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Recent Advances in Personalized Treatment of Cancer in Pregnancy

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Introduction

Cancer that occurs inside the pregnant or during the first postpartum year (or throughout lactation time) is considered gestational. The diagnosis of this entity is intrinsically accompanied by ethical problems when making clinical decisions about the disease and the newborn future [1,2].

Nowadays a modern medical treatment achieves treat cancer with the same prognosis than no-pregnant population and childbirth without any sequela. Spanish consensus of different specializations (Surgery, gynecology, radiology and radiotherapy and medical oncology) on the last year have published recommendations that allow harmonization of management and review the last advances in cancer in pregnancy [3].

The week of gestation at diagnosis of cancer and the characteristics of the tumour are crucial for the clinical decision making. Once the diagnosis is confirmed, the patient should be referred to an institution with expertise in dealing with such cases. It is essential to have specialist physicians in this cancer subtype (gynecology, psychology, oncology, psycho-oncologist...) forming an interdisciplinary group. A complete autonomy of the patient is mandatory based on transparent and clear information on the maternal-fetal health situation [4].

Diagnosis

Diagnosis ionizing imaging procedures should be avoided during pregnancy. However, in the first few days after conception, there are no studies demonstrating damage to the fetus after performing a radiological test that transmits less than 1 mGy (Computed Tomography (CT) or X-Rays (Rx). The most effective way to limit radiation is i) to use non-irradiated imaging modalities such as ultrasound, ii) to justify all explorations and iii) to use the lowest possible dose. For example; from week 2 to week 15 of pregnancy, tests outside the abdomen (e.g., head and neck, thorax and extremities) do not pose a risk to the fetus because the only radiation that is delivered is scattered, very low and may be eliminated with standard precautions [5]. Regarding iodinated contrast agents, no biological effects have been described following administration during pregnancy, but there is a potential risk of hypothyroidism on baby development so it is considered unwise to delay the test until after delivery when no other examination is available [3].

Non-ionizing imaging procedures, such as ultrasonography and MRI that does not exceed 1.5 Tesla (T) are preferred. A recent study found that gadolinium was associated with increased risk of a broad set of rheumatologic, inflammatory or infiltrative skin conditions in the offspring and risk of stillbirth or neonatal death. Thus, the use of gadolinium for imaging in MRI is not recommended during pregnancy unless it would be essential to the health of the woman or fetus [6,7].

Bone scintigraphy and fluorine-18-fluorodeoxyglucose (PET) are not recommended, but it can be performed in selected cases, with a low dose of 18.5 MBq which is not exceeding the absorbed radiation dose of 0.2 mSv to 0.5 mSv by the fetus, PET/MRI might be the ideal combination when available. However, these data are insufficient to establish a recommendation for the use of PET for cancer staging during pregnancy [8].

When the suspicion of tumour is high, pathological examination of suspected lesions should follow standard procedures with important limitations to consider in some tumors of difficult diagnosis (ovarian cancer); for example, colonoscopy can be performed safely in pregnant women with caution [4,9]. Sentinel lymph node biopsy in breast cancer staging with 99mTc-albumin nanocolloids do not cause significant uterine irradiation when optimized protocols are followed, there is no reason to contraindicate SLNB during pregnancy in breast cancer, but in gynecological cancer there are currently no data to establish a recommendation. In other cases, like melanoma

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SLNB with radiocolloids is considered safe and is recommended from the second trimester. The consensus is that SLNB it should be performed no earlier than the second trimester, in a one-day protocol (10 MBq 99mTc to 25 MBq 99mTc) and with surgery scheduled immediately after lymphatic mapping [3].

It is mandatory that the medical team, reviews the indications for and frequency of diagnostic tests individually, as well as their risk-benefit ratios.

Surgical Evaluation

Standard anesthetic procedures are considered safe during pregnancy. Surgeries are usually not recommended in the first trimester, especially in the first 8 to 10 weeks (embryogenesis), with a higher number of miscarriages associated. Nevertheless, surgery should never be postponed if it is crucial for the management plan. For example, a laparoscopy-laparatomy can often be performed before the 14th to 16th weeks of gestation if the balance benefit-risk is positive and also mastectomy in breast cancer with a poor prognostic disease to avoid complementary radiation therapy could be considerate.

In the specific case of cervical cancer, due to frequency of localized tumors, cone biopsy may be used in the early stages and staging lymphadenectomy could be performed safely up to the 22nd week of gestation, but it is preferred to wait until the second trimester to do it [4].

All procedures carried out after week 20 should be performed in a slightly left lateral decubitus position to avoid compression of the vena cava and to maintain cardiac output. A laparoscopic approach is considered feasible and safe during pregnancy until weeks 26 to 28 but the recommended duration is less than 90 min, and the pneumoperitoneum with a maximum intra-abdominal pressure of 10 mmHg to 13 mmHg and open pneumoperitoneum technique [3].

In the postoperative period, paracetamol, tramadol or morphine, and antiemetics (metoclopramide or ondansetron) may be prescribed. In the third trimester, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have been associated with premature closure of the ductus arteriosus and possible pulmonary hypertension and should be avoided [10].

After 28 week of pregnancy abdominal surgery is better to be delayed after deliver, but in general breast cancer surgery should be undertaken much like that in the non-pregnant population [1].

Radiotherapy

Several fetal adverse effects, including the risk of mental retardation, intrauterine growth restriction, childhood cancer, or even fetal death, have been described after gestational radiotherapy.

The dose performed during the standard treatment of breast cancer is 46 Gy to 60 Gy, of which it reaches 0.04 Gy to 0.15 Gy to the pelvic area, doses that can put the risk of embryo development. On first trimester, brain or H&N radiotherapy could be taken into account but only in selected cases [3,11].

Technological improvements in modern radiotherapy such as Three-Dimensional Conformal Radiotherapy (3D-CRT), Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), stereotactic radiotherapy and proton therapy have been introduced into clinical practice on last years. The advantage of this techniques is limiting the exposure of high doses to a more restricted volume, nevertheless, the use of advanced radiotherapy techniques in pregnant women with cancer may increase the probability of short- and long-term adverse effects on the fetus; therefore, radiotherapy should be used with caution in strictly selected patients [12,13].

Systemic Oncospecific Treatments

In recent years, increased chemotherapy treatment has been observed in pregnant states, from 25% of women treated with chemotherapy 20 years ago to nearly 50% of women affected by cancer during pregnancy who are treated safely during pregnancy today.

Chemotherapy during the first trimester may increase the risk of spontaneous abortions, fetal death, and major congenital malformation. This risk has been estimated to be as high as 7% to 17% in monotherapy and 25% in the case of combination therapy [2]. Thus, if pregnancy is known, chemotherapy cancer treatment should be avoided in general in the first trimester unless it is vital for the mother to start, for example, an aggressive, advanced or progressive disease where a delay in therapy adverse may affect maternal survival. In which case, the mother and her family should be informed of the high risk for the growing embryo-fetus [5].

Most standard regimens of chemotherapy can be administered after 14 weeks of gestational age but are not recommended beyond 35 weeks. On the third trimester it would be advisable to delay chemotherapy treatment for after childbirth (especially if the cancer diagnosis is after week 32 to week 35) or use weekly schemes to allow ease of pregnancy monitoring and interruption of treatment if necessary [3].

In the second and third trimester, cyclophosphamide is a classic in cancer treatment during pregnancy, and no higher percentages of congenital malformations have been observed [14]. Cisplatin and Carboplatin has been used during pregnancy successfully and without causing fetal genetic abnormalities. But, a relationship between platinum-based chemotherapy and small gestational age by multiple regression models has been published in a series of 1,170 pregnancies [15]. Epirubicin, doxorubicin, docetaxel and paclitaxel are drugs that can be used in the second and third trimesters, but with a possible relation with small for gestational age [16-18].

The use of antimetabolites is not recommended during pregnancy due to their mechanism of action. There are also isolated cases of pregnant patients with pancreatic cancer treated with Gemcitabine without maternal-fetal incidences in the development of pregnancy and birth [15]. The use of etoposide is also limited to case reports without no patterns of congenital malformations noted but relatively high risk of fetal growth restriction and myelosuprresion on newborn [19]. There is insufficient data about vinka-alkaloids in pregnancy but it has been published with good outcome in some cases [20].

Polychemotherapy is used (Cisplatin, epirubicin in EFC or FAC scheme) but more likely are of pre-or post-natal complications with a percentage extremely low (1% to 5%), so its use can be justified always individualizing the maternal-oncological-fetal situation [20].

Recently, the increasing use of targeted anti-cancer therapies has become even more complicated in treating pregnant patients with cancer. The benefit of the targeted agents, immunotherapy, or cell therapy has been well demonstrated for various malignancies; however, their safety during pregnancy has not been established in general. It only exists significant experience with the exposure during

pregnancy for imatinib in chronic myeloid leukemia, which causes malformations if is taken in the first trimester but is a not documented serious fetal malformation in pregnancies exposes to it in second or third trimesters. Rituximab may be considered also safe on this stage [11,21,22].

Another kind of systemic oncological treatment exposition is the hormone therapy adjuvant in breast cancer, specifically on tamoxifen. When this happens the patients should be informed of the possible increased risk of fetal malformations secondary to the first-trimester exposure [16].

Monitoring and Termination of Pregnancy in Patients with Cancer

Patients diagnosed with any type of cancer during pregnancy should be evaluated by a multidisciplinary tumor committee, including obstetric assessment, for decision-making. These groups have to be met several times during the pregnancy to actualize the information about the health balance between cancer, mother and fetus.

In order to make clinical decisions in this context, it is necessary the complete autonomy of the patient based on transparent and clear information on the maternal-fetal health situation.

Timeline, when it comes to acting and making decisions is fundamental as the different stages of pregnancy mark a benefit and risk when making decisions about the treatment of cancer during pregnancy. The information should be updated during pregnancy, and both pregnancy and the fetus health need to be closely monitored.

In most cases, cancer will not influence the development of a pregnancy, especially regarding extragenital tumors. The most common side effects, seen on 20% to 25% on newborns of mothers with cancer are the intrauterine fetal growth delays, low birth weight and iatrogenic prematurity due to early termination of pregnancy or certain treatments [11].

There is evidence that the therapeutic abortion without medical indications previous to complete maturation does not increase maternal survival related to cancer. If the mother's health deteriorates after 24 to 28 weeks, an early maturation of the fetus can be performed, and an emergency cessation may be considered to save the fetus life [22].

Old data indicate that late-preterm neonates (34 to 37 weeks) had significantly more medical complications compared with their full-term counterparts, but the last data indicates than neonatal problems are mainly due to iatrogenic, and therefore preventable prematurity. Once natural lung maturation of the fetus has been achieved around week 37 it is advisable to induce delivery or carry out a cesarean section [3].

Weekly schemes of chemotherapy are recommended on third trimester to optimize the evaluation of the risk-benefit balance. Delivery should be postponed for 2 or 3 weeks following anti-cancer treatment to allow bone marrow recovery. Neonates, especially preterm, have limited capacity to metabolize drugs because of liver and renal immaturity, so this time could help to allow bone marrow recovery and fetal drug excretion by the placenta [11].

At least 48 h before birth, magnesium sulphate should also be administered to achieve a neuroprotective effect. A significant number of newborns after a risky pregnancy in a mother with active cancer need attention in the neonatology unit due to their prematurity status or simply for observation after a risky pregnancy with possible complications of the pregnant mother from treatments for cancer disease. Tumors with worse prognoses, such as gastrointestinal tumors have a higher rate of need for stays in NICU (Neonatal Intensive Care Unit), probably due to the increased use of chemotherapies during pregnancy [3].

The placenta should be subjected to histological examination whenever possible, and particularly in patients diagnosed with melanoma or leukemia [11].

Informed Consent

Once a diagnosis of cancer on a pregnancy is done, the patient must be informed that her case will be discussed within a multidisciplinary tumor committee that specializes in cancer during pregnancy, who will make a proposal with the best options for the diagnosis and treatment of her pathology.

On the next consultation with the patient and her family, the treatment options should be explained, and doubts and questions that they pose should be resolved. Once an action plan is agreed, the medical team will provide the patient with the necessary appointments with the multidisciplinary team as a priority.

An individual informed consent document is recommended about this offered treatment, personalizing the information about the risk of each of the planned diagnostic and treatment procedures (surgery, chemotherapy or radiotherapy). The documentation regarding the individualized informed consent signed by the patient should be included in her medical history [3].

Conclusions

When considering the treatment of cancer during pregnancy, it is crucial to balance maternal and fetal health. The decisions about the management of cancer in pregnancy should be made individually for each patient. It is necessary a multidisciplinary group of specialists (medical oncologists or radiotherapists, radiologists, gynecologist, psycho-oncologist...) who have to participate in various meetings during the cancer period during pregnancy.

The image test par excellence during pregnancy should be non-contrast-MRI, as it is the most harmless test for the fetus, but in selected cases, CT (including contrast; assuming the risk of neonatal hypothyroidism) or PET/MRI (with a low dose of radiation administered) can be performed.

Surgery is considered safe during pregnancy, mainly during the early stages of pregnancy. In the third trimester, more extraordinary precautions are necessary. It has to be justified and limited as much as possible, mainly the abdominal one, unless it is strictly necessary. Radiation therapy is a treatment that should be excluded during pregnancy; only in selected cases should be considered.

Current data confirm that an optimal cytotoxic treatment administered during the second and third trimesters of pregnancy is secure and does not increase the rate of congenital malformations. However, low birth weight is detected in this population than might be explained partly by the poor maternal general and nutritional status of the oncological disease. Nowadays, if possible, the best oncologic management for the mother should be aimed for.

Cancer during pregnancy cannot rely on rigid guidelines; it should be adjusted to patient's features and wishes. It should be based on

Appendix 1: General recommendations in radiological imaging during pregnancy.

First 8 weeks from conception or pregnant unknown	There are no studies demonstrating teratogenic effects in performing CT or Rx with less than 1 cGy emission (usual in most)	Intensification of monitoring of embryo development.	Chest X-ray and mammography with abdominal shielding can be safely carried out during pregnancy.
First trimester after embryogenesis period	MRI without contrast is the recommended test.	CT should be avoided but if it is strictly necessary safety has been observed on the chest, head and neck or limbs with abdominal shielding. Abdominal/ pelvis CT is not recommended	Ultrasound is preferable always if it is enough
	Iodide contrasts: potential risk of hypothyroidism.		
Second trimester	Same recommendations as in the first quarter. Contrastless MRI is the recommended test.		SLN biopsy in breast cancer is secure in all stages
Third trimester	Equal second trimester		Insufficient data to establish a recommendation about PET/MRI

SLN: Sentinel Limph Node; MRI: Magnetic Resonance Imaging; CT: Computed Tomography

Appendix 2: General recommendations on cancer treatment during pregnancy.

	Chemotherapy	Surgery	Other
General concepts	Balance between aggressiveness of cancer and health of entity mother-fetus to decide monotherapy or polichemotherapy	Can be carried out with relative safety at any time during the course of the pregnancy, ever evaluating case by case	Radiotherapy: preferable to postpone radiation therapy to the postpartum period
First trimester	· On first 4 week's pregnancy loss or no adverse effect.	Preferably wait until second trimester	
	· After, is not recommendable in this stage. High risk of miscarriage and malformation are related.	Cervical cancer: Lymphadenectomy if indicated is possible	
	· Only in case of vital emergency of the mother	Colorectal cancer: Is possible resection but moderate risk for fetus	
		Breast cancer: Mastectomy in aggressive histology, possible conservative surgery	
Second trimester	In case of aggressive disease	More risk for abdominal and pelvic surgeries	High-risk pregnancy if chemotherapy is prescribed
		Breast cancer: Conservative surgery and wait until delivery is good option in most patient	
Third trimester	Weekly application is associated with shorter nadir and better clinical control to prepare the delivery.	Preferably wait until delivery	Full-term delivery (i.e. ≥ 37 weeks) should be targeted whenever possible

close collaborations between different experts and active interaction with the patients and their relatives. The advancement of knowledge of fetal development, the management of toxicities, and the choice of less teratogenic drugs and the generation of management groups of multidisciplinary specialists makes it currently possible that the management of cancer during pregnancy has a high success rate; that is, adequate oncological disease control and healthy gestational development.

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