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Impact of Chemotherapy and Radiotherapy During Pregnancy: Assessment of Effects on Fetal Development

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ABSTRACT:
Cancer during pregnancy is a rare event, with an incidence of about 1 in every 1,000 pregnancies, presenting significant clinical challenges for the health of both the mother and the fetus. Oncological treatment, especially with chemotherapy and radiotherapy, requires careful planning, considering the potential risks to fetal development. Chemotherapy can be administered from the second trimester onwards but should be avoided in the first trimester due to the high risk of malformations. Radiotherapy is generally contraindicated at any stage of gestation due to the risks of damaging brain development, congenital anomalies, and increasing the risk of childhood cancer. Studies reveal that the administration of oncological treatments during pregnancy must be conducted with caution, with the medical team rigorously assessing the risks and benefits of each approach. The need for clear guidelines and well-defined protocols is urgent, as the complexity and ethical dilemmas require a balance between maternal health and fetal well-being. Decisions should involve open communication between the healthcare team and the patient, ensuring that all treatment options are discussed. Ongoing research into the effects of chemotherapy and radiotherapy during pregnancy is crucial for developing alternatives that minimize risks to the fetus, promoting positive

KEYWORDS: Cancer; Pregnancy; Chemotherapy; Radiotherapy; Fetal development.

I. INTRODUCTION

Cancer is characterized by genetic alterations that occur in one or more cells, which directly impact genes —A gene is a sequence of DNA that contains the instructions for protein production and determines the hereditary traits of an organism. Under normal conditions, genes direct the cell to perform specific functions, maintaining control over its division and life cycle, however, when these genes suffer damage, the cell may acquire cancerous characteristics, dividing uncontrollably and invading adjacent normal tissues (Hanahan; Weinberg, 2011). This unregulated proliferation does not prevent healthy cells from performing their functions properly, but it compromises tissue homeostasis contributing to the development and progression of cancer (American Cancer Society, 2021).

The diagnosis of cancer during pregnancy is a rare event, with an estimated incidence of 1 in every 1,000 pregnancies (Wolters et al., 2021). This complex condition is a significant clinical challenge and generates considerable emotional distress for the pregnant woman and her Family (Gomes, Sand, Girardon-Perlini, 2021). The therapeutic approach requires careful planning, considering both the mother's health and fetal development. Treatment options often include chemotherapy and radiotherapy, which pose potential risks to the fetus, especially depending on the gestational stage at which they are administered (Osorio-de-Castro, Paumgartten, Silver, 2004).

Second da Silva et al. (2024) Chemotherapy works by interfering with and interrupting the cell cycle, aiming to inhibit the proliferation of rapidly dividing cells—a characteristic common to both cancer cells and developing cells, such as those of a fetus. This mechanism is particularly important because chemotherapeutic drugs cannot distinguish between malignant cells and normal cells that are also rapidly dividing, as occurs during fetal development. Thus, chemotherapy, by affecting cellular proliferation, can potentially impair fetal development if exposure occurs during pregnancy.

This impact is due to the fact that many chemotherapeutic drugs act on different phases of the cell cycle, such as the S phase (DNA synthesis) and the M phase (mitosis), which are essential for cellular replication. Therefore, administering chemotherapy during pregnancy requires extreme caution and a careful assessment of risks and benefits, taking into account the stage of pregnancy

and the need for treatment to ensure the mother's health (Ashworth, 2016).

Study showed that the effects of chemotherapy can vary depending on the trimester of pregnancy, with the second and third trimesters being critical periods during which exposure can lead to complications such as intrauterine growth restriction and congenital malformations (Esposito et al., 2016).

Radiotherapy also raises similar concerns regarding fetal safety, particularly exposure to ionizing radiation during pregnancy that can cause damage to brain development, increase the risk of childhood cancer, and lead to congenital anomalies (Miyamoto et al., 2016). However, the need for effective oncological treatment may justify the use of these methods, especially in cases of advanced cancer. Therefore, it is crucial for a multidisciplinary team to assess the risks and benefits of each therapeutic approach (Scott, B., 2021).

Given the lack of research on the combination of cancer and pregnancy, further studies are essential to clarify the effects of chemotherapy and radiotherapy on fetal development and to establish guidelines that help healthcare professionals make informed decisions. Understanding these impacts is vital to ensure the safety of both the mother and fetus and to improve clinical outcomes for both parties involved (Cubillo et al., 2021).

To this end, this study aims to evaluate the effects of chemotherapy and radiotherapy during pregnancy on fetal development, analyzing existing literature to identify the risks associated with these therapeutic interventions. Furthermore, it seeks to discuss clinical guidelines that can guide medical practice in oncology scenarios involving pregnant women to contribute to the development of a safe and effective protocol for managing women diagnosed with cancer during pregnancy.

II. METHODOLOGY

The literature review methodology proposed by Gil (2008) involves the evaluation of material already produced through the analysis of books and scientific articles. In this context, the research conducts an integrative review of the literature to explore the impact of chemotherapy and radiotherapy on fetal development during pregnancy, specifically regarding implications for maternal-fetal health. The central hypothesis of this study is that exposure to these oncological treatments may result in significant adverse effects on fetal development, influencing factors such as intrauterine growth, neonatal health, and the incidence of congenital anomalies.

To conduct this review, the work follows a structured methodological sequence consisting, following the methodology of Nava et al., (2024), with the specific steps: defining the research question; searching scientific databases; selecting relevant studies; extracting and analyzing data; and presenting and discussing results. The chosen electronic databases for the research include PubMed, Scopus, and SciELO, recognized for the quality and breadth of their literature. The search will use specific terms such as "Chemotherapy," "Radiotherapy," e "Pregnancy," combined with Boolean operators AND. The research will be limited to studies published in the last eleven years (2013-2024), in Portuguese and English, focusing on the consequences of chemotherapy and radiotherapy on fetal health.The search was conducted in October 2024.

After screening titles and abstracts, the most relevant studies will be selected for detailed analysis. The critical evaluation of the selected studies will consider both methodological quality and relevance to the research question, ensuring that only the most significant data are included in the analysis. The main results and conclusions of the studies will also be recorded. The QUALIS, a Brazilian method for evaluating scientific journals, was used to assess the quality and impact of the studies.

The synthesis of results will involve qualitative analysis aimed at identifying trends and discrepancies among the reviewed studies. The discussion will address the clinical implications of the findings, as well as the methodological limitations of the studies included in the review, providing a comprehensive analysis of the evidence regarding the effects of chemotherapy and radiotherapy on fetal development during pregnancy. In addition to this approach, the study adopts the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline from 2020 as a second methodological option. PRISMA is a widely recognized set of standards for the conduct and transparent presentation of systematic reviews and meta-analyses. The adoption of PRISMA allows for a clear visualization of the number of studies identified, selected, and included in the review through a flowchart, contributing to the transparency and reproducibility of the process (Page et al., 2021). The search and selection strategy used will be detailed in the PRISMA flowchart, which will be presented in Table 1.

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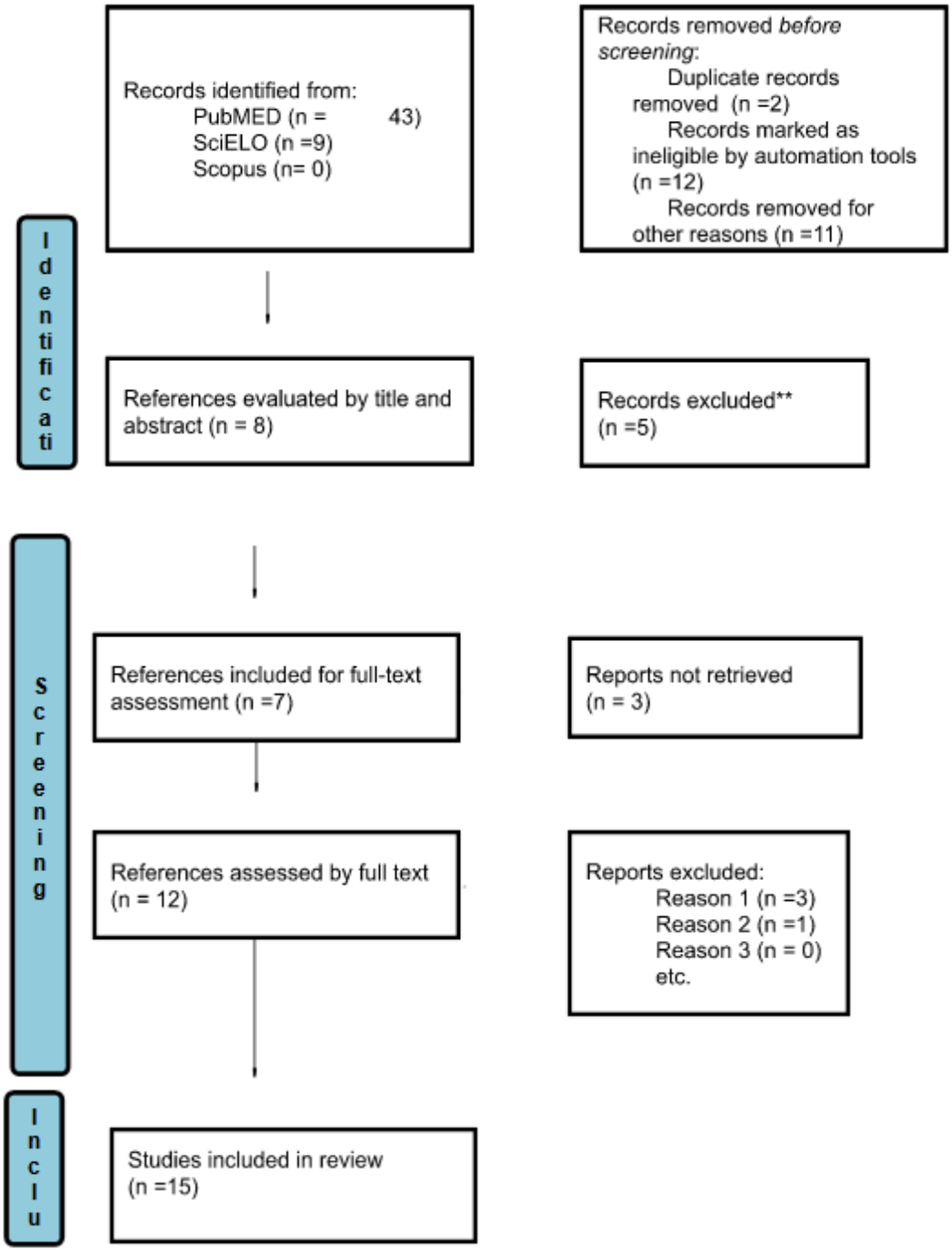
Figure 1. Flowchart of article selection based on established criteria.



III. RESULTS AND DISCUSSIONS

Table 1: Selection of articles based on PubMed, Scopus and SciELO search descriptors

TITLE	AUTHOR AND YEAR	OBJECTIVE	MAIN RESULTS
Maternal and child impact of cancer treatments during pregnancy	Negreiros et al., 2024.	Aims to describe the maternal-fetal impacts of cancer treatments during pregnancy, focusing on the implications of	Chemotherapy and radiotherapy during pregnancy can cause significant adverse effects, such as increased risk of

		chemotherapy and radiotherapy on fetal development and the challenges faced by health professionals in managing cancer in pregnant women.	teratogenicity, fetal growth complications, and spontaneous abortions, especially if administered in the first trimester. Cancer treatment should be carefully planned and monitored by a multidisciplinary team to balance the risks and benefits to the health of the mother and fetus.
Cancer during pregnancy: analysis of cases with emphasis on obstetric and neonatal outcomes	CIETO ; SANTOS, ; DE OLIVEIRA GOZZO 2021.	The aim of the research is to investigate the interference of cancer in the gestational process, identify the most frequent types of neoplasms diagnosed in women during pregnancy and analyze maternal-fetal outcomes related to oncological treatment.	The study found that chemotherapy is the main treatment given to pregnant women diagnosed with cancer, although it should be avoided in the first trimester due to the high risk of fetal malformations. Surgery is considered safer than chemotherapy and radiotherapy, but it still carries significant risks, such as premature birth and maternal complications. Although a cancer diagnosis during pregnancy does not increase maternal mortality, 42.11% of the women in the study died, reflecting the severity of the condition and the complexity of cancer treatment in pregnant women.
Cancer during pregnancy: analysis of cases with emphasis on obstetric and neonatal outcomes	CAMPOS, Cintia Helena Vespoli, 2013.	Identify the main cancers that affect pregnant women and their respective	Chemotherapy, indicated from the second trimester onwards, is relatively safe, but should be avoided in the first trimester to reduce risks to the fetus. Radiotherapy should be avoided at any stage of pregnancy.
Cancer during pregnancy: analysis of cases with emphasis on obstetric and neonatal	MONTEIRO, Denise Leite Maia et al., 2013.	The aim of the study is to investigate the safety of chemotherapy in pregnant women with breast cancer and the	Chemotherapy treatment for pregnant women with breast cancer should not be delayed, and additional care

outcomes		possible complications for mother and fetus.	should be taken to protect the fetus.
CANCERS OCCURRING IN PREGNANCY: INTEGRATIVE REVIEW	CAMPOS, Cintia Helena Vespoli, 2013.		Chemotherapy, indicated from the second trimester onwards, is relatively safe, but should be avoided in the first trimester to reduce risks to the fetus. Radiotherapy should be avoided at any stage of pregnancy.
Breast cancer in pregnancy and chemotherapy: systematic review	MONTEIRO, Denise Leite Maia et al., 2013.	The aim of the study is to investigate the safety of chemotherapy in pregnant women with breast cancer and the possible complications for mother and fetus.	O tratamento quimioterápico para as grávidas com câncer de mama não deve ser protelado, devendo-se adotar cuidados adicionais para proteger o feto

Source: Own author, 2024

The studies highlight a central concern in maternal-fetal oncology: how to treat cancer in pregnant women without compromising the healthy development of the fetus. This issue becomes particularly complex when it involves treatments such as chemotherapy and radiotherapy, which can have profound and adverse impacts on fetal development. According to Negreiros et al. (2024), the administration of chemotherapy and radiotherapy during pregnancy presents significant risks, especially when performed in the first trimester, a period when embryonic development is most sensitive to external agents. Among the identified risks are increased teratogenicity, meaning the possibility of fetal malformations, as well as complications in growth and an increased likelihood of spontaneous abortions (Costa et al., 2024).

Chemotherapy is often necessary for pregnant women diagnosed with cancer but must be administered with extreme caution. Cieto et al. (2021) emphasize that, although it is one of the main therapeutic alternatives, chemotherapy in the first trimester should be avoided whenever possible due to the high risk of malformations. Starting from the second trimester, some chemotherapeutics are considered relatively safe, allowing for greater flexibility in disease management. However, even in these cases, rigorous monitoring and specific care are necessary to ensure the safety of both the mother and the fetus.

Radiotherapy, on the other hand, is even more restrictive and presents substantially higher risks throughout pregnancy. Schünemann Jr. et al. (2007) highlight that exposure to radiation can cause genetic mutations and severely affect fetal development, compromising vital organs and increasing the chances of gestational loss. This risk is so elevated that, in general, radiotherapy is contraindicated for pregnant women, especially in the first trimester, when the development of essential structures occurs at an accelerated pace and sensitivity to teratogenic effects is heightened. Even in later trimesters, if radiotherapy is absolutely necessary, extreme precautions must be taken, such as suspending treatment a few weeks before delivery and advising against breastfeeding immediately after exposure due to the risks of transferring radioactive agents (Fernandes et al., 2014).

Campos (2013) contributes to this discussion by reinforcing that, although cancer in pregnant women is rare, it imposes a series of ethical and clinical dilemmas. Identifying the most common types of cancer among pregnant women and defining less invasive treatment strategies are urgent needs. Chemotherapy, when administered starting from the second trimester, is one of the few options considered safe, although it still presents risks. For many types of cancer, surgery is a safer alternative than chemotherapy or radiotherapy, especially when performed in less advanced stages of pregnancy. However, even surgery can trigger complications, such as preterm births and maternal intercurrences, which underscores the need for

careful and individualized evaluation for each case (Cieto et al., 2021; Monteiro et al., 2013).

Another relevant point raised by Monteiro et al. (2013) and Dos Passos Carvalho et al. (2024) is the importance of additional care for pregnant women diagnosed with breast cancer, one of the most frequent neoplasms during pregnancy. In such cases, chemotherapy should not be postponed, as delays in treatment can significantly compromise maternal prognosis. To protect the fetus, detailed planning is necessary, including the type of chemotherapeutic agent, dosage, and timing of administration, always under the supervision of a multidisciplinary team.

The complexity and ethical challenges related to cancer treatment in pregnant women require clear guidelines and well-defined protocols. The discussed research points to the need for a balanced approach that considers both maternal health and the viability and well-being of the fetus. Achieving this balance is difficult, especially considering the psychological and emotional impact that a cancer diagnosis brings to the mother. As emphasized by Dos Passos Carvalho et al. (2024), informed decisions are essential, and healthcare professionals must involve patients and their families in the decision-making process, providing clear information about the risks and benefits of each treatment.

These conclusions reinforce the urgency of further studies on the impact of oncological treatments during pregnancy, aiming to develop alternatives that minimize the risks of adverse effects on the fetus without compromising therapeutic efficacy for the mother. Campos (2013) suggests that investigating less aggressive therapies and developing new drugs may be promising pathways to provide safer treatment for pregnant women with cancer. Ultimately, these efforts aim to improve the quality of life for patients and increase the chances of a healthy pregnancy, even in the face of such a challenging diagnosis as cancer.

IV. CONCLUSION

Cancer treatment during pregnancy presents a complex challenge that requires careful analysis of the risks and benefits associated with chemotherapy and radiotherapy. Chemotherapy, when administered from the second trimester onward, can be a viable and necessary therapeutic option, as its use may be relatively safe for the fetus. However, its use in the first trimester should be strictly avoided due to the high risk of fetal malformations and other adverse effects that may compromise the baby's development.

In contrast, radiotherapy presents even more substantial risks, regardless of the gestational trimester. Exposure to ionizing radiation can cause damage to brain development, congenital anomalies, and increase the risk of childhood cancer, making its use generally contraindicated during pregnancy. The decision to use radiotherapy should be considered only in exceptional cases where the benefits clearly outweigh the risks.

Given this scenario, it is essential that therapeutic decisions are guided by a multidisciplinary approach, involving physicians, oncologists, obstetricians, and the pregnant woman herself. Open and honest communication between the healthcare team and the patient is crucial to ensure that all aspects of treatment are discussed, allowing for informed decisions to be made collaboratively.

Finally, ongoing research into the effects of chemotherapy and radiotherapy in pregnant women is vital for developing more robust clinical guidelines and therapeutic alternatives that minimize risks to the fetus. The goal should always be to ensure the health and well-being of both the mother and the child, promoting positive outcomes during such a critical time in life.

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