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INTEGRATIVE REVIEW ARTICLE

MATERNAL-FETAL REPERCUSSIONS ARISING FROM CHEMOTHERAPY IN THE TREATMENT OF BREAST CANCER DURING PREGNANCY: INTEGRATIVE REVIEW

REPERCUSSÕES MATERNO-FETAIS DECORRENTES DA QUIMIOTERAPIA NO TRATAMENTO DO CÂNCER DE MAMA DURANTE A GESTAÇÃO: REVISÃO INTEGRATIVA

REPERCUSIONES MATERNO-FETAL DECURRENTES DE LA QUIMIOTERAPIA EN EL TRATAMIENTO DEL CÁNCER DE MAMA DURANTE LA GESTACIÓN: REVISIÓN INTEGRADORA

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ABSTRACT

Objective: to identify studies that describe the maternal-fetal repercussions resulting from chemotherapy in the treatment of breast cancer during pregnancy. ***Method***: it is an integrative review based on the guiding question << ***What scientific is the evidence on the maternal-fetal repercussions arising from chemotherapy in the treatment of breast cancer during gestation?*** >> The LILACS and PubMed/MEDLINE databases were searched, using the Keywords: chemotherapy, breast neoplasms, and pregnancy. The thematic was searched in the 28 selected articles In the analysis. ***Results***: the maternal-fetal repercussions identified were: malformation, oligoamnios, prematurity, abortion, myelosuppression, intrauterine growth restriction, respiratory alteration, low birth weight, preeclampsia, maternal cardiotoxicity, neonatal death and vaginal bleeding. ***Conclusion***: the research findings added knowledge about this problem. However, it is necessary to elaborate new studies with significant methodological content. ***Descriptors*:** Chemotherapy; Breast Neoplasms; Pregnancy; Primary Health Care.

RESUMO

Objetivo*:** identificar os estudos que descrevem as repercussões materno-fetais decorrentes da quimioterapia no tratamento do câncer de mama durante a gestação. ***Método*:** revisão integrativa, partindo da questão norteadora << ***Quais as evidências científicas sobre as repercussões materno-fetais decorrentes da quimioterapia no tratamento do câncer de mama durante a gestação? >>. Foi realizada uma busca nas bases de dados LILACS e PubMed/MEDLINE por meio dos descritores: quimioterapia, neoplasias da mama e gravidez. Na análise, buscou-se a temática em questão nos 28 artigos selecionados. ***Resultados*:** as repercussões materno-fetais identificadas foram: malformação, oligoâmnio, prematuridade, abortamento, mielossupressão, restrição de crescimento intrauterino, alteração respiratória, baixo peso ao nascer, pré-eclampsia, cardiotoxicidade materna, óbito neonatal e sangramento vaginal. ***Conclusão*:** os achados da pesquisa agregaram conhecimentos sobre essa problemática, contudo faz-se necessária a elaboração de novos estudos com teor metodológico significativo. ***Descritores*:** Quimioterapia; Neoplasias da Mama; Gravidez; Atenção Primária à Saúde.

RESUMEN

Objetivo*:** identificar los estudios que describen las repercusiones materno-fetal decurrentes de la quimioterapia en el tratamiento del cáncer de mama durante la gestación. ***Método*:** revisión integradora, partiendo de la pregunta guiadora << ***¿Cuáles son las evidencias científicas sobre las repercusiones materno-fetal decurrentes de la quimioterapia en el tratamiento del cáncer de mama durante la gestación? >> Fue realizada una búsqueda en las bases de datos LILACS y PubMed/MEDLINE, por medio de los descriptores: quimioterapia, neoplasias de mama y embarazo. En el análisis, se buscó la temática en cuestión en los 28 artículos seleccionados. ***Resultados*:** las repercusiones materno-fetal identificadas fueron: malformación, oligohidramnios, parto prematuro, aborto, mielosupresión, restricción del crecimiento intrauterino, alteraciones respiratorias, bajo peso al nacer, la preeclampsia, la cardiotoxicidad materna, muerte neonatal y sangrado vaginal. ***Conclusão*:** los hallados de la investigación agregaron conocimientos sobre esta problemática, sin embargo es necesaria la elaboración de nuevos estudios con tenor metodológico significativo. ***Descriptors*:** Quimioterapia; Neoplasias de la Mama; Embarazo; Atención Primaria de Salud.

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INTRODUCTION

Breast cancer associated with pregnancy is defined as any cancer diagnosed during pregnancy, or up to one year after delivery.[1] International data report an incidence of breast cancer associated with the pregnancy of 0.2 to 3.8%, resulting in a frequency of one case per 3,000 to 10,000 deliveries.[2] The number of new cases of breast cancer expected for Brazil rose from 57,120 in 2014 to 57,960 in 2016, with an estimated risk of 56.20 cases per 100,000 women, but, there are no data on breast cancer in pregnancy in these estimates presented by the National Cancer Institute (INCA).[3,4] The age is one of the most important risk factors for its development. Although recommendations for the early detection of the most age group at risk between 50 and 69 years old, it is observed in Brazil that incidence rates increase from 15 to 50 years old and it continues to grow even after 70 years old, resulting in a cumulative risk rate [0-74] of 6.3%.[3,5]

Adding to this factor, the changes in the woman´s lifestyle and the double working hours, at home and in the professional life have contributed to the decision to postpone gestation to the third and fourth decades of life. This change of behavior has been attributed as a possible cause of the increase in this problem in the pregnant women.[6]

The diagnosis of breast cancer in pregnancy is usually late due to the difficulty in the clinical examination of the breasts by the physiological changes that occurred during the gestational period, such as hypervascularization, hypertrophy, and breast engorgement. It is known that the diagnosis of neoplasia at an advanced stage and with axillary lymph node involvement leads to a decrease in survival and a worse prognosis.[1] In Brazil, the mortality rate in women who have been diagnosed with cancer during pregnancy is unknown. According to INCA, it is known that the number of deaths due to breast cancer in women in the menacme in 2013 was 3,499.[3]

Once diagnosed, even if late, the choice of treatment should always be aimed at the preservation of the pregnant woman and should be carefully evaluated according to the effects that can be generated to the fetus.[7] A treatment option is chemotherapy, where its indication will depend on the factors prognoses that will determine the risk of recurrence and maternal death.[1] Staging of the neoplasm should be performed adequately to identify the presence of metastatic disease, and consideration should be given to the physiological changes in the maternal organism that alter the metabolism of the medication.[1]

During the prenatal consultations in the primary health care service in the city of São Paulo, the situation of the pregnant woman is followed up by the high complexity service for the treatment of breast cancer and concomitantly, the continuity of prenatal care in basic health Unit. Thus, there was a concern about knowing the repercussions of chemotherapy in gestation to guide the management of the clinic.[8]

OBJECTIVE

- To identify studies that describe the maternal-fetal repercussions of chemotherapy in the treatment of breast cancer during pregnancy.

METHOD

This is an integrative review, a method used to determine current knowledge about a specific theme, through the identification, analysis, and synthesis of the results of previous studies, contributing to evidence-based practice.[9]

The option to choose this method is to provide support for guidance and professional follow-up, supporting prenatal clinic management in primary health care.[8] Mendes´s management of the clinic is understood as “a set of micromanagement technologies aimed at providing quality health care: people-centered; effective, structured on the basis of scientific evidence; safe, harmless to patients and health professionals; efficient, provided with the optimal costs; timely, timely delivery; to reduce unfair inequalities; and offered in a humanized way.” Some examples of such health technologies are the use of clinical guidelines and case management.[8]

This study was carried out from the following stages: definition of the guiding question of the research and objective, description of the inclusion and exclusion criteria of the articles, selection and accomplishment of the search in the databases, analysis of the data obtained, discussion and conclusion of the study .[9,10]

The guiding question for this integrative review was: What is the scientific evidence on the maternal-fetal repercussions of chemotherapy in the treatment of breast cancer during pregnancy?

The inclusion criteria of the articles used were: scientific articles available in full on

the Internet, in Brazilian Portuguese and English. The temporal delimitation was in the period between 2005 and 2014 to portray as many publications as possible. The theses, dissertations, monographs, articles that after reading the abstracts did not correspond to the subject of the study and those that were duplicated in the databases were excluded.

The search for articles was carried out by two reviewers in the scientific databases: Latin American and Caribbean Literature in Health Sciences (LILACS) and Medical Literature Analysis and Retrieval System online (MEDLINE), Virtual Health Library), from June to November 2014, with the in Science and Health keywords (DeCS): “chemotherapy” [and] “breast neoplasms” [and] “pregnancy” and the US PubMed (National Library of Medline) was consulted in December 2015 for searching expansion to with the DeCS: “chemotherapy” [and] “breast neoplasms” [and] “pregnancy”.

There were 1089 scientific articles found from the keywords. Considering the inclusion criteria, 186 papers were selected, after reading the titles and abstracts, 143 were excluded, which did not correspond to the subject studied and 15 were duplicated. Thus, this integrative review analyzes 28 scientific articles.

For the organization and extraction of the data, as well as the analysis of the articles, an instrument was carried out containing data about the year of publication, author's name and article title, type of research, objective, results and conclusion of the study. In a second reading of the article, it was possible to verify the level of evidence and to carry out the analysis and the synthesis of the studies, seeking answers to the question of the study to obtain a broad approach to the subject.[10]

The analysis was carried out evaluating the content of the articles, in which it was sought to identify the maternal-fetal repercussions and the times they were cited in the selected articles.

RESULTS

The data presented in Table 1 show information regarding the study sample of the year of publication and the type of research, where most of the studies, 20, representing 71.42% of the sample, opted to perform some literature review. Only 2 (7.14%) are of strong evidence, opting for a systematic review.[10]

Year of publication	N° of articles	Type of research	
2005	02[11,12]	01[11]	Case report
		01[12]	Retrospective
2006	03[1,13,14]	01[1]	Literature review
		01[13]	Case report
		01[14]	Expert Opinion
2007	02[15,16]	02[15,16]	Literature review
2008	06[17-22]	02[17,20]	Literature review
		03[18,19,22]	Case report
		01[21]	Prospective
2009	03[23-25]	02[23,24]	Literature review
		01[25]	Trial
2010	04[26-29]	02[26,27]	Case report
		01[28]	Literature review
		01[29]	Systematic review
2011	05[7, 30-33]	03[7,31,32]	Case report
		02[30,33]	Literature review
2012	02[6, 34]	01[6]	Literature review
		01[34]	Prospective
2013	01[35]	01[35]	Systematic review

Figure 1. Distribution of the articles according to the year of publication and type of research, in 2015.

Regarding the methodological quality of the studies, two are level 1 of evidence, four are level 2, 11 studies are level 5, another 10 studies are level 6 of evidence, and only one is level 7.[10]

It was observed that the maternal-fetal repercussions resulting from the chemotherapy described more frequently in the articles are malformations, followed by oligoamnios and prematurity, as can be seen in Figure 2.

Maternal-fetal repercussions	N° OF ARTICLES
Malformation	14[1,6,15,16,18,20,23,25,28-30,33-35]
Oligoamnio	13[1, 6, 17,19,20,22-24,27,31-33,35]
Prematurity	12[1,7,15,16,19,22,25,26,29,32,34,35]
Abortion	9[1,6,12,20,21,23,30,33,35]
Myelosuppression	5[1,15,16,23,35]
Intrauterine growth restriction	4[1,15,16,23]
Respiratory	4[19,27,29,34]
Low weight at birth	2[1,34]
Preeclampsia	2[1,35]
Maternal cardiotoxicity	2[27,35]
Neonatal death	2[22,34]
Vaginal bleeding	1[22]

Figure 2. Distribution of the maternal-fetal repercussions cited in the articles, in 2015.

DISCUSSION

All articles included in the review were published in different journals, 11 are a literature review, 10 are case reports, two are prospective studies, two are systematic reviews, one is retrospective study, one is a trial and one expert opinion. These results show the lack of research on the subject studied.

The maternal-fetal repercussions were based on the line of reasoning used in the analysis of the articles and 18 articles included in the review had repercussions on the action of chemotherapy in the pregnant woman and the fetus, and seven articles reported only in the fetus.[1,6,7, 12,15-35]

The literature reviews discuss the definition of breast cancer during gestation, report the incidence of this neoplasm between 1/1,000 and 1/10,000 pregnant women depending on the country studied. In Brazil, the main research centers involving breast cancer have not yet presented a current incidence of this type of cancer in pregnant women.[1,6,15,20,24,28,33]

The age range mentioned in the reviews is between 32 and 38 years old, and the more advanced the woman´s age, the greater the risk of developing the disease.[1,3,6,15,24,28] Other risk factors are related to life reproductive history, family history of cancer, alcohol consumption, excess weight, sedentary lifestyle, exposure to ionizing radiation and high density of breast tissue, being for non-pregnant women.[1,3]

The review studies also mention the difficulty in early diagnosis due to changes in the maternal body during pregnancy, the tumor staging that guides the therapy used, as well as the treatments, maternal-fetal repercussions and the prognosis of pregnant women.[1,6,15-17,20,23,24,28,30,33]

Within these literature reviews, it was observed that four studies were deepened in specific chemotherapies, such as Trastuzumab followed by Tamoxifen.[17,23,24,30]

One of the 10 articles that had the case report as a case study described three cases in the same study and another reported on a woman who chose to interrupt her pregnancy before starting chemotherapy.[11,26] In England, Scotland, and Wales, abortion was legalized in 1967 and until the above case report was made, in the UK abortion was allowed up to 24 weeks´ gestation for social, medical or economic reasons and after 24 weeks in cases of risk and cases of risk of fetal malformation.[36]

Regarding the age of eleven six pregnant women were over 35 years old, a study carried out in 2012 reported the increase of late pregnancy due to changes in social profile.[37]

The gestational age at which the fetuses were exposed to chemotherapy was between 3 days to 28 weeks. When tamoxifen was used in the first trimester of pregnancy, a fetus presented craniofacial changes.[18]

Of the five fetuses exposed to Trastuzumab, a pregnant woman discovered pregnancy after seven months without the use of chemotherapy with gestational age of 23 weeks, where four weeks after the diagnosis of pregnancy had oligoamnios and vaginal bleeding after premature birth and multiple organ failures the infant died at 21 weeks postpartum.[22]

In another case report where the fetus was conceived during the third cycle of Trastuzumab therapy, the authors followed this pregnant woman and did not report any maternal-fetal repercussions.[13]

The remaining fetuses exposed to Trastuzumab and one to Paclitaxel with gestational age of 12, 14, 17 and 24 weeks, only those with 17 weeks did not present altered fetal vitality due to the presence of oligoamnios, but presented transient tachypnea requiring a 24-hour ventilatory

contribution after 37 weeks of vaginal delivery and the mother presented cardiotoxicity at 21 weeks of gestation, performing controls even after delivery.[19,27,31,32] Of those presenting oligoamnios, one was able to reverse the life-altering condition after discontinuation of the medication.[31] Prematurity in these four fetuses was present in two cases with a caesarean section of 32 and 36 weeks, where a fetus required a three-day ventilatory contribution and surfactant use.[19,32] In the other case reports, prematurity was present in two of the four cases with cesarean births from 33 to 35 weeks.[07,26]

In the prospective study carried out in 2008, 40 pregnant women diagnosed with breast cancer were followed between 1982 and 2009, where six abortions were reported.[21]

In another prospective study, 413 women who received chemotherapy after the first trimester of pregnancy had the following repercussions: low birth weight related to prematurity, malformation, newborn with oxygen therapy, a neonatal death that. According to the authors, they were not related maternal treatment, but rather the prematurity was associated with adverse events.[34]

In the systematic review carried out in 2010, the objective was to evaluate the use of taxanes during gestation, where it was possible to show a favorable toxicity profile of taxanes during the second and third trimester of pregnancy, but the authors did not rule out the need for studies that may evaluate the transplacental transference of these chemotherapies to improve the safety of these patients.[29]

In another systematic review carried out in 2013, one of the objectives was to verify the possible complications of the use of chemotherapy in the fetus. After the review, it was recommended the adoption of care for fetal protection by administering chemotherapy after the first trimester of pregnancy, with anthracyclines and to suspend three to four weeks before delivery to prevent neonatal transient myelosuppression.[35]

The authors of this review do not recommend the use of Trastuzumab during pregnancy since scientific evidence is limited to a few case reports.[35]

In the retrospective study carried out in 2005 with a time limit of 18 years, 116 pregnant women were followed up using chemotherapy, where abortion was reported in a pregnant woman who started therapy in the first trimester.[12]

In the experimental research, 20 patients who received the Epirubicin chemotherapy after the first trimester of pregnancy were followed weekly. It resulted in low fetal toxicity, presented by a newborn with polycystic kidney and prematurity in 13 of the 20 deliveries. These children were followed up for 2 years on average, where they did not present any neurological, cardiological and immunological changes.[25]

The expert opinion published in 2006 recommends anthracycline in the 2nd and 3rd trimesters of gestation and does not recommend the routine use of new cytotoxic drugs such as taxanes because of the lack of scientific evidence.[14]

This research shows the great number of maternal-fetal repercussions due to the chemotherapy treatment during pregnancy, but until the accomplishment of this work, no specific protocol was found for this population, which is attended following guidelines and protocols recommended by the competent institutions.

The actions of health professionals, including nursing professionals focused on the early diagnosis of breast cancer, are aimed at the postmenopausal woman, and even so, studies indicate their fragility.[38]

This study shows how important it is to perform a clinical examination of the breasts from the earliest age, detecting early breast cancer in these women before gestation, since the detection in this period is difficult, thus avoiding that these repercussions occur.

CONCLUSION

In this integrative review, we noticed the lack of research with a significant methodological content and absence of studies in nursing. There is a need to raise the awareness of professionals and to prepare new studies on this subject that can instrumentalize the evidence-based assistance of health professionals in the care of women with breast cancer during pregnancy since these patients tends to increase due to the changes in the habits of life adopted by our modern society.

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