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**Cancer in pregnancy: proposal of an Italian multicenter study.
Gynecologic Oncology Group of the Italian Society of Gynecology and
Obstetrics (SIGO)**

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ABSTRACT

A pregnancy related cancer is defined as a neoplasm diagnosed in a woman during gestation or within 12 months following childbirth or abortion. Breast, thyroidal, melanoma, cervical and hematological malignancies are those most commonly diagnosed during pregnancy, with a reported incidence considered lower than those estimated of 1 case on 1000 pregnancies. The clinical complexity is generated by the co-presence of mother and fetus, and the consequent conflict represented by the need to identify a therapeutic strategy that is effective for the maternal prognosis and, at the same time, safeguards the fetal well-being. Moreover, the counseling, diagnosis, staging and management of these cases are further complicated because most of the scientific literature consists in case reports or small retrospective studies and lacks in guidelines and prospective clinical trials. On that basis, the Study Group on Cancer in Pregnancy (members of S.I.G.O. - Italian Society of Gynecology and Obstetrics) presents the TIGRE Trial, an Italian multicenter observational study aimed at establishing a shared database for the collection of epidemiological and clinical data of the patients affected by pregnancy related cancer in Italy, with the final objective to improve the outcome of a mother and a child involved in a such pathology.

Key words: Pregnancy related cancer, chemotherapy, teratogenic risk, fetal development, multicenter observational study, TIGER Trial.

SOMMARIO

Un tumore associato alla gravidanza è definito come una neoplasia diagnosticata in una donna durante la gestazione o entro 12 mesi dal parto o dall'aborto. Il carcinoma della mammella, della tiroide e della cervice, il melanoma e le neoplasie ematologiche sono quelle più comunemente diagnosticate durante la gravidanza, con un'incidenza riportata inferiore a quella stimata di 1 caso su 1000 gravidanze. La complessità clinica è generata dalla co-presenza di madre e feto e dal conseguente conflitto rappresentato dalla necessità di identificare una strategia terapeutica che sia efficace per la madre e, al tempo stesso, salvaguardi il benessere fetale. Inoltre, il counseling, l'iter diagnostico e stadiativo ed in fine l'approccio terapeutico sono ulteriormente complicati dal fatto che la maggior parte della letteratura scientifica è costituita da case report o piccoli studi retrospettivi con carenza di linee guida e studi clinici prospettici. Su questa base, il Gruppo di studio sul cancro in gravidanza (membri della SIGO - Società italiana di ginecologia e ostetricia) presenta il TIGRE Trial, uno studio osservazionale multicentrico italiano volto a costituire un database condiviso per la raccolta di dati epidemiologici e clinici di pazienti affette da tumore associato alla gravidanza, con l'obiettivo finale di migliorare la gestione e l'outcome di madre e feto coinvolti in una tale patologia.

INTRODUCTION

A pregnancy related cancer is defined as a neoplasm diagnosed in a woman during a gestation or within 12 months following childbirth or abortion. In fact, it is considered that the tumors diagnosed within 1 year from the termination of a pregnancy originated before or during the pregnancy itself. The diagnosis of cancer in pregnancy is a dramatic event that leads to important consequences in the life of the patient, the unborn child, the entire family and not least of the health care workers involved in the management of the case. This event goes far beyond the clinical complexity generated by the co-presence of mother and fetus, and the consequent conflict represented by the need to identify a therapeutic strategy that is effective in the same time for the maternal prognosis and safeguards the fetal well-being. Multiple areas are involved: medical, personal, social, ethical, spiritual, and religious. The cancer treatment may also affect the future fertility of the patient, compromising both her physical and psychological integrity.

The reaction of the mother and the partner at the time of the communication of the diagnosis of cancer in pregnancy is extremely variable: much depends on factors not related to the clinical status such as the obstetric history, parity, any difficulties related to the conception, the degree of culture, religious beliefs, expectations and, more generally, the approach to life. Also, the way to deal with the disease and pregnancy is strongly influenced by what is being proposed and how this is communicated by the clinicians. The counseling and management of these cases are very complicated because most of the scientific literature consists in case reports or small retrospective studies and lacks guidelines and lack prospective clinical trials. In addition, because of the rarity, the subjective experience is often limited, and it is particularly difficult to conduct large-scale studies.

For many years, the treatment of cancer was considered incompatible with a normal fetal development: for this reason, the most often used treatment strategy required the interruption of pregnancy or the execution of preterm birth as well as to facilitate the start of treatment. Regarding the prognosis of cancer in pregnancy, many scientific speculations have been advanced in the past: it was suspected that the presence of a gestational state could negatively influence the evolution of the tumor, leading to a more biologically aggressive character to the malignant cells. This biological characteristic observed in the past

literature could be justified by the presence in the pregnant woman of high concentrations of growth factors, reduced immune response, increased metabolism; but above all, it is reasonable to think that the poor prognosis of cancer in pregnancy was due to diagnostic delay and to a suboptimal or delayed treatment that was previously proposed to these women, considering the advanced state of pregnancy. In recent data, however, we are more aware of the effects of antitumor therapy on the fetus and a greater number of patients receive adequate treatment already during pregnancy. We also know that termination of pregnancy is not a factor that can significantly improve maternal prognosis in a statistically significant way. In fact, recent data describe a similar prognosis for tumors arising in pregnancy compared to non-pregnant patients. Updated evidences on management of cancer in pregnancy currently show that it is possible to safeguard in almost all cases the fetal outcome without significantly changing the maternal prognosis, through setting a correct diagnostic and therapeutic path⁽¹⁻³⁾.

Incidence

The real incidence of cancer in pregnancy is underestimated, as the cases are not systematically recorded in shared databases: cases that end with an interruption of pregnancy are often overlooked (spontaneous abortions, stillbirths and terminated pregnancies). Therefore, several pregnancies complicated by a neoplasia in the first or second trimester are not reported. The confirmation of this data comes from the observation of the discrepancy between the expected rate of cancer in pregnancy and the recorded data, in particular regarding the first and second trimester of pregnancy. It is assumed that in these gestational ages the diagnosis of cancer tends to be delayed.

The analysis of the incidence of diagnoses of cancer during pregnancy (and in the first 12 months after delivery) is difficult to control due to the lack of publications and structured data; in developed countries it is estimated to be around 1 case on 1000 pregnancies and it is believed to be responsible for 1/3 of maternal deaths during gestation. Basing on the literature, the incidence of pregnancy related cancer has been reported as 50-100:100.000 pregnancies⁽⁴⁻⁸⁾, the incidence of cancer diagnosed during pregnancy is found to be 17-25:100.000⁽⁹⁻¹¹⁾.

However, it must be stated that there is no homogeneity in the selection of the denominators in the collection of data for calculating the

prevalence of pregnancy related cancer, either as incidence (number) per 100.000 pregnancies, deliveries, or live births. For sure, during the last decades the incidence has increased. It is assumed that this trend could be explained by looking at the increasing maternal age at first pregnancy and at the increase of cancer incidence in general population. The age-specific incidence of cancer in pregnancy is directly related to the maternal age but also the age distribution of the cancer type. It is important to underline that we are talking about cancers exposed to pregnancy, and that the age distribution of these cancers is driven by the age distribution of pregnancies (which may be different from the age distribution of cancer in general population). Hence, any comparison between cancer in pregnancy or cancer not related to a pregnancy must be finely adjusted for maternal age.

Breast, thyroidal, melanoma and cervical cancers are those most commonly diagnosed during pregnancy, followed by hematological malignancies. Breast cancer is listed as the most frequent cancer type diagnosed during pregnancy or shortly thereafter. Breast cancer is also the overall most frequent cancer diagnosed in the age group 15-44 years. Malignant melanoma and cervical cancer are the two other malignancies most frequently diagnosed as pregnancy related cancer. While cervical cancer incidence is decreasing in most populations due to screening effects, malignant melanoma is increasing. Incidence rates for breast cancer, cervical cancer and malignant

melanoma diagnosed during pregnancy and in the postpartum period combined have been reported in several population-based studies, showing different results. There is a substantial variation in incidence across different populations and calendar periods. In **Table 1** is shown the incidence in Lombardy (Italy) of pregnancy associated cancer in a population of 1475 women⁽¹²⁾.

Diagnosis and staging

Diagnostic investigations are substantial for the identification and staging of tumor pathology. It is necessary to extend the knowledge related to the effects on the fetal development of the exposure to ionizing radiation, as the imaging techniques are a substantial part of the tumor assessment. For the assessment of the tumor staging it may be necessary to perform investigations such as MRI, CT scan, X ray, ultrasound; however, there is confusion regarding the safety of these methods in pregnancy and lactation. Standard staging modalities are often precluded to pregnant patients in order not to affect fetal development, on the other side a too conservative attitude could unnecessarily lead to avoid useful instrumental investigations or to induce the suspension of breastfeeding. The major risks associated with radiological imaging techniques are radiation-induced teratogenesis and radiation-induced carcinogenesis. Teratogenic risk is substantially related to the gestational age at the time of exposure^(13, 14). It has been observed the induction of lethal effects on embryo at exposures above 1 Gy

Table 1.

Incidence of pregnancy associated cancer in Lombardy (Italy). Taken from Parazzini F, Franchi M, Tavani A, Negri E, Peccatori F.A.. Frequency of Pregnancy Related Cancer: A Population Based Linkage Study in Lombardy, Italy. International Journal of Gynecological Cancer. 2017.

Cancer Site	During pregnancy (n/100,000)	12 months after pregnancy (n/100,000)	All (n/100,000)
Breast	7.7	32.2	39.9
Thyroid	2.3	13.2	15.5
Lymphoma	2.4	10.7	13.1
Skin (excluding melanoma)	1.9	5.7	7.6
Melanoma	1.9	5.2	7.2
Cervix	1.4	4.1	5.5
Colorectal	0.7	4.5	5.2
Ovary	1.2	2.6	3.7

during embryogenesis. This dose is not achieved in common diagnostic imaging techniques; the effects on embryo-fetal development of ionizing radiation exposure consist rather in growth restriction, microcephaly or intellectual deficit. As regards the risk of tumor development following exposure to ionizing radiation in utero, this correlation seems to be weak and, in any case, controversial. It may increase the risk of developing childhood leukemia for fetal exposition to doses of 10-20 mGy^(15, 16).

If the CT Scan is considered indispensable, it is necessary to ensure that the fetus is exposed to the lowest dose of ionizing radiations. The exposure of the fetus to background radiation is 1mGy. The estimated fetal dose during a CT Thorax is 2 mGy increasing to 30 mGy for a CT scan of the abdomen and the pelvis. The dose can be further reduced if the fetus is outside the irradiation field. In conclusion, examinations using ionizing radiation should be avoided if possible during pregnancy, if indicated careful steps must be undertaken to keep the radiation dose as low as is reasonably achievable.

Available data illustrate that the use of ultrasound is safe during pregnancy, as long as the fetal exposure is limited to the strictly necessary tests. The U.S Food and Drug Administration has recommended that the spatial-peak temporal average intensity of the Ultrasound beam be less than 720 mW/cm² in obstetric patients to reduce the theoretical risk of fetal tissue heating⁽¹⁷⁾.

MRI in pregnancy is a fairly safe test, that has the property to accurately describe deep soft tissue structures in an operator independent manner. No harmful effects have been identified at magnetic field strengths of 1.5 Tesla. Animal studies have demonstrated potential toxic effects of Gadolinium including congenital abnormalities and growth restriction in doses significantly exceeding those administered in clinical practice⁽¹⁸⁾. A prospective study on 26 patients periconceptionally exposed to Gadolinium reported no adverse perinatal or neonatal adverse outcomes⁽¹⁹⁾; a retrospective study demonstrated no association between Gadolinium exposure in pregnancy and population-based risk of congenital anomaly⁽²⁰⁾.

In summary, Gadolinium chelates can be administered in any trimester of pregnancy, if clinically justified.

Therapeutic strategies

After the diagnosis of cancer in pregnancy, the therapeutic strategy must be personalized for each patient, considering the gestational age, the type and stage of the disease, the age and the desire of

the patient. A pregnant woman should be treated as close as possible to the standard therapy to ensure an optimal maternal outcome. Cancer treatment could include surgery, chemotherapy, radiotherapy. The patient and the partner must be involved in the decision-making process, informed of the therapeutic opportunities and of the prognostic expectations.

The therapeutic options can be distinguished in:

- Termination of pregnancy before neonatal viability is reached and within the terms of the law in force per country (22 weeks in Italy). this option is preferred in women with low survival expectations and prognosis. It is important that women are informed that the oncological outcome for most tumor types is not influenced by the pregnancy.
- Initiation of anti-cancer treatment during pregnancy (surgery, chemotherapy or radiotherapy). When cancer diagnosis is made during the first trimester of pregnancy, in most cases, treatment can be delayed until the second trimester (with the exception of some hematological cancers) when most treatment modalities can be used without affecting fetal development.
- Waiting and observation behavior up to delivery (at the pre-established gestation period), with the start of anti-tumor therapy after birth.

In cases of an ongoing chemotherapy treatments, delivery should be planned between 37 and 39 weeks of gestation and at least 3-4 weeks after the last chemotherapy administration, in order to avoid accumulation of medication in the newborn and problems of hematopoietic suppression for mother and child. Mode of delivery should be mainly based on obstetric indications. Preterm birth is often iatrogenic, basing the decision on the urgent maternal need for cancer treatments or deterioration of maternal health, although an increased risk for spontaneous premature rupture of membranes and preterm labor has also been reported after chemotherapy administration during pregnancy⁽²¹⁾. Antenatal corticosteroids administration accelerates fetal lung maturation and is associated with a reduction of adverse neonatal outcomes related to prematurity. A single course of antenatal corticosteroids should be considered in those cases in which it is actually likely to have a preterm birth⁽²²⁾.

In general, surgery can be safely performed after the first trimester without compromising the fetal outcome. Still, if possible, it is preferred

to postpone the procedure until postpartum. In specific cases, surgery can directly follow cesarean section. If surgery is essential and cannot be postponed, certain extra precautions are required because of the physiologic changes of pregnancy. Local or regional anesthesia is preferred over general anesthesia. Most important risks of surgery in pregnancy are miscarriage, premature delivery or fetal distress. The outcome of pregnant patients that undergo laparoscopic surgery compared with laparotomy seems comparable. There are no randomized controlled trials that compare laparoscopy and laparotomy in pregnancy. Abdominal surgery is preferably planned in the second trimester because the risk of miscarriage is decreased, and the size of the uterus still allows a certain degree of access. Laparoscopic surgery by an experienced surgeon can be performed in pregnant patients without increased risk to the mother or fetus⁽²³⁾. The gestational age limit for successful completion of laparoscopic surgery during pregnancy depends on the procedure and experience of the surgeon but usually the limit is 26th-28th week of pregnancy.

The transplacental transition of chemotherapeutic drugs is influenced by the characteristics of liposolubility. Liposoluble, low molecular weight, and non-conjugable substances are more likely to cross the human placenta. Transplacental studies have shown low levels of doxorubicin, epirubicin, vinblastine and the active metabolite of cyclophosphamide in fetal plasma in non-human studies⁽²⁴⁾. Carboplatin is a relatively small molecule that binds protein only 24-50%. Fetal plasma concentrations of Carboplatin averaged 50% of maternal concentrations. Transplacental studies in a baboon model have also demonstrated low levels of paclitaxel and docetaxel in fetal plasma⁽²⁵⁾. Regardless of the properties of chemotherapeutic agents, multiple physiological changes during pregnancy may potentially affect pharmacokinetic processes such as the absorption, distribution, metabolism and excretion of drugs by the pregnant patient⁽²⁶⁾.

Such changes have not translated into a lower efficacy for chemotherapy regimens during pregnancy nor a lower maternal survival compared to non-pregnant women. In the absence of more consistent data, the dose and the scheme of therapy for pregnant patients is the same of non-pregnant women, observing the standard dosage calculated on actual weight during pregnancy⁽²⁷⁾. It is especially not recommended to reduce doses in pregnant women in order to avoid fetal damage.

Concerning the therapeutic option of

radiotherapy in pregnancy, patients should be informed that at an early pregnancy stage (when often pregnancy is not yet diagnosed) radiation can lead to abortion. When planning the treatment for a pregnant patient, the benefits and disadvantages for pregnant women should be combined with those for the fetus in order to obtain an informed consent. All usual tumor/patient/treatment-related factors have to be taken into consideration⁽²⁸⁾.

In general, radiation therapy should be considered during pregnancy if it is indicated in non-pregnant patients. In some cases (e.g., breast cancer) omitting radiation or postponing it might be possible using other effective treatments. Factors to be added into treatment consideration include the stage of gestation and the distance from the target volume to the fetus.

STUDY PROPOSAL: THE TIGRE MULTICENTER OBSERVATIONAL STUDY

Against this background, it is easy to understand the need to improve knowledge and skills of the clinicians involved in the management of pregnancy related cancer, in order to promote the integration of the professional roles involved in the management of these patients. The Study Group on Cancer in Pregnancy (members of S.I.G.O. - Italian Society of Gynecology and Obstetrics) presents the institution of the TIGRE Trial, an Italian multicenter observational study aimed at establishing a shared database for the collection of epidemiological and clinical data of the patients affected by pregnancy related cancer in Italy.

The objective of the study is to monitor the incidence, diagnosis and type of treatment of cancer during pregnancy and to record maternal and fetal outcomes.

The data will be analyzed with the aim of obtaining information on two aspects of cancer in pregnancy:

- "Longitudinal evaluation": assessment of the relationship between pregnancy and cancer in the Italian female population of reproductive age.
- Definition of shared clinical choices, in order to simplify and unify the management of the patients of the population in question.

The TIGRE study consists of a multicenter observational cohort study, with data analysis

of the cases in study. More than 100 Centers, including hospital and university clinics in Italy, were informed about the project and invited to participate in the study. Up to July 2018, 32 Centers reported their interest in participating to the trial, collecting data on patients in the study population. These Centers, after the approval of the local ethics committee, are committed to gathering clinical information regarding women with cancer pathology diagnosed during and after pregnancy, upon collection of the informed consent. The study is carried out under the supervision and coordination of S.I.G.O. - Italian Society of Gynecology and Obstetrics. In this observational trial, it is expected to enroll approximately 200-300 patients from Italian Centers with diagnosis of cancer during pregnancy or in the 12 months following childbirth. The diagnosis of neoplasm may concern any body district.

Being an exclusively observational study, there are no potential risks for the subjects enrolled. Patients participating in the study will receive informed consent. Patients need to give their signed and written informed consent to participate in the trial after fully understanding the implication of the protocol. Patient can also leave the study at any time for any reason.

Epidemiological and clinical data of the patients referred to the various participating Centers will be systematically collected for the establishment of a shared database. With the authorization of the patient and after obtaining informed consent, the study group aims to collect information obtained from direct interviews to patients and from the analysis of clinical files (outpatient access, ordinary hospitalization); the data may be either retrospective or prospective.

The data will be collected by each participating Center by filling a pre-established data entry form. This sheet has several sections: will be recorded details of the patient's anamnestic data, the diagnosis of neoplasia, the cancer staging, the type of anticancer treatment performed, the timing of onset, the response to treatment or possible tumor evolution, and of course the oncologic follow-up of the maternal illness. Obstetrical data on the characteristics of pregnancy, on the modality and timing of delivery, on obstetric and neonatal outcomes will be collected. Details on the characteristics of placenta weight and histology

will also be recorded, in order to identify whether chemotherapy exposure is associated with changes in placental histology between cancer patients with or without chemotherapy during pregnancy.

The child's data will also be recorded and will be part of the follow up. Data in the collection form will be then collected on a unique database anonymously. It will be possible to gather in a single database all the information related to the clinical management of these patients affected by neoplastic pathology during pregnancy and to evaluate their outcomes.

CONCLUSIONS

In conclusion, there is the need to standardize the diagnostic and therapeutic strategy in pregnancy related cancers in order to give an evidence-based support in the management of these patients. To achieve this goal, it is necessary that the scientific community participate by providing the largest possible number of information about the incidence and behavior of this infrequent pathology. The management of these cases must be done by specialists who are experts in oncology and obstetric pathology, and these patients must be referred to the centers with the greatest experience, where oncological and perinatal competences can be shared. In this population of patients is observed an increased incidence of absolute risk of stillbirth and neonatal mortality, mostly associated with iatrogenic preterm delivery and low weight at birth; on the other hand, available scientific evidence does not claim that early interruption of pregnancy improves maternal survival, and in most of cases an adequate anticancer treatment could be started during pregnancy without effecting the fetal development. These elements suggest a call for action to improve awareness, knowledge, and the quality of care of the women affected by pregnancy related cancer. Hereby, we propose the TIGRE observational study with this purpose, and solicit the greatest possible number of centers in Italy to participate in this observational study, joining the forces with the ambitious goal of helping to improve the outcome of a mother and a child involved in a such a worrying pathology arising during a joyful event in the course of life.

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