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Management of rare malignant neoplasms during pregnancy

Manejo de neoplasias malignas raras durante el embarazo

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ABSTRACT

Cancer during pregnancy occurs in 0.07% to 0.1% of all pregnancies. Due to the marked increase in maternal age at delivery, the incidence of malignant tumors diagnosed during pregnancy has increased. Although it is a rare condition, it must be identified and treated immediately, since pregnancy can produce conflicts for maternal treatment and optimal fetal development. The most common cancers during pregnancy are breast, cervical, melanoma, leukemia and lymphoma. However, there are less frequently reported cases of the pancreas, kidney, adrenal glands, bladder, lung, hepatobiliary, vulva, and central nervous system. Lack of experience and knowledge could lead to late diagnosis, imprecise treatment, and maternal-fetal complications. Cancer treatment strategies during pregnancy should not differ significantly from treatment regimens in non-pregnant women. The decision about the initiation and continuation of treatment should be preceded by a detailed analysis of the possible benefits and risks. Therefore, it is necessary to take into account diagnostic guidelines and weigh fetal safety with a multidisciplinary approach to establish potential therapeutic options.

Keywords: Cancer, Pregnancy complications, neoplastic.

RESUMEN

El cáncer durante el embarazo ocurre en 0,07% a 0,1% de todos los embarazos. Debido al notable aumento en la edad materna al momento del parto, la incidencia de tumores malignos diagnosticados durante el embarazo ha aumentado. Aunque es una condición rara, debe ser identificada y tratada de inmediato, ya que el embarazo puede producir conflictos para el tratamiento materno y desarrollo fetal óptimo. Los casos de cáncer más frecuentes durante el embarazo son los de mama, cuello uterino, melanoma, leucemia y linfoma. Sin embargo, existen casos reportados en menor frecuencia de páncreas, riñón, glándulas suprarrenales, vejiga, pulmón, hepatobiliar, de vulva y sistema nervioso central. La falta de experiencia y conocimiento podría conducir a diagnóstico tardío, tratamiento impreciso y complicaciones materno-fetales. Las estrategias para el tratamiento del cáncer durante el embarazo no deberían diferir en forma significativa de los esquemas de tratamiento en mujeres no gestantes. La decisión sobre el inicio y la continuación del tratamiento debe ir precedida de análisis detallado de los posibles beneficios y riesgos. Por lo tanto, es necesario tener en cuenta las pautas diagnósticas y ponderar la seguridad fetal con un enfoque multidisciplinario para establecer las potenciales opciones terapéuticas.

Palabras clave. Cáncer, Embarazo, complicaciones neoplásicas.

Introduction

Cancer during pregnancy is a rare event, occurring approximately once per 1,000 pregnancies annually, which corresponds to between 0.07% - 0.1% of all cases of malignant tumors[1,2]. These most common malignancies associated with pregnancy are breast cancer, cervical cancer, melanoma, lymphoma, and leukemia[3]. These histologic types of malignant tumors are also among the most frequent cancer sites in nonpregnant women at younger ages. However, another group of malignant tumors such as pancreatic, kidney, adrenal, bladder, lung, hepatobiliary, vulvar and central nervous system has also been reported in pregnancy, but much less frequency. Melanoma, hematopoietic neoplasms and lung cancer are the most common cancers that metastasize to the placenta and fetus. Melanoma accounts for about one third of all cases[4]. Even so, most data may be underreported because of difficulties involving diagnosis and data reporting.

The pathophysiology of pregnancy-associated cancer has not been fully defined. However, factors such as hormonal changes, immune suppression, increased permeability and vascularization are implicated in its etiopathogenesis. As the increase in frequency is a proven fact, due to trends in delayed childbearing[5], physicians should be aware of particularities of diagnosis and multidisciplinary management of these rare malignant neoplasms in pregnant women. The aim of the review is to analyze the management of rare malignant neoplasms during pregnancy.

Methodology of the information search

Between July and December 2019, electronic databases of biomedical scientific literature (UPToDATE, OVIDSP, ScienceDirect, SciELO and PUBMED) were examined to investigate eligible articles in the last 30 years (1989 - 2019), with the following search terms: "Cancer", "Pregnancy", "Malignant neoplasms", "Pancreas", "Kidney", "Adrenal glands", "Bladder", "Lung", "Hepatobiliary", "Vulva", "Central nervous system", "Diagnosis and treatment". Articles in English and Spanish from human studies were included, followed by an analysis of different aspects of diagnosis, treatment and management of rare neoplastic lesions in pregnant women.

Pancreatic cancer

The incidence of pancreatic cancer is estimated at 12.4 cases per 100,000 people and represents 3.1% of all cancers diagnosed. The mortality rate is considered to be 0.2% - 1.2% and the 5-year survival rate is 7.7%. Pancreatic cancer during pregnancy is extremely rare, there are only reports of less than 20 cases and most in advanced stages of the disease. The age range was 32-43 years and gestational age between 16-30 weeks. Two thirds of cases are diagnosed in the second trimester of pregnancy. A common feature of patients is epigastric pain and the presence of pancreatic tumor. About 40% have bile stasis and jaundice. The diagnosis can be confirmed by ultrasound and MRI, since half of the cases have liver metastases[6,7].

For laboratory diagnosis, it is useful to determine CA19-9 concentrations, whose sensitivity is 55% and specificity 99% with a cut-off value of 100 IU/mL. Surgical treatment is the standard of treatment, but can only be performed in 15-20% of cases. Other therapeutic options are: immediate surgical treatment with simultaneous interruption of pregnancy (before 28 weeks of gestation), delay of surgery until fetal lung maturity is reached, with knowledge of the risks of disease progression and worse prognosis, or surgery after at 28 weeks of pregnancy, which appears to be safe for the fetus. The prognosis is poor, as only 50% of cases died within 4 months after delivery, indicating the more aggressive nature of cancer during pregnancy[6,7].

Kidney cancer

In the general population, kidney cancer occurs with a frequency of 15.6 / 100,000 people. In 2016, 62,700 new cases of kidney cancer were detected in the United States, representing 3.7% of all cancers diagnosed. The 5-year survival rate is 73.7%. Renal tumors occur with a frequency of approximately 1:1,000 pregnancies[8], although these figures seem exaggerated. Eighty-four percent of renal tumors are adenocarinomas and in 99% there is no evidence of metastasis. The most frequent symptoms are pain in the lumbar region (50%), hematuria (47%) and hypertension (18%)[9,10].

In the absence of the possibility of routine radiological diagnoses, ultrasound and MRI are the most useful tools. Renal ultrasound evaluation should be performed in all pregnant women with symptoms. MRI is also possible in case of doubt. Surgery should be considered in these cases at the end of the first trimester of pregnancy or at the beginning of the second trimester.

Adrenal tumors

Pheochromocytoma occurs with a frequency of approximately 1 case per 50,000 people[11]. Suspicion arises from the diagnosis of hypertension during pregnancy that is difficult to control, associated with headache, tachycardia, nausea, hirsutism, but without proteinuria (which differentiates it from preeclampsia). Diagnosis is based on laboratory tests, in which serum and urinary catecholamine concentrations should be determined. Adrenal ultrasound evaluation is inconclusive, as 90% of tumors are in the adrenal glands, but the remaining 10% are found elsewhere in the abdomen. Magnetic resonance imaging allows localization of lesion[12]. Treatment consists of resection of the tumor after stabiliza-

tion of blood pressure (alpha-adrenergic blocker such as phenoxybenzamine, followed by atenolol or metoprolol). Surgical treatment should be performed during second or third trimester of pregnancy. Cesarean section is the preferred method of termination of pregnancy in these cases. After removal of the tumor, vaginal delivery can be attempted. When the diagnosis is made during pregnancy, maternal mortality is 4% and perinatal mortality is 15%[13].

Other tumors of the adrenal cortex during pregnancy are extremely rare. Symptoms depend on adrenocortical hormones they produce[14]. Excess cortisol produces Cushing's syndrome and excess aldosterone leads to hypertension with hypokalemia. In addition to the determination of hormone concentrations, ultrasound and magnetic resonance imaging are useful for diagnosis[15]. Surgical treatment, as in the case of pheochromocytoma, depends on gestational age.

Bladder cancer

It has a frequency of 20.1 per 100,000 people. Bladder cancer accounts for 4.6% of all diagnosed cancer cases. The mortality rate is 0.1% - 0.5%. About 20% of cases are reported in women. The 5-year survival rate is 77.5%. Cases of bladder cancer during pregnancy are rare. The main symptom is hematuria (81% of cases). They are usually diagnosed with urolithiasis. Ultrasonography allows to recognize only half of the cases. Cystoscopy is a complementary diagnostic technique that allows obtaining material for histopathological analysis. In advanced pregnancies and with tumors no larger than 3 centimeters, treatment can be postponed until after delivery[16]. In other cases, it may be necessary to perform surgery during pregnancy or cesarean section. Because of the proximity between the bladder and the pregnant uterus, steroids must be administered before surgery to accelerate fetal lung maturity. Chemotherapy will be initiated after delivery.

Lung cancer

It is the third most frequent type of cancer. It occurs with a frequency of 57.3 cases per 100,000 people. Lung cancer accounts for 13.3% of all cancers diagnosed. Mortality in the 20-34 years and 35-44 age groups is 0.1% and 0.8%, respectively. More than 40% of lung cancer cases are detected in women. The overall survival rate at 5 years is 17.7%. In pregnant women, this cancer is relatively rare, as only about 60 cases have been described to date[17].

In 80% of cases, lung cancer in pregnant women is diagnosed in stage III - IV and most frequently in the second trimester. The average age is 38 years and 60% of the cases are in smokers[17-20]. The main symptom is chronic cough (period longer than 6 weeks) or recurrent pneumonia that does not respond to antibiotic treatment. In each case, chest radiography can be performed, due to the low radiation dose which has no negative fetal effects. Magnetic resonance imaging makes it possible to evaluate the extent of tumor dissemination in case of suspicion. In 18% of cases there are placental metastases, in 5% to fetus, for this reason histopathological examination of the placenta and extensive evaluation of the newborn after delivery is necessary.

Treatment depends on the gestational age and extension of the tumor. In the available reports, pregnant women were treated with chemotherapy (cisplatin, carboplatin, taxanes). There are cases of successful lobectomy during pregnancy[21,22]. Treatment is initiated after delivery. The interruption of pregnancy should be considered only after the patient's consent, if it brings real benefit to the treatment or the possibility of using a contraindicated treatment during pregnancy[22,23]. In most cases, due to the maternal condition, pregnancy should be terminated no later than 35 weeks. The prognosis is poor, as only 19% of pregnant women with lung cancer survive more than 12 months after delivery.

Hepatobiliary cancer

Hepatobiliary cancer is rare (8.4 cases per 100,000 persons) and represents 2.3% of all diagnosed cancers. The mortality rate is 0.5% - 1.5%. About a quarter of the cases occur in women. The 5-year survival rate is 17.5%[24]. Imaging studies are the basic tool for diagnosis. In pregnancy, suspicious cases can be studied with ultrasound and MRI. In addition, ultrasound of the liver and bile ducts is mandatory in all cases of intrahepatic cholestasis of pregnancy. The presence of suspicious changes must be differentiated from metastases from other organs. In the case of individual nodules and smaller than 1 centimeter, after the possibility of metastasis, observation and re-evaluation at 3 months may be sufficient[25,26]. There are not enough case reports of hepatobiliary cancer during pregnancy

to reach clear conclusions. In such a situation, both diagnosis and treatment should be based on similar schemes as in non-pregnant women.

Vulvar cancer

It occurs relatively rarely (2.4 cases per 100,000 women). Vulvar cancer represents 0.4% of all malignant neoplasms diagnosed. The mortality rate is 0.6% - 1.9% and the 5-year survival rate is 71.9%. About 40 cases have been reported in pregnant women[27]. In suspected cases, vulvoscopy with directed sampling is necessary. In half of the cases, the tumor is located in the labia majora and measures between 2 and 5 centimeters.

Management depends on the stage of the cancer and the gestational age. In the case of limited lesions, it is possible to perform a partial vulvectomy without interrupting the pregnancy. In cases with advanced stages, modified radical vulvectomy is the treatment of choice. Surgery can be delayed until after delivery. About half of the cases described in the literature were resolved by cesarean section. There is no association between type of delivery, disease-free period and long-term survival. In half of the cases described, vulvectomy was performed after delivery. The prognosis of patients depends on the clinical stage and size of the tumor. If the diagnosis is delayed more than 8 weeks, with a tumor larger than 5 centimeters and stage III - IV lesions, the survival time does not exceed 2 years[28].

Tumors of central nervous system.

In the general population, they occur with a frequency of 6.4 cases per 100,000 inhabitants. They represent 8.9% of all malignant tumors diagnosed. Mortality is 3.6% - 5.5%. These tumors affect 41.5% of women. The 5-year survival rate is 33.8%. Tumors of the central nervous system are characterized by the appearance of two types of symptoms. Headache, nausea, and vomiting are nonspecific and may appear in the first trimester of pregnancy. If they appear in the second or third trimester, gastrointestinal, laryngeal and / or neurological diseases should be excluded. Visual disturbances, paresis and seizures should alert to the possibility of central nervous system disorders. Magnetic resonance imaging, computed tomography, and ophthalmic examination are studies that can confirm or exclude the presence of a brain tumor[29,30].

Treatment depends on the patient's general condition, gestational age, location of the tumor, type of cancer and progression of the disease. The administration of steroids or anticonvulsants can reduce the severity of symptoms. Chemotherapy, radiotherapy (with abdominal protection) and craniotomy may be used in these cases[29-31]. The choice of the route of delivery depends on the neurological evaluation[30,32].

Placental and fetal metastases

In all cases of maternal cancer, there is a risk of placental and fetal metastases[33,34]. Tumor foci often spread hematogenously. Placental metastases are most frequently detected in melanoma (30%), leukemia and lymphoma (15%), breast cancer (14%) and lung cancer (13%). Suspicion of placental metastases should require histopathological evaluation, which is only possible after delivery. For this reason, in cases of maternal cancer, a pathology study of the placenta should always be performed. Fetal metastases occur less frequently than placental metastases and are usually diagnosed in the scalp or internal organs of the newborn. Any suspicious changes should be evaluated by the pathologist.

Conclusion

In clinical practice, due to the later age at which women decide to have children and higher incidence of malignancies in the general population, the number of pregnant women with various malignancies will be increasing. These patients require multidisciplinary care provided by a team of specialists. This problem, rare in the last century, is now a major challenge for health professionals.

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