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Cancer during pregnancy: analysis of cases with emphasis on obstetric and neonatal results

Câncer durante a gravidez: análise dos casos com ênfase nos resultados obstétricos e neonatais

Cáncer durante el embarazo: análisis de casos con énfasis sobre resultados obstétricos y neonatales

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ABSTRACT

Objectives: To know how cancer interferes with pregnancy to identify the most frequently diagnosed neoplasms in women in the reproductive period. **Methods:** Information was collected from the medical records of women who experienced cancer during pregnancy, from 2011 to 2018, and were treated at a reference hospital. **Results:** The most prevalent cancers during pregnancy were breast, cervix, leukemia and lymphoma. 64.29% of pregnant women were in the second trimester. The age range was between 27 and 44 years. 80% of these weomen received chemotherapy, 73.68% had complications during pregnancy / postpartum, and 42.11% died. There were 70.59% preterm newborns, 56.25% underweight, two spontaneous abortions and one stillbirth. **Conclusion:** The incidence of neoplasms associated with pregnancy have increased and contributed to indirect mortality in pregnancy and postpartum. The multidisciplinary approach is centeredon mother-fetus well-being, in addition to including women and family in the process.
Descriptors: Pregnancy Complications, Neoplastic; Pregnancy Outcome; Infant, Newborn.

RESUMO

Objetivos: Conhecer as interferências do câncer no processo gestacional e seu desfecho, identificar as neoplasias mais frequentemente diagnosticadas em mulheres no período reprodutivo. **Métodos:** Foram coletadas, informações dos prontuários de mulheres que vivenciaram o câncer, durante a gestação, no período de 2011 a 2018, acompanhadas em um hospital de referência. **Resultados:** Os cânceres mais prevalentes, durante a gestação foram: mama, colo do útero, leucemia e linfoma, 64,29% das grávidas estavam no segundo trimestre. A faixa etária foi de 27 a 44 anos, 80% receberam quimioterapia, 73,68% apresentaram complicações na gestação/puerpério, 42,11% das mulheres foram a óbito. Observaram-se 70,59% recém-nascidos pré-termo, 56,25% baixo peso, ocorrência de dois abortos espontâneos e um natimorto. **Conclusão:** Neoplasias associadas à gravidez têm aumentando em incidência e, contribuindo para a mortalidade indireta na gravidez e no pós-parto. Desca-se a abordagem multidisciplinar, centrada no bem-estar materno-fetal, além de incluir a mulher e a família no processo.
Descritores: Complicações Neoplásicas na Gravidez; Resultado da Gravidez; Recém-Nascido.

RESUMEN

Objetivos: Conocer las interferencias del cáncer en el proceso gestacional y su desenlace, identificar las neoplasias más frecuentemente diagnosticadas en mujeres en período reproductivo. **Métodos:** Se recopiló información de las historias clínicas de mujeres que experimentaron cáncer durante el embarazo, de 2011 a 2018, acompañadas en un hospital de referencia. **Resultados:** Los cánceres más prevalentes durante el embarazo fueron: mama, cérvix, leucemia y linfoma, el 64,29% de las gestantes estaban en el segundo trimestre. El rango de edad fue de 27 a 44 años, el 80% recibió quimioterapia, el 73,68% presentó complicaciones durante el embarazo/puerperio, fallecieron el 42,11% de las mujeres. Hubo 70,59% de recién nacidos prematuros, 56,25% de bajo peso, dos abortos espontáneos y un mortinato. **Conclusión:** Las neoplasias asociadas al embarazo han aumentado en incidencia, contribuyendo a la mortalidad indirecta en el embarazo y posparto. El enfóque se centra en el punto de vista multidisciplinario, dirigido al bienestar materno-fetal, además de incluir a la mujer y la familia en el proceso.
Descriptores: Complicaciones Neoplásicas del Embarazo; Resultado del Embarazo; Recién Nacido.

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INTRODUCTION

Cancer is currently considered the second leading cause of death among women during reproductive years, which has contributed to the rise of a new problem for modern health systems, the association between neoplastic disease and the gestational process[1]. Currently, it is estimated that the number of cancer diagnoses affects 0.01 to 0.02% of pregnant women, and the incidence of this association presents an upward trend, the main contributing factor being the postponement of the first pregnancy, which is a result of significant social changes[2-4].

Cancer associated with pregnancy can be defined as the diagnosis of the disease that occurs three months before the abortion, nine months before the delivery or 12 months after the pregnancy test result[4]. The most frequent cancers associated with pregnancy are: melanoma, breast, cervix, lymphomas and leukemia[2-3]. These are also the most frequent in non-pregnant women of equivalent age[5]. Less frequently, ovarian, thyroid and colorectal cancer[6] are also observed.

However, the data may be underestimated due to the challenge of diagnosing neoplasms during pregnancy. This is justified because, many times, the signs and symptoms presented are masked by the physiological changes in the gestation itself[5], leading to delays in the diagnosis and worse prognosis[7-8]. As in cases of breast cancer, which is characterized as one of the most prevalent during pregnancy, the natural sensitivity and engorgement of the breasts of pregnant and breastfeeding women may make diagnostic tests difficult and confuse professionals as to their clinical symptoms[9].

Due to the historically low incidence of cancer during gestation, there is no conclusive information in the literature regarding the prognosis of the condition in these cases[10-11]. Also, there is an ethical dilemma in the decision making in relation to the best treatment to be performed and the most appropriate moment to initiate it, in addition to which procedures should be performed subsequently[12].

Currently, the main oncologic treatment options considered possible to be performed during pregnancy are: surgery, chemotherapy and radiotherapy[11]. The main factors to be considered when choosing the appropriate therapy are: the gestational period, the evolution of the neoplasm in the organism, the tumor location and the expectation of benefits and risks of the procedure, both for the mother and the fetus[12].

Thus, the main obstacle for the management of the treatment during pregnancy is to achieve a balance between the possibility of immediate intervention, considering the maternal conditions, or the delay in therapy until the resolution of the pregnancy, aiming at maintaining fetal vitality. However, chemotherapy should not be performed in the first trimester, especially during organogenesis, as it presents a high risk for fetal malformation, and therefore is administered preferably in the second and third trimesters[9].

In relation to neonatal outcomes, the evidence obtained in the literature so far is limited. However, it still refutes the idea that cancer, during pregnancy, may be responsible for all adverse outcomes, as well as for the premature birth, which would affect the physical or intellectual development of the offspring in early childhood[8].

It is concluded, therefore, that the decision on the best conduct in cases of gestational cancer must balance the maternal-fetal impacts, considering the specificities of each case and, especially, the mother's interests and wishes. Patients should always be guided by a multidisciplinary team, in order to have sufficient knowledge about their condition, and about the risks and benefits of each therapy, leading them to be in a position to decide on the conduct to be followed, in conjunction with the team[13].

In this context, this research aimed at assessing the interferences of cancer in the gestational process and its outcome, as well as identifying the types of neoplasms most frequently diagnosed in women during the reproductive period.

METHOD

This is a quantitative, descriptive, cross-sectional, and retrospective study, which was developed using secondary data extracted from the medical records of pregnant women attended in the high-risk prenatal care of a reference hospital in the interior of the State of São Paulo.

For the identification of cases, the Medical Data Section was consulted, respecting the following inclusion criteria: medical records of women of any age who presented some type of cancer during the gestational process, in the period between January 2011 and December

2018, due to the change to electronic records. The records with incomplete data were excluded from the study.

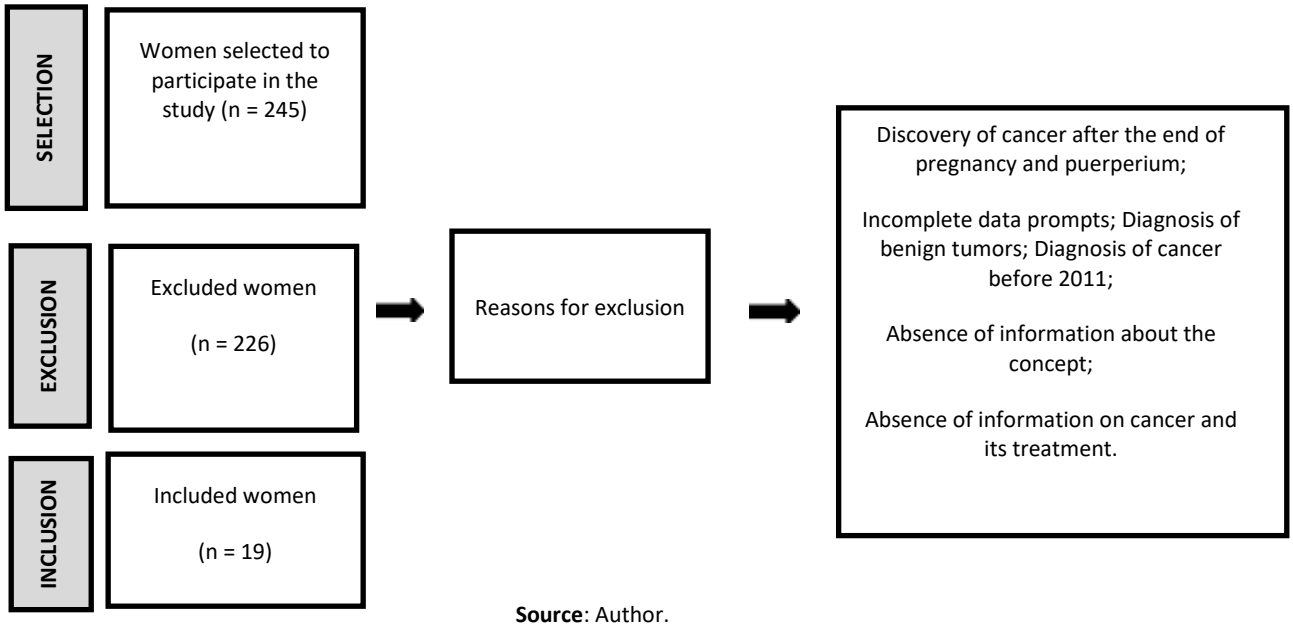
The data were collected from January to May 2019 with the help of an instrument that contained information related to the sociodemographic conditions of women, as well as the disease, type of cancer, date of diagnosis and treatment used. In addition, obstetric information was obtained regarding the possible complications that arose during pregnancy and the outcome of pregnancy. The newborn's data were: weight at birth, congenital malformations, Apgar score in the first and fifth minute of life, admission in neonatal intensive care unit (ICU), occurrence of stillbirth and preterm births.

With regard to data standardization in this study, the parameters of the São Paulo State Health Department[14] were used to define the birth period: preterm births when occurring before 37 weeks of gestation; term birth with delivery between 37 and 42 weeks; post-term births when occurring after 42 weeks[14].

For interpreting the weight of neonates, the following parameters were used[14]: adequate weight ranging from 2500 to 4500 grams; underweight at birth if lower than 2500 grams; very low weight when lower than 1500 grams and extremely low weight when lower than 1000 grams. In the case of the Apgar Index, neonates with scores between eight and 10 are considered healthy and in good general condition; scores between six and seven are a warning sign for possible problems, and scores between zero and three are considered critical conditions[14].

In total, 245 medical records were reviewed, 226 of which were excluded. The main reasons for exclusion being medical records with incomplete data, diagnosis of benign tumor and diagnosis of cancer after the puerperal period. At the end of the collection, 19 cases were included in the study (Figure 1).

Figure 1 - Selection, exclusion and inclusion flowchart of participants.



Source: Author.

The data obtained were arranged in a spreadsheet with support of Excel 2010 software (Microsoft Office). Descriptive, central tendency, and dispersion analyses were performed for numerical variables, and simple frequency for absolute and relative variables.

This research was approved by the Research Ethics Committee, according to the guidelines and rules regulating research, involving human beings, contained in Resolution NHC 466/2012 (CAAE Protocol: 95580418.0.0000.5393).

RESULTS

The age of the women included in the study ranged from 27 to 44 years, with a mean age of 31.81 years (standard deviation = 5.76 years). It was observed that the majority (63.16%) of women completed high school, and 63.16% reported household care as an occupation and 78.95% had a partner (Table 1).

Table 1 - Distribution of the population of women selected to participate in the study, according to the sample's social demographic characterization. Ribeirão Preto, 2020

Variable	Frequency	%
Age		
< 30	7	36.84
30 to 39	9	47.37
40 to 44	3	15.79
Civil Status		
With partner	15	78.94
Without partner	2	10.53
No information	2	10.53
Schooling		
From 5 to 8 years	4	21.05
From 9 to 12 years	12	63.16
Over 13 years	3	15.79
Ocupation		
Housewife	10	52.63
Health Licence	2	10.53
Other*	7	36.84

Source: Research database.
*Other: Teacher, Merchant, Billing Assistant, Student, Diarist, Office Assistant, Secretary, Administrative Manager and Cleaning Assistant.

Regarding the most prevalent types of cancers during pregnancy, it was observed that breast, cervix, leukemia, and lymphoma had an incidence of 15.79%. Of the pregnant women studied, 73.68% were diagnosed with cancer during the gestational period, and most remained pregnant (64.29%) during the second trimester (Table 2).

Of the ten pregnant women who underwent some treatment, 30% received neoadjuvant chemotherapy, 50% received adjuvant chemotherapy and 30% were submitted to surgery. Both radiotherapy and hormone therapy were not used as intervention. Only one of the patients started the treatment, during the first gestational trimester, because she did not know she was pregnant. The case resulted in spontaneous abortion (Table 2).

Table 2 shows the gestational complications and the period during which births occurred. It can be observed that 73.68% of pregnant women presented some complication during pregnancy, the most frequent being maternal anemia (42.86%). It can be observed that 52.89% of the deliveries were cesarean sections, with only one being considered emergency, and 70.59% of the neonates were born at less than 37 weeks. There were of complications after delivery in 36.84% of cases, and the majority (71.43%) were puerperal bleeding.

Table 2 - Distribution of women in relation to the main types of cancers and treatment during pregnancy and type of treatment. Ribeirão Preto, 2020

Variable	Frequency	%
Cancer type		
Breast	3	15.79
Cervix	3	15.79
Lymphoma	3	15.79
Leukemia	3	15.79
Others*	7	36.84
Period in which cancer was diagnosed		
Before gestation	2	10.53
During gestation	14	73.68
Puerperium	3	15.79

(Continues)

Table 2 - Distribution of women in relation to the main types of cancers and treatment during pregnancy and type of treatment. Ribeirão Preto, 2020

Variable	Frequency	%
Gestational period of the diagnosis		
First quarter	2	14.29
Second quarter	9	64.29
Third quarter	2	14.29
No information	1	7.14
Treatment during gestation		
Yes	10	52.63
No	9	47.37
Types of treatment		
Chemotherapy	8	70
Surgery	3	30
Gestational period in which the treatment started		
First quarter	1	10
Second quarter	7	70
Third quarter	1	10
No information	1	10
Gestational complications		
Yes	14	73.68
No	4	21.05
No information	1	5.26
Types of complications		
Gestational diabetes	2	14.29
Premature labor	2	14.29
Vaginal bleeding	5	35.71
Maternal anemia	6	42.86
Urinary tract infection	3	21.43
Others**	8	57.14
Type of delivery		
Vaginal	6	31.58
Cesarean section	11	52.89
Spontaneous abortion	2	10.53
Gestational age at birth (weeks)		
< 33	7	41.18
33 – 36	5	29.41
37 – 39	3	17.65
40 or more	2	11.76
Postpartum complications		
Yes	7	36.84
No	12	63.16
Types of complications		
Bleeding	5	71.43
Others***	2	28.57

Source: Research database.

*Others: Ovarian cancer, melanoma, renal cancer, Frantz's tumor, larynx cancer, thyroid cancer and rectal neck cancer.

**Others: Preeclampsia/eclampsia, fungal infection (candidiasis), hematemesis, bacterial vaginosis, placental detachment.

***Others: infection, vulvar edema, large lip hematoma.

****Notes: one of the patients performed both types of treatment during pregnancy (chemotherapy and surgery).

As for neonatal outcomes, there were two cases of miscarriage and one stillbirth. Of the 16 newborns, 50% were male, 56.25% were born with weight less than or equal to 2500 grams, the Apgar obtained by the babies was greater than seven in the first minute of life in 62.5% of the cases. No cases of congenital malformation were found at birth, and 25% of newborns required admission to the ICU (Table 3).

Table 3 - Distribution of birth concepts and their characteristics, such as weight, length, Apgar and need for hospitalization. Ribeirão Preto, 2020

Varible	Frequency	%
The concept was born		
Alive	16	94.12
Dead	1	5.88
Sex		
Female	8	50
Male	8	50
Birth weight (grams)		
< 1000	2	12.5
1000 – 1500	2	12.5
1500 – 2500	5	31.25
More than 2500	7	43.75
Stature		
Smaller or equal to 30	1	6.25
31 – 40	2	12.5
41 – 50	10	62.5
No information	3	18.75
Apgar 1st minute		
0 – 3	1	6.25
4 – 7	4	25
8 – 10	10	62.5
No information	1	6.25
Apgar 5th minute		
0 – 3	1	6.25
8 – 10	14	87.5
No information	1	6.25
Need for hospitalization		
Yes	4	25
No	12	75
Type of hospitalization		
Neonatal ICC	4	25
Joint accommodation	12	75

Source: Research database.

Of the eight women who received chemotherapy during pregnancy, two had spontaneous abortions. According to the results shown in Table 4, all neonates who were exposed to chemotherapy during pregnancy were born premature, and 83.3% of the concepts in this same group were born with a weight equal to or less than 2500 grams and 20% required admission to the neonatal ICU. However, regarding the Apgar index, performance was slightly worse in newborns (NB) that were not exposed to chemotherapy.

Among the pregnant women submitted to the surgical procedure, all three NBs were born full-term, weighing over 2500 grams, and Apgar between nine and 10, both in the first and fifth minute of life, all being referred to the joint accommodation (Table 4).

Table 4 - Comparison between the birth conditions of babies who have or have not undergone chemotherapy treatment during pregnancy. Ribeirão Preto, 2020

	With chemotherapy treatment	Without chemotherapy treatment
Variable	**Frequency (%)**	**Frequency (%)**
Gestational age at birth (weeks)		
< 33	3 (50%)	3 (30%)
33 – 36	3 (50%)	2 (20%)
37 – 39	0 (0%)	3 (30%)
40 ou mais	0 (0%)	2 (20%)
Birth weight		
< 1000	0 (0%)	2 (20%)
1000 – 1500	2 (33.3%)	0 (0%)
1500 – 2500	3 (50%)	3 (30%)
More than 2500	1 (16.7%)	5 (50%)
Apgar 1st minute		
0 – 3	0 (0%)	1 (10%)
4 – 7	2 (33.3%)	2 (20%)
8 – 10	4 (66.7%)	6 (60%)
No information	0 (0%)	1 (10%)
Apgar 5th minute		
0 – 3	0 (0%)	1 (10%)
4 – 7	0 (0%)	0 (0%)
8 – 10	6 (100%)	8 (80%)
No information	0 (0%)	1 (10%)
Admission to neonatal ICU		
Yes	2 (20%)	5 (50%)
No	4 (80%)	5 (50%)

Source: Research database.

It was observed that eight (42.11%) women of the study died, six (31.58%) were alive until the end of the data collection, and four (21.05%) lost the follow-up in the service.

DISCUSSION

From January 2011 to December 2018, 19 cases of cancer were identified during pregnancy and the most frequently found were leukemia, lymphoma, breast cancer and cervical cancer. Data similar to that observed in the literature, indicate that the most common malignancies associated with pregnancy, in descending order are: melanoma and breast cancer, cervical cancer, lymphomas and leukemia[5].

The majority (73.68%) of pregnant women received the diagnosis of cancer during pregnancy and 10 of them started treatment still in this phase, being chemotherapy the main treatment. It is observed that the use of chemotherapy during pregnancy has increased progressively over the last 20 years, however, it is important that this modality of treatment is always avoided in the first trimester, since the risk of fetal malformation is 10 to 20% with monotherapy, rising to 25% with combined chemotherapy[4]. In the second and third quarters, teratogenic risk returns to baseline (3%), although with an increased risk of premature birth, stillbirth, fetal myelosuppression and possibly intrauterine growth restriction. It is not clear whether the use of chemotherapy, during the second and third trimesters of pregnancy, is responsible for the birth of small NB for gestational age (SGA)[4].

In a survey conducted by the International Network on Cancer, Infertility and Pregnancy (INCIP), with 95 children exposed to chemotherapy treatment, 25% of them were born small for gestational age. Growth restriction can be attributed to fetal, maternal or placental

factors[15]. Other studies have also observed an increased risk of premature birth or growth restriction in infants born to cancer survivors[16-17].

On the other hand, there is the belief that surgery, during the gestational period, may be the procedure of choice for most neoplasms, as it is safer than chemotherapy and radiotherapy. However, the surgical procedure requires a lot of care and precise monitoring, because it also presents significant risks for the fetus, such as abortion or premature birth. For the mother, there is a risk of hypotension, hypoxia and hypoglycemia if the necessary precautions are not taken[15].

Maternal surgery with the intrauterine fetus may be associated with a risk of premature labor and altered utero-placental perfusion, putting the fetus at risk of hypoxia, brain injury and intrauterine fetal death[4]. In the study, we had only three patients who underwent surgery, all of which were born full-term NB and with satisfactory Apgar, between nine and 10, both in the first and fifth minute of life.

Radiotherapy, in turn, offers greater risks and, therefore, it is recommended to postpone the procedure to the postpartum period, regardless of the tumor site[18]. In cases of extreme need for this type of therapy, the radiation site must be located far enough away from the uterus and the dose used must be lower to ensure minimum safety for the fetus[18]. In this study, radiotherapy was not the treatment of choices for pregnant women.

The importance of analyzing each pregnant woman and the specificities of each type of tumor stands out. Because the choice of oncologic therapy will require caution, by the medical team, as well as possible changes in the form and dose of administration[15].

In a survey that analyzed 142 questionnaires from specialists, including oncologists, gynecologists and obstetricians, it was observed that 44% of the interviewees defended that the pregnancy should be interrupted, so as not to coincide with the beginning of the chemotherapy and radiotherapy treatment, with the objective of avoiding harm to both the mother and the fetus. The conduct of choice for 58% of the doctors was to wait for the postpartum period, and in some situations, they chose to anticipate the delivery, and then begin the recommended treatment. They also mention that 37% of the interviewees were against chemotherapy and radiotherapy during pregnancy, considering that there is no way to guarantee the safety of fetal development. Besides that, 66% of them believe that the interruption of pregnancy between 32 and 34 weeks are safe for the survival of the newborn[19].

Cancer during pregnancy can also increase the risk of stillbirths, mostly for those born small to gestational age, and can be associated with increased risk of newborn mortality, especially for premature infants[8]. However, the idea still prevails that cancer, during pregnancy, cannot be responsible for all adverse outcomes and represents great challenges for doctors, as well as for mothers and their families[8].

With this, besides trying to minimize the harmful effects of oncologic treatment for the pregnant woman and the fetus, birth planning should also be considered. As, for example, if it is necessary to deliver the baby before 34 weeks, prenatal steroids should be administered to minimize fetal lung injury[20].

This is due to the fact that studies point out that severe prematurity is directly associated with short-term neonatal risks and complications in childhood and adult in the long term[4], in addition to being a contributing factor to the emergence of neurodevelopmental disorders, lung dysfunctions and ophthalmic disorders[20].

A study conducted at a reference hospital in the state of Washington (USA) in 1987 and 2012 compared gestational complications and the obstetric and neonatal outcome of women diagnosed with a benign or malignant tumor during pregnancy with others who did not. They concluded that for some factors such as gestational diabetes, maternal anemia, pre-eclampsia/eclampsia, oligohydramnios or polyhydramnios, as well as the rate of cesarean section, premature birth, newborn with low weight and Apgar less than seven, the incidence was higher in the group of women who had some type of neoplasia during pregnancy compared to the group of women who did not have any type of tumor. In addition, the newborns of pregnant women with cancer needed hospitalizations more frequently after birth[21].

In this study, it was observed that 42.11% of women died. The diagnosis of cancer in pregnancy does not increase the incidence of maternal mortality[23], but the occurrence of death may be unavoidable[22]. In a multicenter study, published in 2013, with patients diagnosed with breast cancer, pregnant patients (311) were compared with non-pregnant women (865), and it was found

that 42 pregnant patients (14%) and 103 non-pregnant women (12%) died from the disease during follow-up. In the end, both the overall survival of the patients and the disease-free survival were analyzed, however, no significant differences were obtained between the groups[22].

CONCLUSION

Due to the fact that the malignant tumors associated with pregnancy are increasing in incidence and thus contributing significantly to indirect mortality in pregnancy and postpartum, the study on the subject becomes relevant. However, many are the challenges that arise from the association of the disease with the gestational process, such as the masking of cancer symptoms resulting from physiological changes in pregnancy, as well as the doubts and uncertainties that still prevail regarding the best therapeutic conduct that should be adopted in these cases. Moreover, it is observed that the approach to the cases needs to be multidisciplinary and centered on the maternal-fetal well-being, besides privileging the inclusion of the woman and the family in the process.

Finally, the research presents limitations, resulting from the small number of cases obtained, due to the difficulty of identifying such cases and the exclusion of records with lack of information.

Therefore, it aims to assist future works on the subject, as well as to contribute with the empirical-theoretical gap on the repercussions for the mother-child binomial, resulting from the association of cancer in pregnancy.

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