

SPECIAL PAPER

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Management of colorectal cancer during pregnancy

Manejo del cáncer colorrectal durante el embarazo

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ABSTRACT

Cancer during pregnancy has increased due to delayed motherhood and the known occurrence of age-dependent malignant tumors. With the increase in colorectal cancer diagnosed in young adults, the number of cases during pregnancy is likely to increase. Colorectal cancer is one of the 3 most common types of cancer in women, but the occurrence during pregnancy is rare and is associated with a large number of diagnostic and therapeutic challenges since the diagnosis is usually made in advanced stages. Besides, early diagnosis is difficult because the signs/symptoms (vomiting, constipation, anemia, rectorrhagia, pain and bloating) can simulate those observed during pregnancy. After diagnosis, the therapeutic plan must be established immediately, according to gestational age, by a multidisciplinary medical team. Doctors who care for pregnant women with colorectal cancer face two problems: the need for early maternal cancer treatment and timing of pregnancy termination. Professionals must become familiar with the challenges associated with systemic treatment, since antineoplastic treatment presents several unknowns for its use.

Key words: Colorectal neoplasms, Pregnancy, Pregnancy complications, neoplastic.

RESUMEN

El cáncer durante el embarazo ha aumentado debido a la postergación de la maternidad y la aparición conocida de tumores malignos dependientes de la edad. Con el aumento del cáncer colorrectal diagnosticado en adultos jóvenes, es probable que aumente la cantidad de casos durante el embarazo. El cáncer colorrectal es uno de los 3 tipos de cáncer más comunes en las mujeres, pero la aparición durante el embarazo es rara y se asocia con gran número de desafíos diagnósticos y terapéuticos, ya que generalmente el diagnóstico se hace en estadios avanzados. Además, el diagnóstico temprano es difícil, porque los signos / síntomas (vómitos, estreñimiento, anemia, rectorragia, dolor y distensión abdominal) pueden simular los observados durante el embarazo. Luego del diagnóstico, el plan terapéutico debe ser establecido de forma inmediata, de acuerdo a la edad gestacional, por un equipo médico multidisciplinario. Los médicos que atienden a embarazadas con cáncer colorrectal enfrentan dos problemas: necesidad de tratamiento temprano del cáncer materno y momento de interrupción del embarazo. Los profesionales deben familiarizarse con los desafíos asociados con el tratamiento sistémico, ya que el tratamiento con antineoplásicos presenta varias incógnitas para su uso.

Palabras clave. Cáncer colorrectal, Embarazo, Complicaciones neoplásicas del embarazo.

INTRODUCTION

Colorectal cancer (CC) is the second cause of morbidity and third cause of mortality from malignant neoplasms in women. In Peru, it is the sixth leading cause of cancer mortality⁽¹⁾. About 10% of cases affect women under 40 years of age and only 2% under 30 years⁽²⁻⁴⁾. Appearance of malignant tumors in pregnant women is a rare phenomenon and one of the rarest neoplasms is CC (Table 1). The incidence in pregnant women varies between 0.002% and 0.007%^(2,3). Different studies show that risk of suffering from it during pregnancy is 0.028 cases per 1 000 births⁽⁴⁾.

Due to the low frequency of CC in pregnant women, there are no diagnostic and therapeutic schemes supported by clinical trials. Current knowledge is based primarily on case reports. Treatment is determined by clinical stage of disease and gestational age of pregnancy at the time of diagnosis. The TNM classification is the most widely used in clinical practice and allows a precise determination of the severity of condition (Table 2). The objective of this review is to establish the management of colorectal cancer during pregnancy.

TABLE 1. MOST COMMON MALIGNANT TUMORS IN PREGNANT WOMEN⁽³⁾.

Type of cancer	Frequency
Breast cancer	1 case / 3 000 to 10 000 pregnancies
Cervical cancer	1.2 cases / 10 000 pregnancies
Hodgkin lymphoma	1 case / 1 000 to 6 000 pregnancies
Melanoma	2.6 cases / 1 000 pregnancies
Ovarian cancer	1 case: 10 000 to 100 000 pregnancies
Colorectal cancer	1 case / 13 000 pregnancies
Leukemia	1 case / 75 000 to 100 000 pregnancies

METHODOLOGY OF THE INFORMATION SEARCH

Between July and December 2019, electronic databases of biomedical scientific literature (UP To DATE, OVIDSP, ScienceDirect, SciELO and PUBMED) were examined to investigate eligible articles in the last 30 years (1989 to 2019). The search terms were: "Colorectal cancer", "Pregnancy", "Colorectal malignant neoplasms", "Diagnosis", and "treatment". Articles in English and Spanish of studies carried out in humans were included, subsequently carrying out an analysis of the different aspects of diagnosis, treatment, and management of CC in pregnant women.

DIAGNOSIS

Changing bowel habits, constipation, or rectal bleeding are common symptoms of CC. However, the appearance of these manifestations during pregnancy does not lead to diagnostic suspicion of CC and they are often underestimated. This can lead to late diagnosis and treatment.

The simplest, cheapest and most accessible clinical evaluation is digital rectal examination. It

often allows the tumor to be diagnosed during first visit. All patients with symptoms, especially when they appear before pregnancy and / or intensify despite treatment, should undergo a rectal examination, even more so if they refer to a history of rectal or anal pathology. The most common reasons that do not allow rectal exam are when it is considered that the symptoms are related to pregnancy, such as hemorrhoids, and patient's reluctance.

In case of suspected CC in pregnant women, it is advisable to perform a colonoscopy. This method is safe during pregnancy, especially during second and third trimesters⁽⁵⁾. Endoscopic evaluation should not be delayed, especially if symptoms persist and are not related to pregnancy. An additional advantage is the ability to sample suspicious sites and make a reliable histopathological diagnosis. Most tumors in pregnant women appear in rectum or sigmoid colon (60% to 80%)⁽⁶⁾. Therefore, sigmoidoscopy may be sufficient for diagnosis, shortening examination time and reducing risk of complications. Colonoscopy during the first trimester of pregnancy is associated with increased risk of miscarriage. Other adverse effects include: teratogenic effects of anesthesia, increased risk of placental insufficiency, hypoxia, hypotension and premature detachment of the placenta^(5,7). To reduce these risks, it is advisable to use meperidine (instead of benzodiazepines), an oxygen mask, gentle abdominal pressure, and continuous fetal monitoring.

If imaging is necessary, methods of choice are ultrasound and magnetic resonance imaging⁽⁸⁾.

TABLE 2. STAGING CRITERIA FOR CANCER ACCORDING TO THE TNM CLASSIFICATION⁽⁹⁾.

Primary tumor (T)		Regional lymph nodes (N)		Distant metastases (M)	
TX	Tumor evaluation is impossible	NX	Impossible evaluation	M0	Distant metastases absent
TO	No primary tumor	N1a	Single lymph node metastasis	M1a	Distant metastasis in 1 organ
Tis	Cancer <i>in situ</i>	N1b	Metastasis in 2 or 3 lymph nodes	M1b	Distant metastasis in > 1 organ or peritoneal metastases
T1	Infiltration of submucosa	N1c	Tumor cells in serum layer, mesentery, peritoneal tissues not covered with periarterial / rectal tissue		
T2	Adequate Infiltration of muscle membrane	N2a	Metastasis in 4 to 6 lymph nodes		
T3	Infiltration of serum layer or pericecal / perianal tissues	N2b	Metastasis in more than 6 lymph nodes		
T4a	Visceral peritoneal infiltration				
T4b	Infiltration of other organs or structures				



However, visualization of colorectal tumors by ultrasound is difficult. However, sensitivity to detect liver metastases is 75%⁽⁹⁾. Magnetic resonance imaging is most useful to accurately detect pathological changes in bowel and liver. Other diagnostic imaging methods, such as plain abdominal radiography and computed tomography, have an increased risk of fetal complications, mainly due to ionizing radiation, a known teratogenic factor⁽¹⁰⁾.

Fetal effects of ionizing radiation depend on dose, location of irradiated site, and gestational age^(11,12). There is evidence showing that gestational age is not associated with fetal radiation absorption. Estimated fetal dose for abdominal radiographs in two views is 0.02 rads. Abdominopelvic computed tomography produces a fetal irradiation dose of 2.6 rads⁽¹³⁾. Several studies have shown that a fetal radiation dose greater than 5 rads does not produce adverse effects, especially after organogenesis^(11,12,14). A dose of 10 to 20 rads causes malformation and lowers intelligence quotient in newborns⁽¹¹⁾. Fetal exposure to doses less than 1 rad increases risk of childhood neoplasms (especially leukemia) from 2 to 4 cases per 1 000 pregnancies^(11,12).

In some situations, it is necessary to use diagnostic methods that use radiation. For example, acute intestinal obstruction requires quick and accurate diagnosis. This occurs secondary to CC in 7% to 30% of the general population⁽¹⁵⁾. However, during pregnancy, it is extremely rare and there are only 2 cases described^(16,17).

In pregnant women, serum determination of tumor markers has limitations. Concentrations of CA-125, human chorionic gonadotropin, alpha-fetoprotein, and protein 4 of the human epididymis are variable during pregnancy and cannot be considered reliable indicators of tumor process nor useful in routine clinical practice⁽¹⁸⁾. On the other hand, concentrations of carcinoembryonic antigen, CA 19-9 and lactate dehydrogenase do not show significant changes during pregnancy⁽¹⁹⁾. Serum carcinoembryonic antigen concentrations may be useful in cases of CC. However, they have too low sensitivity and specificity to be used routinely in the diagnosis of CC. And, in pregnancy, although it is one of the first tests performed, it is not very useful⁽²⁰⁾, especially since the increase in concentrations is proportional to the CC stage, and 60% of cases

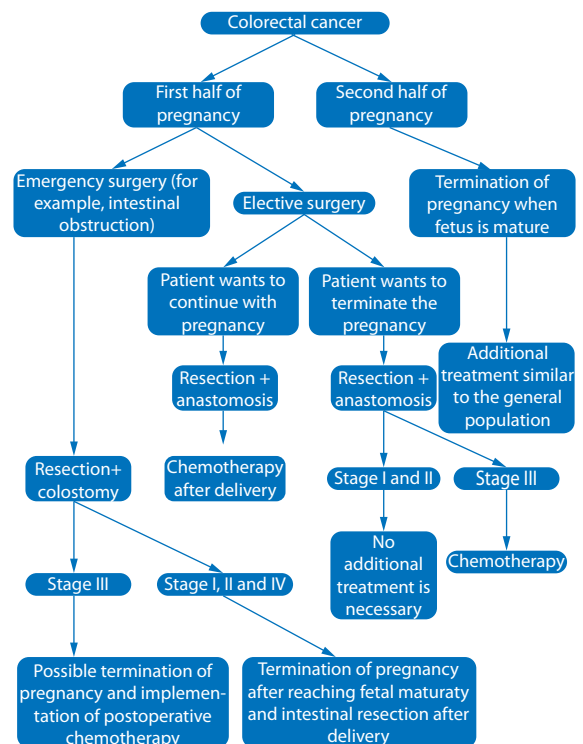
in pregnant women are diagnosed in Dukes C stage⁽⁶⁾. However, it can be useful for evaluating therapeutic effectiveness and monitoring for recurrences. Neither can it be used to complete diagnosis, especially in cases where alarm symptoms persist.

TREATMENT

Choosing appropriate therapeutic strategy is a challenge for physicians (Figure 1). Decision on method, technique, treatment time and delivery method must be considered individually for each case by a multidisciplinary team. The ethical problem is to establish the moment of termination of the pregnancy, the chances of fetal survival, the risk of disease progression, and the prognosis. Therefore, gestational age, maternal age, number of children, and stage of cancer must always be taken into account.

Although there is no evidence that CC can have direct fetal effects, even in advanced stages, it is clear that fetal development depends on maternal well-being⁽²¹⁾. During evolution of cancer, anemia, hypoproteinemia and malnutrition can be found, which can interfere with fetal growth.

FIGURE 1. DIAGRAM OF THERAPEUTIC MANAGEMENT OF COLORECTAL CANCER DURING PREGNANCY (ADAPTED FROM SALANI ET AL., 2014⁽¹⁹⁾).





If CC is diagnosed during the first half of pregnancy (less than 20 weeks' gestation), all therapeutic options should be considered, including termination of pregnancy⁽²²⁾. Due to the small number of cases in pregnancies less than 20 weeks, there are limited data on optimal management⁽²³⁾. In those women who do not wish to interrupt the pregnancy, it is advisable to postpone surgery until the second trimester, since performing it in the first trimester is associated with a higher risk of miscarriage⁽²⁴⁾.

Recommended procedure in pregnant women is tumor resection. There is evidence that Miles surgery can be performed in the first trimester without manipulation of the pregnant uterus⁽⁹⁾. Low anterior resection is the preferred method, due to fewer side effects and better quality of life⁽²⁵⁾. In the case of elective surgery, intestinal anastomosis is recommended. Hartmann surgery should be reserved for emergencies.

In those cases of CC detected after 20 weeks, treatment should be postponed until postpartum, unless there are urgent indications⁽²⁶⁾. The time for termination of pregnancy is between the 32nd and 35th week⁽²⁷⁾, but it can be planned before this period⁽⁹⁾. In cases of interruption before 34 weeks, corticosteroids should be administered to accelerate fetal lung maturation. If there are indications for cesarean section or the tumor size prevents delivery, it is possible to perform a cesarean section together with intestinal resection. In cases of vaginal delivery, surgery should be postponed until 6 weeks after delivery, when uterine size and vascularity decrease, increasing the possibility of better results. Regardless of route of delivery, the placenta should always be subjected to histopathological examination, due to the possibility of metastasis⁽²⁸⁾.

For acute intestinal obstruction, colonoscopic stents may be placed. This allows stabilization of the patient, preparation and planning of surgery, as well as administration of steroids to stimulate fetal lung maturation^(16,17).

CC with metastases to ovaries with high concentrations of carcinoembryonic antigen is an unfavorable prognostic factor⁽²⁹⁻³¹⁾. Prevalence in general population is 3% to 8%, but in women under 40 years of age it increases to 23%^(6,31). In pregnant women, ovarian metastasis is present in 25% of cases^(21,30,32). There is no agreement as to whether appendectomy is necessary during the initial surgery. Some authors recommend

bilateral adnexectomy, as it reduces risk of disease progression and protects against primary ovarian cancer. However, this therapeutic approach increases the risk of miscarriage, especially during the first trimester⁽³³⁾. Removal of adnexa and cecal appendix prolongs survival by 10 months⁽³⁴⁾. Other authors have not been able to confirm these findings⁽³⁵⁾.

Chemotherapy is widely used in the treatment of CC. However, almost all cytotoxic drugs cross the placental barrier and fall into category D⁽³⁶⁾. The effect on the fetus / neonate depends on the drug, dose, time and duration of exposure. In addition, multi-drug treatment increases the risk of side effects (25%) compared to monotherapy (17%)⁽³⁷⁾. The greatest fetal risk is associated with alkylating agents and antimetabolites⁽³⁸⁾. The safest are platinum derivatives, and taxanes⁽³⁹⁾. The unfavorable fetal effect is more marked during the first trimester, and especially during organogenesis⁽⁴⁰⁾. The risk of adverse outcome in the first trimester of pregnancy is 10% to 20%, compared with 3% in healthy pregnant women⁽⁴¹⁾. After organogenesis, the most vulnerable organs and systems are the reproductive, central nervous, bone marrow and ocular.

Although there are no doubts about the fetal effects of chemotherapy during the first trimester, the effect of cytostatics after this period is unclear. The risk of birth defects in the second and third trimesters is 8% and 6%, respectively⁽³⁹⁾. Chemotherapy after 13 weeks increases the risk of intrauterine growth restriction⁽⁴²⁾. Several authors contradict these findings, showing that chemotherapy in this period does not increase the risk of birth defects, preterm delivery, or intrauterine growth restriction⁽⁴³⁾. Different studies have not shown effects of the chemotherapy after the first trimester, on growth, development or any type of hematological and immunological abnormalities⁽⁴⁴⁾.

The basic drug for the treatment of CC is 5-fluorouracil, which belongs to the antimetabolites by interrupting DNA synthesis, and is independent of the cell cycle. In animal studies it produces fetal death and in humans it is dangerous during the first trimester of pregnancy. There are reports of fetal congenital malformations in 14% to 19% of cases. After 13 weeks, the birth defect rate decreases to 1.3%⁽⁴⁵⁾. Oxaliplatin, a third-generation platinum derivative, damages and blocks DNA and RNA synthesis. In animals it causes spontaneous abortions and fetal intrauterine growth



restriction. Adverse effects of chemotherapeutics on pregnancy have only been confirmed in animal studies. Therefore, the simple transfer of these results to humans can be unreliable⁽⁴⁶⁾. The most common chemotherapy regimens used in pregnant women with CC is the combination of folinic acid, 5-fluorouracil and oxaliplatin or 5-fluorouracil and leucovorin. Only one neonate with endocrine and neurological alterations has been reported⁽⁴⁷⁾.

The use of radiotherapy in the treatment of CC in pregnant women is limited. Doses greater than 20 rads are teratogenic and cause spontaneous abortion⁽³⁸⁾. Most treatment regimens propose alternative treatment methods (for example, preoperative chemotherapy) and recommend postponing radiotherapy until after delivery⁽⁴⁷⁾.

An additional risk is the indirect adverse effects of chemotherapy. These include neutropenia, thrombocytopenia, cardiotoxicity, and increased risk of infection. Its effects on the fetus are difficult to assess and require further investigation.

As conclusions, CC is rare in pregnant women. Gastrointestinal symptoms are common in them, but cancer warning signs (anemia, lower gastrointestinal bleeding, or change in bowel habits) can also occur during pregnancy without complications. All these symptoms deserve attention in situations of persistence or increase in severity despite treatment. Diagnostic possibility of cancer must be taken into account. The diagnosis of CC is based on colonoscopic findings during the second or third trimester. Imaging studies (ultrasound and MRI) are helpful to assess the severity of the condition. Serum carcinoembryonic antigen concentrations may be helpful in evaluating treatment success and early detection of recurrence. The main treatment is tumor resection, followed by end-to-end anastomosis. The adjuvant treatment is based on chemotherapy, with side effects demonstrated in animal studies. Radiation therapy should not be used in pregnant women with CC.

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