the latter lacks in routine practice and therefore the follow-up is best done in the reference centre.
- Medical expertise required: A paediatrician with expertise in the neurocognitive development is best placed to interprete the results.
- Para-medical expertise required: psychological support should be offered, both for the mother and father.

E. General and specific criteria for Reference Centres

Human Resources and dedicated team

The experienced and multidisciplinary setting, inclusive perinatologists and obstetricians, is the essential element here. Also the habit to have the interdisciplinary discussions is pivotal. Given the low frequency of the co-incidence of cancer, a strong centralisation only will allow some teams to have a better experience.

Teams should include medical oncologists, radiation oncologists, 'organ surgeons', obstetricians, fertility specialist, psychologists, and a nurse specialised in pregnant cancer women. Given the particular situation, all should have sufficient expertise in their field. At two occasions a COM/MOC should be done. The first COM/MOC is organised to confirm diagnosis and to define the staging strategy. The second COM/MOC should be planned when treatment modalities are decided upon. Per reference centre, one specialist of the team (less important which specialty), should be appointed who co-ordinates the cancer in pregnancy program.

Required facilities and equipment

The required facilities refer to those used for the standard cancer care. The reason for sending patients to a reference centre is the multidisciplinary setting and expertise, but not the particular facilities and equipment.

Patient centred care

Given the stressful situation and high level of uncertainty for pregnant cancer patients, they should be seen within one week after their announcement. They should be seen by the reference clinicians (organ specialized oncologist and obstetrician) dedicated to the cancer in pregnancy program. Already at the first consultation, a psychologist or specialized nurse should be available to support the patient and her partner.

Minimal volume of patients

In order to allow centres to gain and maintain the experience, sufficient centralisation is needed. Given an estimated incidence of 60-120 cases a year in Belgium, we do believe that no more than 6 centres should diagnose and treat pregnant cancer patients. We make a distinction between A and B centres and propose 1 A centre and 5 B centres. Both A and B centres can diagnose and treat pregnant cancer patients. However, the diagnosis and treatment of all patients is discussed with the A centre which is a national centre that coordinates the B centres that are dispersed throughout the country. At least one consultation of a new pregnant patient in the A centre is mandatory. Reference centres should be chosen based on available multidisciplinary teams, their expertise, motivation and interest in the management of cancer during pregnancy. Apart from expertise and numbers, the importance of motivation and interest in the field of cancer and pregnancy is underscored. The selection of the A centre is based on its current experience in the diagnosis and treatment of pregnant cancer patients. In addition, centre A should be actively involved in the writing of international consensus statements that are published. Also, centre A should conduct research within the field of cancer during pregnancy, both on a national and international level. This system for A and B centres should be evaluated after 5 years and adapted where necessary.

We do believe this proposal is much better than the alternative that consist to impose a minimal yearly caseload of 20 cases by centre in order to built sufficient expertise. Given the low incidence of 60-120 patients per year, 3-6 centres would reach this minimal requirement in Belgium. This number per centre can be evaluated after 5 years and the number of centres needs to be adapted according to the actual numbers (since the number of 60-120 is only a very rough estimate).

Quality Assurance

The reference centre should treat the pregnant patients according to guidelines where available. Registration in the national cancer registry is mandatory. Quality assurance can be assessed both on the short and long term. On the short term surgical and obstetrical complications should be reported. Also the perinatal assessment of the child fits well within the short term outcome. On the long term, the maternal prognosis and development of the child can be assessed as a parameter of long term quality.

We do believe that the co-incidence of pregnant cancer patients is that uncommon, that each patient should be referred to one of the 6 reference centres that are dispersed throughout the country. All pregnant cancer patients seen in a reference centre B should be discussed with the reference A centre. Diagnostic steps and treatment modalities should be agreed on. Where needed, a patient is referred from reference centre B to reference centre A for treatment.

In order to improve the national collaboration among the 6 reference centres, a national work group should be established with at least one representative of each reference centre (A and B). Collaboration should be discussed and can be adapted according to experience. An annual meeting should be planned, resulting in an annual activity report. Yearly updates on the maternal and pediatric outcome should be part of the follow-up registry.

Research and other scientific activities

As the incidence is low, treating clinicians should do a maximal effort to study the problem. Apart from the clinical approach, they should be involved in research programs on cancer in pregnancy. This will finally allow us to learn and draw conclusions. This information will be beneficial for future patients of course. Given the low incidence, the research efforts should be embedded in an international setting. Clinicians should not only add clinical data, though also imaging studies, biopsies,… where needed. Participation to existing international initiatives is strongly recommended in order to collect clinical data for further research. Such an international task force for all cancers in pregnancy is currenty running in the European Society of Gynaecological oncology (ESGO). Practice guidelines are developed within the network of this task force, and should be applied among reference centres.

Educational activities: Teaching and dissemination

Treating clinicians should be able to teach the approach in practice to peers, nurses and students. They should be recognised as experts in the field through their participation in the above mentioned task force, panel of specialists involved in the construction of guidelines and participation to the international registry.