

MINI REVIEW

A mini review on pregnant mothers with cancer: A paradoxical coexistence

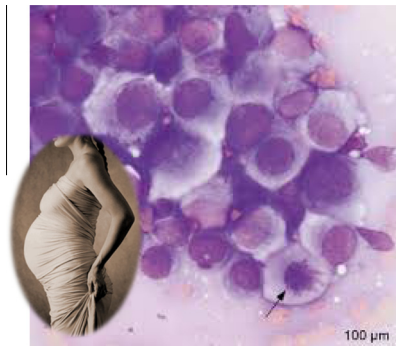


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GRAPHICAL ABSTRACT



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ABSTRACT

The diagnosis of cancer during pregnancy at least in the Western world is a rare phenomenon, but this might be raised into the future due to late pregnancies in the modern societies. The

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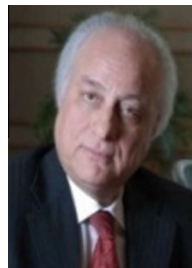
Cancer
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Treatment

coexistence of pregnancy and cancer implicates numerous medical, ethical, psychological and sometimes religious issues between the mother, the family and the treating physician. Breast, cervical cancer, melanoma and lymphoma are the most common malignancies diagnosed during pregnancy. Diagnostic or therapeutic irradiation requires careful application, whereas systemic chemotherapy is not allowed during the first trimester of pregnancy due to lethal or teratogenic effects as well as to congenital malformations. In some gestational cancers, tumor cells can invade the placenta or the fetus.

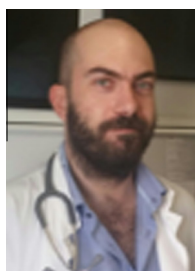
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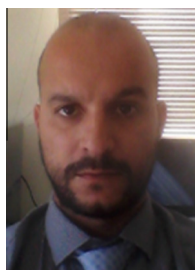
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Introduction

Cancer during pregnancy represents a medical paradox in humans and a dramatic event in a woman's life, her partner and her family. The management of gestational cancers is a clinical dilemma since it involves two persons, the mother and the fetus. Therefore, both diagnostic and therapeutic management should be individualized and should be undertaken by a dedicated multidisciplinary team. It is of paramount importance that obstetricians and oncologists should offer at the same time optimal treatment to mother and optimal protection to the fetus.

Diagnosis of cancer during pregnancy in developed societies has an incidence of 1:1000 pregnancies ranging from 0.07% to 0.1%. The trend of this coexistence is becoming more common over the last decades and it will probably be seen more frequently, due to delaying pregnancy into the later reproductive years. The most common gestational cancers are those with a peak incidence during the woman's reproductive period such as breast and cervical cancers, hematological malignancies and melanoma (Table 1). However, most of the gestational cancers have been described including gastrointestinal, renal or pulmonary malignancies [1–3].

Diagnostic and staging workup

With the increased use of radiation in diagnostic oncology, concern for its biological effects continues to grow. Therefore, rules and guidelines for the protection of people have been

Table 1 Incidence of cancers per pregnancies or deliveries.

Cancer type	Incidence
Breast cancer	1:3.000–10.000
Cervical cancer	1:2.000–10.000
Hodgkin's lymphoma	1:1.000–6.000
Melanoma	2–5:100.000
Leukemias	1:75.000–100.0000
Ovarian cancer	4–8:100.000
Colorectal cancer	1:13.000
Thyroid cancer	14:100.000

Courtesy by Voulgaris et al. [2].

Table 2 Imaging procedures and fetal radiation.

Imaging tests	Fetal radiation dose (mGy)
Chest X-ray	0.001
Mammography	< 0.01
CT of the head	< 0.005
CT of the chest	0.06
Abdominal X-ray	1.4
⁹⁹ mTc bone scintigraphy	3.3
CT of the abdomen	8.0
CT of the pelvis	9.4

established. Electromagnetic radiation, ultraviolet radiation and X and gamma rays are the main types of radiation. Radiation effects during pregnancy are depended on the gestational age, dose, radiation field and fractionation.

Due to serum tumor marker production by both the tumor and the pregnancy, the value of measuring them is limited i.e. markedly elevated levels of CA125, CA15-3, and AFP [4].

From animal data, during the pre-implantation and implantation period (0–2 weeks) irradiation with 100 mGy (10 rads) results in embryonic death; however, during the organogenesis period (3–12 weeks) additional developmental malformations or teratogenesis can be seen. Exposure to irradiation during the second or third trimesters is associated with growth or mental retardation, malformations of central nervous system or gonads as well as premature death. With the use of various imaging procedures the associated average uterine/fetal doses range between 0.001 mGy for a chest X-ray and 25 mGy for an abdominal pelvic CT-scan Table 2 [5–10].

In summary, for radiological staging in pregnant mothers with cancer, chest X-ray, abdominal ultrasound and mammography are considered as safe procedures. In certain cases however, magnetic resonance imaging (MRI) can be recommended (i.e. brain MRI) especially after the first trimester of pregnancy. Abdominal plain films, abdominal CT, radionuclide isotope scans or PET/CT should be avoided.

Radiotherapy during pregnancy

Pregnant women with cancers removed from the pelvic field (i.e. breast cancers and brain tumors) can be treated with radiotherapy, always based on a very careful planning of fetal dose and additional shielding. The proper treatment with radiotherapy requires a very advanced multidisciplinary team. In addition, special devices to shield the fetus are needed.

Despite these measurements, several oncologists prefer to postpone radiotherapy after delivery in order to avoid scattered radiation to the placenta or fetus [7].

Systemic treatment during pregnancy

Systemic chemotherapy can be provided to pregnant mothers with cancer under certain circumstances. Chemotherapy administration during the first trimester of pregnancy increases the risk of spontaneous abortion, fetal death, teratogenicity and congenital malformations. Teratogenic effects have been reported to be between 10% and 20%. However, chemotherapy exposure during the second and third trimester, although is followed by several fetal effects such as intrauterine growth restriction, low-birth weight or myelosuppression, is generally considered as safe.

In general, pregnancies are not allowed during cancer treatment. If pregnancy occurs while the patient is under endocrine treatment (i.e. tamoxifen) or chemotherapy a pregnancy termination should be recommended. Regarding monoclonal antibodies trastuzumab administration is not allowed due to mother's and infant toxicity while rituximab is more safe. Similarly, tyrosine kinase inhibitors in which no adequate data are available administration during gestation is contraindicated [1,11,12].

Antimetabolites

Antimetabolites especially methotrexate have the higher teratogenic potential, while cytosine arabinoside is associated with conflicting reports on the effects on fetal life.

Alkylating agents

Among the alkylating agents busulfan, chlorambucil and dacarbazine have been reported to exhibit teratogenic effects.

Antibiotics

Anthracyclines are considered as safer cytotoxic during pregnancy especially when administered during the second or third trimester. No early or late cardiotoxicity has been seen in embryos, newborns, childhood or adolescence.

Vinca alkaloids

Vincas are considered to be the less potent teratogens or drug-induced malformations.

Taxanes

The use of taxanes (parclitaxel or docetaxel) appears to be feasible after the first trimester although less than 50 cases are available in the literature.

Platinum compounds

These drugs are found to be safe during pregnancy, although some cases of ototoxicity have been documented.

Biological agents

Trastuzumab is associated with oligohydramnios or anhydramnios, neonatal deaths, and transient respiratory or renal failure. Rituximab can be administered with no congenital anomalies. For imatinib, sunitinib, sorafenib or nilotinib, there are no adequate data yet.

Hormonal treatment

Generally, it is not recommended during pregnancy.

Therapeutic management of the most common cancers during pregnancy*Breast cancer*

Pregnant women with breast cancer present with poor prognostic factors and more advanced disease. Surgically, modified radical mastectomy with axillary node dissection is recommended for stage I–II and for selected stage III patients during the first and second trimester. Breast conserving surgery following by breast irradiation is advised for patients with localized disease during the third trimester or during postpartum.

Adjuvant chemotherapy can be administered with CMF or anthracycline-based regimens. No hormonal or trastuzumab treatments are indicated. Patients with metastatic breast cancer should be directly treated with chemotherapy. Overall survival is similar to the corresponding stage of non-pregnant women with breast cancer. Termination of pregnancy may be considered when immediate therapy should be initiated especially during the first trimester of gestation [1–3,13].

Cervical cancer

There is evidence that cervical cancer during pregnancy has a 3.1-fold higher chance of being diagnosed with early disease (stage I) due to frequent gynecological examinations.

Cervical intraepithelial neoplasia (CIN) should be followed up with cytology and colposcopy. Almost 80% of cases regressed after delivery. For stage IA1 disease conization during the second trimester is sufficient providing that surgical margins are negative. Pregnancy termination with immediate treatment might be advised for more advanced stages (IA1 with positive margins, IA2, IIA or locally advanced disease) [1–3,14].

As an alternative, neoadjuvant chemotherapy can be recommended in patients who refuse pregnancy termination. Overall survival is similar to non-pregnant women of the same stage disease.

Melanoma

For localized disease, treatment of choice includes wide surgical excision (with 1–3 cm margins) and sentinel lymph node biopsy. Adjuvant high-dose interferon has not been well studied. Pregnant patients with metastatic disease have a poor outcome since no effective chemotherapy is advocated. In addition, no data are available concerning targeted treatment i.e. vemurafenib and ipilimumab. The choice of termination of pregnancy should be discussed with the patient. Overall

survival remains the same to non-pregnant women with melanoma [1–3,15].

Hodgkin's lymphoma

If the diagnosis of Hodgkin's lymphoma is made during the first trimester a "watch and wait" approach is preferred until the patient reaches the second trimester. Pregnant patients with Hodgkin's lymphoma after the first semester can be safely managed with the gold standard chemotherapy of ABVD (adriamycin, bleomycin, vinblastin, and dacarbazine) regimen. Prognosis does not seem to be inferior to that of non-pregnant patients [11,16].

Thyroid cancer

Pregnant mothers with well differentiated carcinomas (follicular or papillary) can be candidates for delayed surgical management. Radioactive iodine is a contraindication in breast feeding women, while patients on levothyroxine should be carefully monitored [17].

Monitoring of pregnancy and mode of delivery

Pregnancy in women with cancer should be considered as a high risk situation especially when chemotherapy is initiated. Therefore, regular fetal monitoring is highly recommended as well as continued follow-up of newborns until puberty. In addition, therapeutic drug monitoring for appropriate drug disposition due to pregnancy changes is essential [18,19].

In general, a normal vaginal delivery in the absence of maternal or neonatal complications is recommended apart from cervical and vulvar cancers, although the mode of delivery is determined by the obstetricians [20].

Metastases to the product of conception

Metastatic transmission to placenta or fetus mostly occurs through the hematogenous route, whereas lymphatic dissemination or contiguous invasion is less common metastatic pathway. The real incidence is lacking, since routine histological and cytological examination of the placenta and of the umbilical cord are not usually performed and most newborns are missing a close follow-up.

Metastatic lesions to placenta or fetus are most frequently observed in melanoma (30%), cancer of unknown primary (22.5%), leukemias and lymphomas (15%), breast cancer (14%), and lung cancer (13%).

In these cases, histological examination of the placenta revealed tumor cell sequestration in the intervillous spaces. Fetal metastases always preceded by infiltration of the chorionic villous by tumor cells. The clinical manifestations of newborn metastases were mainly located on the skin (scalp) or internal organs. In some infants metastases exhibited spontaneous resolution [21–23].

Pregnancy in cancer survivors

It has recently been shown that pregnancy rates found to be 40% lower among women cancer survivors compared with

the general population but this depends on the tumor type. Mothers diagnosed with thyroid cancer or melanoma had pregnancy rates highly compared with the general population. However, females with breast cancer had the lowest pregnancy rates close to 70% lower, compared to the general population probably due to previous chemotherapy or endocrine treatment.

The optimal timing to allow patients to become pregnant cannot be easily predicted since it depends on the time of completion of treatment and the risk of relapse. For breast cancer patients postpone of pregnancy for two years is recommended [24].

Conclusions

In conclusion, the coexistence of cancer and pregnancy is rare phenomenon with the most common tumors diagnosed are breast, cervical cancer, melanoma and hematological malignancies. Chemotherapy can be used with safety after the first trimester of pregnancy. In difficult cases mainly during the first trimester, the final decision should be taken after thorough discussion between the mother, the father and the treating physician. All obstetricians should be aware that cancer in pregnant women could rarely invade the products of conceptions. Therefore, meticulous examination of the placenta and the umbilical cord is necessary.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics requirements

This article does not contain any studies with human or animal subjects.

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