A CASE REPORT

Dual Challenge: Diagnosis and Treatment of Colorectal Cancer in Pregnancy

by Siming Shen, Debra Goldstein

INTRODUCTION

Cancers of the breast, the cervix, the ovary, lymphoma and melanoma are the most frequently seen neoplasms during pregnancy.[1] Colorectal cancer (CRC) during pregnancy is very rare, with a reported incidence of 0.028 maternal cases per 1,000 births.[2,3,4] The probability of developing CRC increases with age, however, and as childbearing is being put off until a later time in life, the incidence of CRC complicating pregnancy may be on the rise. From the 1980s to 2003, approximately 300 cases of CRC in pregnancy were reported.[5] The mean age of presentation was 31 years and most tumors were in advanced stage, with the majority Dukes class B or greater.[6] CRC in pregnancy carries an overall poor prognosis, with 5 year survival rate ranging only from 0 to 42% compared with the general population.[6,7,8] Here we report a case that clearly demonstrates the confusion of non-specific pregnancy complaints and symptoms of colon cancer during pregnancy, along with the challenges of diagnosis and subsequent management. An updated discussion and literature review is also presented.

Case Report

A pregnant 38 year old Brazilian female, G2P0001, at 21 weeks of gestation, with past medical history only of internal hemorrhoids and one early stage miscarriage, presented to the emergency department with severe abdominal pain for one day. The pain was associated with several episodes of nausea and non-bloody emesis. Two weeks prior to this time, she had had one episode of tarry stool. There had been a 5 kg weight loss during the first trimester. There was no history of smoking or of alcohol use and no history of abdominal surgery. Family history of uterine cancer, prostate cancer, leukemia, but no gastrointestinal cancer was noted. Physical examination revealed diffuse abdominal tenderness, more localized to the LLQ. Laboratory results showed a WBC of $12.3X10^9$/L with 89% neutrophils. The hemoglobin was 10.0 with an MCV of 78.1 and RDW of 16.9. Comprehensive metabolic profile was normal. Fetal growth ultrasound revealed normal fetus without distress. The patient was discharged to home on the same day, following IV hydration and pain control, with oral ampicillin prescribed for a diagnosis of urinary tract infection.

She returned on the subsequent day with persistent LLQ pain. MRI without gadolinium revealed prominent wall thickening in the sigmoid colon. After receiving metronidazole for a presumptive diagnosis of diverticulitis, the symptoms improved and she was discharged to home with a scheduled outpatient sigmoidoscopy.

The patient presented for sigmoidoscopy at 28 weeks of gestation. A large tumor was found in the sigmoid colon and biopsy demonstrated a moderately differentiated adenocarcinoma. Serum CEA level was 72.9 ng/ml. Right upper quadrant ultrasound revealed no evidence of liver metastases. A consensus of the obstetric, surgical and oncological teams was reached: the patient received steroids to expedite fetal lung maturation and underwent a scheduled induction of vaginal delivery at 32 weeks of gestation. A healthy baby boy was delivered.

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Adjuvant chemotherapy was considered, but because of unknown potential fetal toxicity and lack of institutional experience, it was not administered. Postpartum colonoscopy re-evaluated tumor size and location, and ruled out metachronous lesions. A CT scan showed retroperitoneal adenopathy and was suggestive of invasion of the tumor into the surrounding mesentery. Robotic surgical resection was performed at 3 weeks postpartum. There was local invasion into the small intestine, but no obvious liver metastases were appreciated. Pathology revealed a Stage III C, poorly differentiated mucinous adenocarcinoma of the sigmoid colon.

DISCUSSION

CRC in pregnancy is a rare entity. Except for hereditary colon cancers, which are known to have early age of onset, the incidence of CRC in the general population increases with age over 50 years.[9] The diagnosis of young patients with CRC during pregnancy may indicate the presence of one or more predisposing factors compared with the general population, as seen in hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), Gardner syndrome, Peutz-Jeghers syndrome and history of inflammatory bowel disease.[10] These high-risk groups, however, represent only a small portion of CRCs diagnosed in pregnancy.[11]

Genetic defects, such as mutation of tumor suppression gene p53, play a critical initiating role,[12,13,14] but most often a second mutational hit is required for cancer to manifest.[15,16,17] Since 20-54% of CRC are estrogen receptor (ER) positive and 42.8% progesterone receptor (PR) positive,[18,19,20] one proposed theory is that elevated estrogen and progesterone levels in pregnancy, together with other stimulating growth hormones, lead to rapid cancer cell division and early induction of CRC. This hypothesis is supported by in vitro evidence of diminished growth-stimulatory effect of estrogen when ER expression is decreased in cancer cells and by evidence of correlated PR receptor activity in the proliferative behavior of CRC.[20,21,22] However, the data to strongly support the role of these receptors in the pathogenesis of CRC during pregnancy are limited and conflicting in the literature.[18]

Insulin-like growth factor-1 (IGF-1) is another growth hormone that has potent mitogenic and anti-apoptotic features in the cell proliferation of epithelial cells of breast, prostate, colon and lung.[23] IGF-1 derived from placenta is slightly increased throughout pregnancy. One of its functions is that of stimulating the synthesis of vascular endothelial growth factor (VEGF), an angiogenic factor which promotes tumor growth.[24] It is not clear, however, whether the amount of IGF-1 produced during pregnancy plays a role in the early development of CRC. Similar questions pertain to another pro-angiogenic factor, placenta growth factor (PGF), a dimeric glycoprotein with 53% homology to VEGF that is found to be overexpressed in a number of tumor types, including CRC.[25] Although there is data showing that the pre-operative PGF level is elevated in pregnancy and could function as a growth promoter for malignant cells,[26,27] there are no studies of the role PGF in CRC during pregnancy.

Cyclooxygenase-2 (Cox-2) enzyme is found to be essential for each stage of pregnancy.[28] Interestingly, the Cox-2 enzyme has also been implicated in the growth of cancers by inhibiting apoptosis, increasing invasiveness and modulating inflammation and immunosuppression. Cox-2 is found in high levels in CRC cells;[29] Prostaglandin F (2alpha) (PGE2alpha), the product of COX-2, has been shown to stimulate motility and invasion in colorectal tumor cells.[30] Cox-2 inhibitors have been used as chemoprevention in the non-pregnant patient[31,32] and there is clear evidence showing that inhibition of Cox-2 in colon cancer enhances tumor regression in vivo.[33,34] More studies are needed to investigate whether targeting Cox-2 in CRC during pregnancy will change the mortality and/or survival rate.

Initial signs and symptoms of CRC often include fatigue, malaise, nausea, vomiting, rectal bleeding, anemia, altered bowel habits and abdominal mass or distension.[3,5,35,36] Unfortunately, some of these signs and symptoms may be physiological in the setting of pregnancy, are often attributed to normal pregnancy and result in the diagnosis of advanced stage CRC in pregnancy. As a consequence, colonic obstruction, perforation and metastasis are more frequent in pregnant women with CRC than in the average population.[37] The differential diagnosis of rectal bleeding during pregnancy should include hemorrhoids, infectious colitis, ulcerative colitis and CRC, just as in the setting of non-pregnant patients.[37,38,39,40] An important 'take home message' from our and all other cases of CRC during pregnancy is that rectal bleeding during pregnancy may be an ominous sign, and should always be properly assessed.

There are no generally accepted guidelines for the diagnosis and treatment of CRC during pregnancy. Three key components that help to make the diagnosis are serum CEA level, abdominal imaging and endoscopy with biopsy. CEA level is generally not increased by pregnancy. Elevated CEA before surgery is associated with advanced disease and greater recurrence rates.[41] CEA provides a basis upon which to monitor response to resection and detect recurrences. Because of its low sensitivity and specificity, CEA level should not be used as a CRC screening tool.

In the non-pregnant patient, abdominal CT is useful for detecting a colorectal mass and is helpful for staging. Due to radiation teratogenicity, however, abdominal CT is contraindicated during pregnancy, especially during the first trimester.[42] Between the gestational ages of 10-17 weeks, the fetus is particularly sensitive to developmental defects and abdominal ultrasound is the preferred imaging modality. In addition to tumor detection, ultrasound has 75% sensitivity for detection of hepatic metastasis, especially for metastatic liver lesions greater than 2 cm in diameter.[43,44] In the second half of pregnancy, MRI is a safer imaging modality than CT scan for assessing maternal diseases of the abdomen and pelvis.[39,45] There is no scientific evidence in humans to suggest that the risk to the fetus from a routine MRI examination is significantly increased during the first trimester, but it has been difficult to establish the absolute safety of MRI during this period. Gadolinium administered intravenously does cross the placenta and enter the fetal circulation; therefore, gadolinium should be used in pregnancy only when a compelling clinical indication exists and the potential benefits to the patient outweigh the potential risks to the fetus.[46,47]

Colonoscopy is the preferred procedure to confirm the diagnosis of CRC in the average population; however, it is relatively contraindicated in pregnancy. Its risks include placental abruption due to mechanical pressure on the uterus, potential teratogenicity of endoscopic medications, and uteroplacental insufficiency from intra-procedural maternal hypotension or hypoxia.[48,49] Colonoscopy is generally indicated before surgery to obtain a pathologic diagnosis and to exclude synchronous colonic lesions.[50,51] Interestingly, in contrast to the 65% of CRC in average-risk non-pregnant women that occur in the proximal colon[52] most cases of CRC during pregnancy are rectal carcinomas, and one review showed that approximately 64-86% of CRC in pregnancy are below the peritoneal reflection.[6] During pregnancy, therefore, sigmoidoscopy is the preferred initial endoscopic modality for evaluation of rectal bleeding when a rectosigmoid mass is suspected.[53] In addition to the advantage that sigmoidoscopy does not require sedation, there are no reports of sigmoidoscopy-induced labor, increased incidence of poor pregnancy outcome or Apgar scores different from the national mean due to the procedure itself.[53,54,55]

Surgery is the mainstay for CRC during pregnancy,[5,56] with type and timing of surgery dependent on maternal age, gestational age, CRC stage, maternal cancer prognosis, intraoperative findings and maternal desire for future fertility. The treatment goal is to deliver therapy to the mother as soon as possible without compromising the fetus' life and safety. When CRC is detected during the first half of pregnancy, termination of the pregnancy is recommended to minimize risk for metastases.[56] Total abdominal hysterectomy may be necessary for surgical access to the rectum or when tumor extends into the uterus.[57,58] If the tumor is unresectable, palliative colostomy until the fetus becomes viable is an option. During the later stage of pregnancy, it is recommended that surgery to resect the tumor be delayed until the fetus is viable.[5,10,56]

Although chemotherapy improves the survival rate for stage II and III CRC in the general population,[59] there are no established guidelines for chemotherapy treatment during pregnancy. Virtually all chemotherapeutic agents cross the placental barrier, and teratogenicity depends on the timing of exposure, the dose and the characteristics of placental transfer. Chemotherapy is not recommended during the first trimester of pregnancy.[10] It has been reported that 10-20% of fetuses exposed to chemotherapy agents during the first trimester of pregnancy have major malformations as compared with 3% of the average population. Chemotherapy agents may be administered in the second or third trimesters with close maternal and fetal surveillance, but they have been associated with increased risk of low birth weight and IUGR.[59] 5-FU is the most studied chemotherapeutic agent during pregnancy, and has been shown to provide significant survival advantage in patients with stage III disease when initiated within 5 weeks of tumor resection.[60,61,62] Newer chemo-agents such as irinotecan, capecitabine and oxaliplatin are pregnancy category D drugs. A recent prospective study has reported no significant difference in neonatal survival, preterm birth, small for gestational age or congenital malformations

between chemotherapy delivered during or after pregnancy; it was concluded that in utero exposure to chemotherapy during the second and third trimester of pregnancy carries minimal morbidity to the unborn fetus.[63] Radiotherapy plays a major role in the treatment of Dukes B2 and C rectal cancers. However, pelvic radiation for rectal cancer is generally contraindicated during pregnancy, as the fetus will inevitably be exposed to the radiation. Radiotherapy can be only used after delivery or termination of pregnancy.

Pregnant patients with CRC carry an overall poorer prognosis secondary to delayed diagnosis and lack of standard guidelines for treatment during pregnancy. Large clinical studies of pregnant women and 5-year survival from rectal cancer have reported 83% survival for Duke's class B, 27% for Duke's class C and 0% for Duke's class D patients. With respect to 5-year survival of pregnant patients with colon cancer, Duke's class B has been reported at 75%, Duke's class C 33%, and Duke's class D 0%.[5,64] A review by Chan et al.[7] revealed 56% of patients with CRC during pregnancy were deceased at the time of case report in the literature. The majority of these patients died within 1 year of diagnosis, and the median survival for the group was less than 5 months. One patient survived for 3.5 years after surgery but had multiple recurrences. Patients tended not to survive beyond 5 years. Poor prognostic factors included mucinous histology, poorly differentiated histology, presence of synchronous tumors, as well as advanced disease status with colonic obstruction or perforation, ovarian metastases, elevated CEA level preoperatively and inability to obtain wide surgical margins. The incidence of ovarian metastases in pregnant women with CRC is 25% compared with 3-8% in non-pregnant women,[65] and has therefore led some physicians to recommend prophylactic bilateral salpingo-oophorectomy simultaneous with CRC surgery.[66]

CONCLUSION

Colorectal cancer is rare during pregnancy and carries a poor prognosis. CRC in the pregnant patient presents both a diagnostic and therapeutic challenge. In the absence of clear clinical guidelines, treatment during pregnancy still presents significant ethical, religious and scientific challenges. In the setting of overlapping signs and symptoms of CRC and pregnancy, the primary care physicians and obstetricians are urged to consider the early potential ominous signs of CRC during pregnancy.

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