The Contradictory Phenomena: Development of a New Life and a Life-Threatening Illness: Colorectal Cancer in Pregnancy

Authors: Melissa Kyriakos Saad,[1] Imad Hajj,[2] *Elias Saikaly[2]

1. Institut Bergonié, Department of Surgical Oncology, Bordeaux, France
2. Saint George Hospital University Medical Center, Department of General Surgery, University of Balamand, Beirut, Lebanon

*Correspondence to dreliassaikaly@gmail.com

Disclosure: The authors have disclosed no conflicts of interest.

Received: 04.02.22

Accepted: 01.07.22

Keywords: Colorectal cancer (CRC), pregnancy.

Citation: EMJ Oncol. 2022; DOI/10.33590/emjoncol/22-00040. https://doi.org/10.33590/emjoncol/22-00040.

Abstract

Colorectal cancer (CRC) is a common and lethal disease. Genetic and environmental factors contribute to the development of CRC, with different incidence and mortality rates around the world. Geographic differences appear to be attributable to exposures that are superimposed on a background of genetically determined susceptibility. Globally, CRC is the third most commonly diagnosed cancer in males and the third in females, with 1.8 million new cases and approximately 861,000 deaths in 2018, according to the World Health Organization (WHO). Epidemiologically, it is a disease of the middle-aged and elderly. However, it may occur in young patients, presenting with an aggressive biological behaviour and poor prognosis. Among this young age group are childbearing women, with CRC in pregnancy being rarely diagnosed and reported. Its diagnosis is a challenge to the unaware and, once diagnosed, management options are limited. This study aims to elucidate the presentation, diagnosis, anatomical location, pathogenesis, and treatment options of CRC in pregnancy.

Key Points

1. Colorectal cancer (CRC) in pregnancy is a rare event; however, rates are increasing as risk of CRC is increased in women >40 years and more women are opting to have children later in life.

2. Diagnosis of CRC in pregnancy can be difficult due to wide-ranging presentations of the disease and overlapping symtpoms with pregnancy.

3. Treating CRC in pregnancy presents a unique challenge; a tailored, patient-specific approach is recommended, that considers legal, ethical, emotional, and scientific challenges.

INTRODUCTION

Colorectal cancer (CRC) ranks as the third most common type of cancer in women.[1] Patients aged 50 years and above constitute the highest percentage of patients diagnosed with the disease.[2] Furthermore, women above the age of 40 years are 11-times more likely to have CRC, compared with women aged 30 years and younger.[3,4] Aytac et al.[5] reported a growing incidence of CRC in the younger population; additionally, Khangura et al.[2] concluded that 3% of patients with CRC are under 40 years old. This increase in the incidence of CRC in younger patients translates directly to an increase in incidence during the reproductive age,[5] and therefore during pregnancy.

Despite this, pregnancy-related CRC is an extremely rare disease, with inadequate published data to guide its management. From here, CRC in pregnancy may be considered an independent entity from CRC in the general population. In fact, fewer than 300 cases have been reported in the medical literature,[5] with the first case reported by Cruveilhier in 1842.[6] CRC now ranks as the seventh most common cancer type in pregnancy,[2,7] with a predicted incidence of 0.0076% of pregnancies (one in 13,000),[8] a mean age at diagnosis of 31 years,[7] and an age range of 16 years to 48 years.[9]

PRESENTATION

A substantial similarity exists in the clinical presentation between a pregnancy-related CRC and normal pregnancy, which can delay a timely diagnosis.[1,10] This is particularly true in multiparous women, whose anxiety levels are usually lower compared with women who are pregnant for the first time. Consequently, women who have had at least one previous birth may present later to healthcare providers. With such a wide spectrum of presentation, patients may present with nausea, vomiting, abdominal pain, weight loss, fatigue and anaemia, rectal bleeding, and altered bowel habits (e.g., constipation). From here, what is considered normal in pregnancy may be alarming. For instance, uterine cramps cause abdominal pain, and so may CRC. Furthermore, rectal bleeding is commonly seen in pregnancy and is attributed to pregnancy-related engorged haemorrhoids.[11] On the other end of the spectrum, and as previously reported by different studies, pregnancy-related CRC can present without a specific presenting complaint.[2,3,12]

DIAGNOSIS

With such a wide spectrum of presentation and overlapping signs and symptoms between pregnancy and CRC, the diagnosis is a challenge. Therefore, healthcare providers should keep CRC in mind when considering differential diagnoses in patients presenting with these overlapping symptoms. Pregnant women presenting with such symptoms must be closely followed up or investigated using paraclinical tests that are safe during pregnancy. Above all, it is vital to investigate further symptoms that are specific, severe, or relapsing.[1,13]

Colonoscopy is considered the gold standard for diagnosing CRC. It also has the advantage of localising the tumour and obtaining tissue biopsy. However, pregnancy is considered a relative contraindication for colonoscopy because of the potential teratogenic medications, placental blood supply insufficiency and the resulting decrease in blood pressure or O_2 supply to the mother, and the risk for placental abruption due to the pressure from manipulation of the endoscope and the change in a patient's position during colonoscopy.[1,5,7,9,10,14] Having said this, it is preferable to proceed with endoscopy when a strong indication or highly suspected case of colorectal malignancy is present. Where possible, the procedure should be delayed until the second trimester.[5,7] It is also advisable to take all of the necessary precautions to minimise procedural risk. Hence, the time during endoscopy must be reduced. Practitioners should also aim to use the lowest possible dose of sedative.[10] Meperidine should be used as a sedative because of its safer fetal profile, O_2 should be supplied to the mother during the procedure to decrease the risk of hypoxia, and gentle abdominal compression should be used to avoid placental abruption.[9,14]

The carcinoembryonic antigen test (CEA) is utilised in pregnancy to follow up on CRC and for prognostic purposes. Unfortunately, CEA levels during pregnancy are usually within the normal limits, and sometimes mildly above the normal limits.[14-16] For this reason, CEA levels cannot

be used to screen for CRC nor diagnose CRC because of their low sensitivity and specificity.[9]

Contrast-enhanced CT is of limited value in diagnosing CRC in general. Its use is also limited during pregnancy because it may compromise fetal well-being.[17,18] Conversely, MRI is believed to be relatively safe in pregnancy. Of note, MRI should be performed without administration of a contrast agent,[13] as the use of these substances has not been approved for the fetus.[12,19] Moreover, gadolinium is considered a teratogenic agent.[10]

ANATOMICAL LOCATION

In the general population, two-thirds of CRC cases arise from the extrapelvic colon.[1,14,16] In contrast, pregnancy-related CRC involves the rectum and sigmoid colon in two-thirds of cases. In fact, it has been reported that approximately 85% of CRC cases in pregnancy are below the peritoneal reflection.[5,7,9,15]

PATHOGENESIS

The pathogenesis of pregnancy-related CRC is complex and not entirely understood. A complex hormonal interaction between oestrogen, progesterone, growth factors, the immune system, and environmental factors is thought to trigger CRC in pregnancy.[20,21] Furthermore, conflicting data are present in the medical literature, especially with regard to the impact of hormonal changes during pregnancy. Some authors reported the expression of oestrogen receptors in 20–80% of CRC cases in pregnancy,[22,23] and progesterone receptors in nearly 50% of cases.[24] However, other authors have not documented similar rates.[25] Having said this, it is believed that the role of hormones in the pathogenesis of CRC in pregnancy is manifested by the higher incidence of CRC in the second and third trimesters, and only one-fifth of patients present during the first trimester of gestation. Furthermore, in a study of over 2,000 women diagnosed with CRC, Arem et al.[26] proved that current use of hormonal replacement therapy is associated with lower CRC mortality risk (hazard ratio: 0.79; 95% confidence interval: 0.66–0.94). Hence, the relation between hormonal exposure and CRC progression should be revisited. Furthermore, Ho et al.[21] proposed an association between growth factors in pregnancy and the development of pregnancy-related CRC. Moreover, it has been found that COX-2 enzymes are essential for normal pregnancy. At the same time, high levels have been detected in many colorectal tumour cells. Thus, it has been postulated that COX-2 inhibitors such as aspirin can alter the course of CRC.[27] In brief, this field has not been adequately explored. Conflicting data exists regarding the pathogenesis of CRC in pregnancy, with complex hormonal interfaces between oestrogen levels, progesterone levels, pregnancy-related growth factors, the immune system, COX-2 enzymes, and environmental factors underlying the development of CRC in pregnancy.[20,21]

TREATMENT

Once diagnosed, the real challenge is treatment. Management requires cautiously individualised strategies after detailed patient counselling. Gestational age and consequently fetal lung maturity, stage of cancer, the role of neoadjuvant chemotherapy and its associated toxicity, the urgency of surgery, and the resulting emotional and physical stress on the mother should all be considered. The main goal is to initiate treatment as soon as possible,[2,19] taking into account the best possible balance for the fetus, and aiming for the optimal neonatal result.[5,9,15,19] From here, the urgency of surgery in combination with the gestational age dictates the management plan. Diagnosing CRC in the first 20 weeks of pregnancy is a rare event, which translates directly into inadequate data on fetal outcomes after surgical resection during this period.[9] With this in mind, and knowing that surgery is the gold standard for treatment of CRC, if imaging suggests a resectable tumour, surgery will be the first-line option.[10] This is particularly true given that postponing treatment can lead to disease progression. Therefore, some case reports recommend aborting the pregnancy, followed by surgical resection.[7,14,15,19] Having said this, cases of colonic resection, including low anterior resection and abdominoperineal resection, have been reported in the first 20 weeks of pregnancy without interfering with the normal pregnancy.[9] On the other hand, pregnancy-related CRC diagnosed after 20 weeks of gestation can be managed by delaying surgery until delivery is an

option in order to save the fetus,[7,14,15,19] keeping in mind the risk of disease progression in view of the proangiogenic state of pregnancy.[10] From here, the balance will be achieving fetal lung maturity and a scheduling delivery between 28 weeks and 32 weeks of gestation.[2,9,10] The patient will then be treated as a non-pregnant individual.[10,14,28]

Moreover, patients presenting with surgical abdomen due to obstructive CRC should be managed as an emergency. Having said this, patients presenting with large bowel obstruction due to CRC early in the course of their pregnancy should be managed surgically.

Surgery includes oncologic surgical resection with two options regarding reconstruction of the gastrointestinal continuity: either by a primary anastomosis or without an anastomosis. On the other hand, patients diagnosed later in pregnancy can be managed by colonic decompression using a loop colostomy, followed by delivery and then an oncologic colorectal resection. For patients with colonic obstruction not requiring urgent surgical intervention, a colonic stent can be used to delay immediate surgery in patients close to term and postpone oncologic surgical resection until after delivery.[29,30]

There may be a need for neoadjuvant chemoradiotherapy, especially considering that a large proportion of patients are diagnosed in an advanced stage because of delays in diagnosis. This also takes into account the fact that 85% of CRC cases diagnosed in pregnancy are anatomically located below the peritoneal reflection,[5,7,9,15] which translates directly to a higher proportion of pregnant patients diagnosed with rectal cancer suitable for neoadjuvant chemoradiotherapy. From here, conflicting data arises regarding neoadjuvant chemotherapy. In fact, some studies proposed that chemotherapy administration during the second and third trimester of pregnancy is safe.[5,7,28] The chemotherapeutic agent of choice for pregnancy-related CRC is 5-fluoruracil (5-FU),[1] especially given that 5-FU is known to have a negligible risk of adverse reproductive outcomes.[31,32] On the contrary, other studies have tackled the risk of spontaneous abortion and teratogenic effect of 5-FU.[5,7,9,15,28] Moreover, oxaliplatin has also been described as being safe.[33] A combined 5-FU, leucovorin, and oxaliplatin (FOLFOX) chemotherapy regimen seems to have been adopted in the management of pregnancy-related CRC. Indeed, there are cases of patients receiving FOLFOX on the 13th week of pregnancy and giving birth to healthy infants.[34] On the other hand, radiotherapy is not advised during pregnancy[7,15,28] because it is associated with lethal damage to the fetus, and may lead to embryonic death, malformation, or growth retardation.[19,28] Furthermore, van Calsteren et al.[35] concluded an overall good outcome of patients diagnosed with cancer during pregnancy, but a high rate of preterm labour induction and consequently a high rate of admission to neonatal intensive care units.[35]

CONCLUSION

Pregnancy-related CRC is a rare event with an expected increasing incidence. This is because more and more women are delaying pregnancy, and also because of the heightened risk of CRC in women older than 40 years of age.[7,32] It appears that there is still much to be studied, especially in the management of this rare entity. Management plans vary widely and pose significant legal, ethical, religious, emotional, and scientific challenges. From here, a tailored patient approach should be adopted by a multidisciplinary team, with accurate diagnosis and prompt treatment as the cornerstone of effective management.

References

1. Kraljević M et al. Obstructing adenocarcinoma of the descending colon in a 31-year-old pregnant woman. Int J Surg Case Rep. 2014;5(12):958-60.
2. Khangura RK et al. Metastatic colorectal cancer resembling severe preeclampsia in pregnancy. Case Rep Obstet Gynecol. 2015;2015:487824.
3. Gabriel I et al. Colon cancer in pregnancy - a difficult diagnosis. Eur J Obstet Gynecol Reprod Biol. 2016;203:340-1.
4. Dahling MT et al. Pregnancy-associated colon and rectal cancer: perinatal and cancer outcomes. J Matern Fetal Neonatal Med. 2009;22(3):204-11.
5. Aytac E et al. Management of colorectal neoplasia during pregnancy and in the postpartum period. World J Gastrointest Oncol. 2016;8(7):550-4.

6. Cruveilhier JJ, Anatomie pathologique du corps humaine (1829) Volume 2, Paris: JB Baillière; 1829, pp.7-10.
7. Yaghoobi M et al. Challenges to diagnosing colorectal cancer during pregnancy. Can Fam Physician. 2009;55(9):881-5.
8. Woods JB et al. Pregnancy complicated by carcinoma of the colon above the rectum. Am J Perinatol. 1992;9(2):102-10.
9. Longo SA et al. Gastrointestinal conditions during pregnancy. Clin Colon Rectal Surg. 2010;23(2):80-9.
10. Bukhari Y et al. Surgical management of rectal cancer in pregnancy. Int J Colorectal Dis. 2012;28:883-4.
11. Khodaverdi S et al. A case of colorectal cancer during pregnancy: a brief review of the literature. Case Rep Obstet Gynecol. 2013;2013:626393.
12. Castresana D et al. Rectal mass in a pregnant patient: how come? Dig Dis Sci. 2015;60(12):3549-51.
13. Ossendorp RR et al. Advanced colorectal cancer resulting in acute bowel obstruction during pregnancy; a case report. Ann Med Surg (Lond). 2016;8:18-20.
14. Dhull AK et al. Exploring signet-ring cells in pregnant female. J Gastrointest Oncol. 2015;6(2):E10-5.
15. Makoshi Z et al. Chemotherapeutic treatment of colorectal cancer in pregnancy: case report. J Med Case Rep. 2015;9:140.
16. Mechery J, Ikhena SE. Cancer of the descending colon during pregnancy. J Obstet Gynaecol. 2007;27(3):311-2.
17. Peccatori FA et al.; ESMO Guidelines Working Group. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(6):vi160-70.
18. Baysinger CL. Imaging during pregnancy. Anesth Analg. 2010;110(3):863-7.
19. Toosi M et al. Rectal cancer in pregnancy: a diagnostic and therapeutic challenge. J Egypt Natl Cancer Inst. 2014;26(3):175-9.
20. Antonelli NM et al. Cancer in pregnancy: a review of the literature. Part I. Obstet Gynecol Surv. 1996;51(2):125-34.
21. Ho MY et al. Colorectal cancer in pregnancy: driven by pregnancy-associated growth factors? J Gastrointest Cancer. 2012;43(Suppl 1):S239-42.
22. Sica V et al. Estrogen and progesterone binding proteins in human colorectal cancer. A preliminary characterization of estradiol receptor. Tumori. 1981;67(4):307-14.
23. Slattery ML et al. Estrogen and progesterone receptors in colon tumors. Am J Clin Pathol. 2000;113(3):364-8.
24. Stedman KE et al. Estrogen receptor proteins in diverse human tumors. Arch Surg. 1980;115(3):244-8.
25. Dawson PM et al. Oestrogen receptors in colorectal carcinoma. J Clin Pathol. 1990;43(2):149-51.
26. Arem H et al. Reproductive and hormonal factors and mortality among women with colorectal cancer in the NIH-AARP Diet and Health Study. Br J Cancer. 2015;113(3):562-8.
27. Giovannucci E et al. Aspirin use and the risk for colorectal cancer and adenoma in male health professionals. Ann Intern Med. 1994;121(4):241-6.
28. Basta P et al. Cancer treatment in pregnant women. Contemp Oncol (Pozn). 2015;19(5):354-60.
29. Healey AJ et al. Colorectal stenting: a bridge to both Caesarean section and elective resection in malignant large-bowel obstruction in pregnancy: a multidisciplinary first. Colorectal Dis. 2011;13(8):e248-9.
30. Alonso-Lázaro N et al. Insertion of selfexpanding metal stent for treatment of malignant obstruction in a pregnant woman. Rev Esp Enferm Dig. 2014;106(3):216-9.
31. Haggar F et al. Maternal and neonatal outcomes in pregnancies following colorectal cancer. Surg Endosc. 2013;27(7):2327-36.
32. Robson DE et al. Synchronous colorectal liver metastases in pregnancy and post-partum: sCRLMs in pregnancy and post-partum. ANZ J Surg. 2015;87(10):800-4.
33. Gensheimer M et al. Administration of oxaliplatin to a pregnant woman with rectal cancer. Cancer Chemother Pharmacol. 2009;63(2):371-3.
34. Jeppesen JB, Østerlind K. Successful twin pregnancy outcome after in utero exposure to FOLFOX for metastatic colon cancer: a case report and review of the literature. Clin Colorectal Cancer. 2011;10(4):348-52.
35. van Calsteren K et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. J Clin Oncol. 2010;28(4):683-9.