Case Report

Colorectal cancer in pregnancy: a case report and literature review

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Abstract: Colorectal cancer (CRC) in pregnancy is rare. The clinical manifestations of CRC during pregnancy are not specific, and diagnosis and treatment pose a significant challenge. Patients are often found to have advanced tumors, and have a poor prognosis. In this case study, the patient was 36 years old, and had no obvious clinical manifestations in the first and second trimesters. Since gestational week 38, she experienced left upper abdominal pain and constipation, with no nausea or vomiting. Imaging examinations revealed malignant tumors of the sigmoid colon (colon cancer was highly suspected), multiple liver metastases, omental metastases, and multiple swollen lymph nodes in the abdominal cavity. After discussion, the patient received lower cesarean section. A large amount of hematochezia with a volume of approximately 1,000 mL occurred 8 days after the operation. In the emergency department, superior and inferior mesenteric angiography was performed, and the inferior mesenteric artery was continuously pumped with pituitrin to stop bleeding. After the condition was stabilized, she underwent surgery for radical sigmoid resection and colon single-cavity fistula. During the operation, light bloody ascites were observed inside the abdominal pelvis, approximately 500 mL, with multiple touchable stiff metastatic nodules in the liver. At the side of the sigmoid mesocolon, a giant tumor of approximately 12 cm diameter was found, continued by the intestinal wall, and the sigmoid mesocolon was almost occupied by the tumor. The mesentery was hard to recognize, with possible movement of the tumor, and no sign of infiltration into the abdominal pelvic wall or adnexa. The surgical pathological stage was Dukes' stage D, which was an advanced tumor. Postoperative radiotherapy and chemotherapy were not performed, and the patient died of systemic multiple organ failure 32 days after colon cancer surgery (postpartum day 43). So for patients with digestive system symptoms during pregnancy, CRC should be considered in differential diagnosis. Auxiliary examinations should be actively carried out to strive early diagnosis and treatment to improve patient prognosis.

Keywords: Colorectal cancer (CRC); pregnancy; case report

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Introduction

The incidence of cancer during pregnancy is approximately 0.07% to 0.1%. In recent years, with the delay of reproductive age and the increased incidence of tumors in young persons, the incidence of malignant tumors during pregnancy has an increasing trend. Colorectal cancer (CRC) during pregnancy is rare, with an incidence rate of approximately 0.002%, or 1 in 13,000 pregnancies (1,2). As of 2015, there have been more than 300 cases of CRC in pregnancy reported worldwide (3). This article reports a case of sigmoid colon cancer diagnosed during pregnancy, combined with a literature review, to discuss the etiology, clinical manifestations, diagnosis, treatment, and prognosis of pregnancy complicated with CRC. Based on the case report, this article emphasizes that attention should be paid to the digestive system symptoms of pregnant patients. With the increased incidence of malignant tumors during

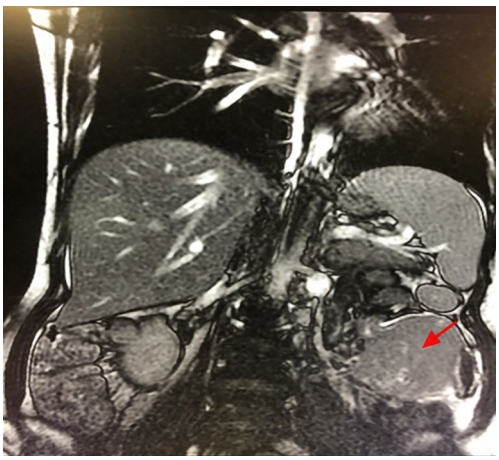

Figure 1 Abdominal MRI examination revealed a mass in the left middle and lower abdomen (indicated by the red arrow), which was highly suspected of being malignant.

pregnancy, the possibility of pregnancy complicated with digestive system tumors should be considered in the clinical differential diagnosis. Auxiliary examinations should be actively carried out to strive early diagnosis and treatment to improve patient prognosis.

We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/jgo-21-31).

Case presentation

A 36-year-old patient was admitted to hospital on October 26th, 2017 for left upper abdominal pain which had persisted for 4 days. She was 38 weeks and 5 days pregnant, and the pregnancy period was smooth. Four days ago, there was pain in her upper left abdomen with no obvious cause. There was no nausea, vomiting, or fever, though the patient experienced constipation and exhaust. Blood leucocyte levels were 12.99×10^9/L, C-reactive protein was 20 mg/L, and biochemical and coagulation functions were approximately normal. Tumor markers were increased, including carcinoembryonic antigen (CEA) 89.58 ng/mL (0–5 ng/mL), cancer antigen 15-3 (CA 15-3) 148.60 U/mL (0–31 U/mL), CA-125 104.50 U/mL (0–35 U/mL), CA 19-9 1957.00 U/mL (0–35 U/mL), CYFRA 21-1 12.6 ng/mL (0–3.3 ng/mL), neuron-specific enolase (NSE) 45.6 ng/mL (0–18 ng/mL), squamous cell carcinoma (SCC) antigen 4.04 ng/mL (0–1.5 ng/mL), while alpha-fetoprotein (AFP) was normal. B-type ultrasonography showed multiple hypoechoic nodules inside the liver. The biggest one was in the left liver, approximately 3.4 cm × 2.5 cm, while the one in the right liver was approximately 5.7 cm × 5.2 cm. Both boundaries were clear and regular, and blood flow signs could be seen inside. MRI examination suggested multiple masses inside the liver, with the possibility of metastatic disease. A mass in the lower left abdomen was found, which had a high possibility of being malignant (*Figure 1*). After discussion, the patient received lower cesarean section on October 30th, 2017. The operation was smooth. Four days after surgery, the patient was discharged and was advised to have a surgical visit. Four days later, she experienced hematochezia with blood clots, with a volume of approximately 1,000 mL, along with dizziness. The patient visited our hospital emergency. Rehydration and anti-shock treatment were performed. Chest CT showed scattered double lung nodule shadows, suggestive of potential metastatic disease. Abdominal pelvic enhanced CT firstly showed a sigmoid malignancy (colon cancer?), and after three-dimensional reconstruction of the lesion blood supply from the superior mesenteric artery, the lower lesions of the sigmoid and rectum showed a huge amount of clots. Secondly, around the root of the lower mesenteric artery, retroperitoneum gap, and portacaval gap, multiple enlarged lymph nodes were observed, along with necrosis, suggesting possible metastasis. Third, the liver had multiple metastatic tumors, and additionally, a highly dense greater omentum, which appeared to have nodules, open to planting metastasis. Emergency arterial angiography of the superior and lower mesenteric artery was performed in the interventional room, and hemostasis treatment was also performed by continuously pumping pituitrin to the lower mesenteric artery (*Figure 2*). Twelve hours later, the patient's condition was stable, and she was transferred to the surgical ward. After active improvement, the preoperative preparation was followed by laparotomy on November 9th, 2017. During the operation, light bloody ascites were observed inside the abdominal pelvis, approximately 500 mL, with multiple touchable stiff metastatic nodules in the liver. At the side of the sigmoid mesocolon, a giant tumor of approximately 12 cm diameter was found, continued by the intestinal wall, and the sigmoid mesocolon was almost occupied by the tumor. The mesentery was hard to recognize, with possible movement of the tumor, and no sign of infiltration into the abdominal pelvic wall or adnexa. The patient underwent surgery for radical sigmoid resection and colon single-cavity fistula. Postoperative pathology confirmed a sigmoid colon malignant tumor, with low

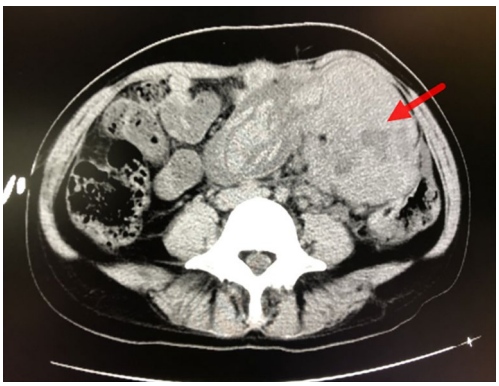

Figure 2 Enhanced CT examination of the abdomen and pelvis revealed a malignant tumor of the sigmoid colon (colon cancer?) (indicated by the red arrow).

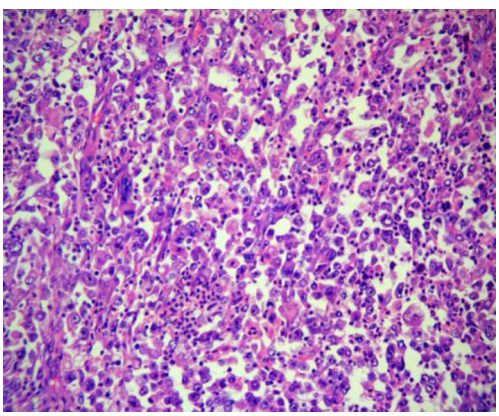

Figure 3 Postoperative pathological examination revealed a poorly differentiated carcinoma of the sigmoid colon. The tumor cells showed diffuse and infiltrating growth, the cells were highly atypical, and a large number of inflammatory cells infiltrated around the tissue. HE ×200.

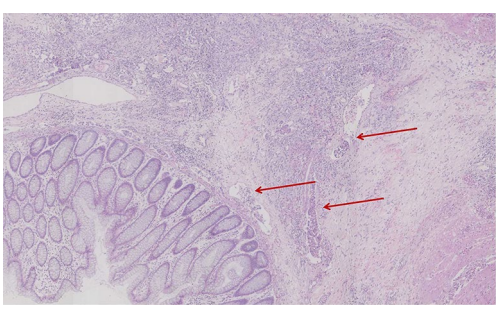

Figure 4 Vascular tumor thrombus could be seen (indicated by the red arrows). HE ×200.

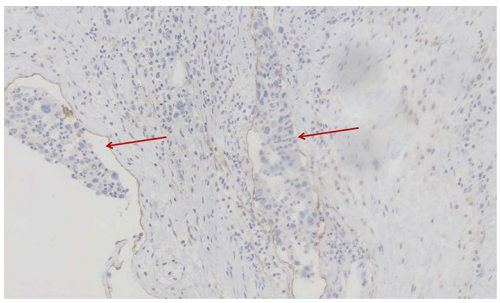

Figure 5 Lymphatic tumor thrombus could be seen (indicated by the red arrows). HE ×200.

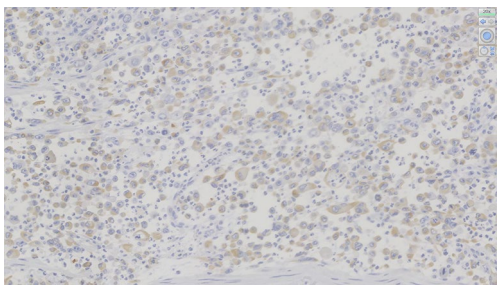

Figure 6 Immunohistochemistry showed CK positive expression (×200).

differentiation (*Figure 3*). The cancer penetrated the serous layer. Tumor thrombosis was seen in the vein (*Figures 4,5*). No cancer residues were found at the end of the operative part on both sides. A total of 9/10 mesenteric lymph nodes were found to be metastatic. The immunohistochemistry results were as follows: CK part +, vimentin part +, CK-H partial weak +, CK-L part +, DOG-1 focal +, CD117–, CD34–, CK 5/6–, p63–, D2-40–, CD31–, MyoD1–, desmin–, CK20–, EMA–, HMB45–, MalanA–, S-100–, CD3–, CD20–, CD30–, hepatocyte–, GPC3–, TTF-1 (liver) –, Ki-67 index (approximately 80%), ER–, PR–, p53–, c-erbB-2–, MSH2+, MSH6+, PMS2+, and MLH1+ (*Figures 6-10*). In situ hybridization showed that tissues were EBER-. After the operation, the patient was given antibiotic and nutrition support treatment. The patient experienced intermittent fever of 38.3–38.7 ℃ after the surgery. Blood leukocytes were significantly elevated, and on the 25th day after surgery, blood leukocytes reached 37.58×10^{9}/L. The patient was transferred to the tumor hospital for further treatment. On the 32nd day after surgery (the 43rd day after childbirth), the patient died due to multiple

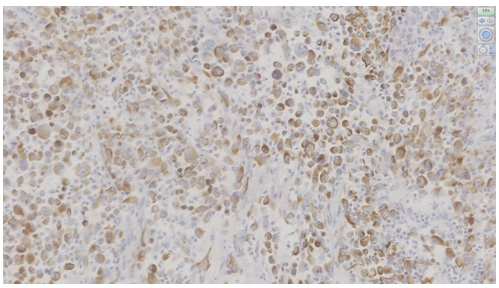

Figure 7 Immunohistochemistry showed CK-L positive expression (×200).

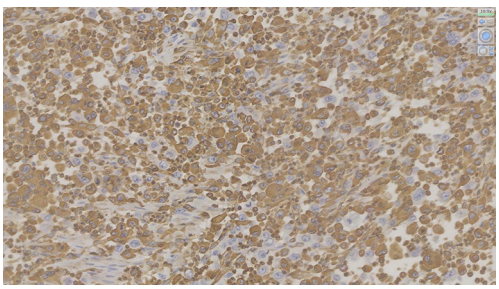

Figure 8 Immunohistochemistry showed vimentin positive expression (×200).

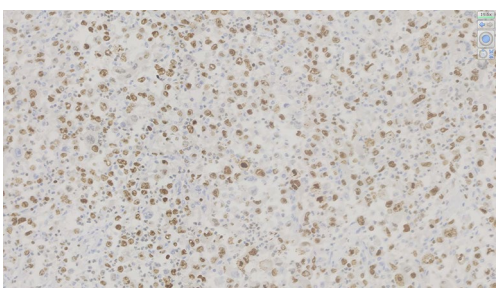

Figure 9 Immunohistochemistry showed Ki-67 positive expression (×200).

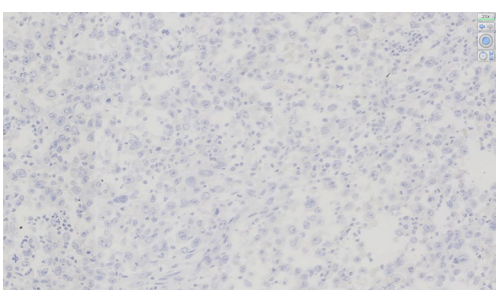

Figure 10 Immunohistochemistry showed MyoD1 negative (×200).

metastasis of the tumor and systemic multiple organ failure. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Discussion

CRC during pregnancy is rare. According to the literature, the median age of patients with CRC during pregnancy is 31 years (range from 16 to 48 years old) (1). Most tumors are located in the rectum or sigmoid colon, and most patients are already at an advanced stage when they are diagnosed. Furthermore, 60% of tumors are Dukes' C stage and above (4,5).

The cause of CRC in pregnancy is not yet clear, though 23% of patients have a family history. The predisposing factors include hereditary non-polyposis CRC (such as Lynch syndrome), familial colon adenoma, Gardner syndrome, Peutz-Jeghers syndrome, and chronic inflammatory bowel disease. However, patients with high-risk factors account for only a small proportion of CRC patients during pregnancy (6). Girard *et al.* (7) investigated 19 patients with CRC during pregnancy, and only 4 patients had strong susceptibility factors. Therefore, clinicians should pay attention to predisposing factors and family history for suspected patients. The patient in this case report had no family history or predisposing factors after repeated questioning.

Common clinical manifestations of CRC during pregnancy include nausea, vomiting, abdominal pain, constipation, anemia, and rectal bleeding (2). Nausea and vomiting are also common during pregnancy, especially during the first trimester. Gastrointestinal symptoms such as abdominal pain and constipation are common complaints during pregnancy, which are mostly thought to be related to physiological changes, such as slow bowel movements during pregnancy and increased uterine compression. Anemia during pregnancy can mask the bleeding symptoms caused by the tumor. Hemorrhoids and anal fissures are common causes of rectal bleeding during pregnancy. Although some pregnant women lose weight in the first trimester, overall, weight during the entire pregnancy increases. Pregnancy status can confuse weight loss secondary to tumors in the second and third trimester. Therefore, it is precisely because of these non-specific

symptoms that most patients with CRC are often missed during pregnancy and are not diagnosed until the third trimester. Patients often have a poor prognosis. This patient was young and only 36 years old. There were no obvious clinical manifestations during early and middle pregnancy. The left upper abdominal pain and constipation occurred at 38 weeks of gestation. There was no nausea or vomiting, and the clinical symptoms were also atypical.

The diagnosis and staging of tumors during pregnancy are challenging. Most patients with CRC in pregnancy are diagnosed after 20 weeks of gestation, and the prognosis is poor. Most patients have metastases when tumors are discovered, and are staged as Dukes' C and D. Bernstein *et al.* (4) studied 39 CRC patients during pregnancy and found that 41% (16 cases) were in stage B, 44% (17 cases) were in stage C, 15% (6 cases) were in stage D, and none were in stage A. According to the surgical pathological staging, the patient in this report was Dukes' stage D, which was an advanced tumor.

The difficulty of diagnosis is how to distinguish common symptoms during pregnancy which are normal, with those related to tumors, so as to achieve early diagnosis. During pregnancy, patients with complaints of abdominal pain should undergo a detailed abdominal physical examination. Some patients may have abdominal masses. Auxiliary examinations such as X-ray, ultrasound, sigmoidoscopy, and MRI are relatively safe during pregnancy, while CT, barium enema, and radioisotope scanning may have adverse effects on the fetus due to ionizing radiation (3). Colonoscopy and biopsy are the gold standards for diagnosing CRC. For patients with suspected CRC during pregnancy, a gentle rectal sigmoidoscopy can be considered, preferably after the second trimester. Abdominal ultrasound has low accuracy for detecting colon and rectal masses, but is helpful for detecting liver metastases. The sensitivity of ultrasound for detecting large metastatic lesions in the abdominal cavity is approximately 75% (1). CT is conducive to the detection of local lesions and distant metastases of CRC, and is very useful for planning surgery and radiotherapy. However, due to radiation-related teratogenicity and carcinogenicity, abdominal CT examination in early pregnancy is contraindicated (8). MRI examination during pregnancy is safer than CT and can effectively assess pelvic and abdominal cavity lesions (1).

In this case, the patient went to the doctor because of abdominal pain and constipation. Abdominal ultrasound showed that there were multiple hypoechoic nodules in the liver, which grew rapidly. Tumor markers including CEA, CA 15-3, CA-125, and CA 19-9 were significantly higher than normal. The possibility of malignant tumors was not excluded. Further abdominal MRI examination revealed multiple tumors in the liver, possibly metastases, and there were masses in the left middle and lower abdomen, which were potentially malignant. Based on the results of auxiliary examinations, intestinal tumor with liver metastasis was clinically suspected. With the delay of reproductive age and the trend of younger tumor patients, the incidence of malignant tumor during pregnancy is gradually increasing. For patients with digestive system symptoms during pregnancy, blood and imaging examinations should be actively performed for differential diagnosis. This patient's symptoms are atypical, with the chief complaint were just pain in the upper left abdomen and constipation. After performing the ultrasound and MRI, combined with the elevated blood tumor markers, intestinal tumor with multiple metastasis was suspected.

There is no recognized standard treatment for CRC in pregnancy. Treatment methods include surgery, radiotherapy, and chemotherapy. When formulating a treatment plan, gestational age, tumor location, stage, presence of complications, and the patient's wishes need to be taken into consideration. Generally speaking, if treatment for CRC found within 20 weeks of pregnancy is delayed, tumor progression may occur, endangering the mother's life. Therefore, surgery is recommended after termination of pregnancy to prevent obvious disease progression in the third trimester. CRC discovered after 20 weeks of gestation can be delayed to 32 weeks of gestation after informed consent, as the fetal lungs have developed and matured, which ensures that the fetus may survive (8). The choice of delivery method is based on the presence or absence of obstruction of the birth canal and obstetric indications. The tumor itself is not an indication for cesarean section. When a CRC patient undergoes a cesarean section, surgical treatment can be performed at the same time during the cesarean section, or it can be performed a few weeks after the uterus regenerates and the pelvic congestion improves (3,9). All conservative treatments and delayed surgery must be fully communicated with patients and their families to inform them of the possibility of disease progression. In this case, the patient was diagnosed with an advanced tumor at the time of diagnosis, and 8 days after cesarean section, there was a large amount of blood in the stool, approximately 1,000 mL. Upper and lower mesenteric angiography was performed in the emergency department and the inferior mesenteric artery

was continuously pumped with pituitrin to stop bleeding. After stabilization, the patient was transferred to the surgical ward for radical sigmoid colectomy and single-lumen fistula of the descending colon. The general condition of the patient postoperatively was poor, and radiotherapy and chemotherapy were not performed. Because of the obvious pelvic congestion during the puerperium, there may be more bleeding loss during the CRC surgery. Therefore, if the patient's condition is stable, surgical treatment for CRC maybe preferred after the puerperium.

Most CRCs are found during the second trimester of pregnancy, and the prognosis is poor. Therefore, most patients require neoadjuvant radiotherapy and chemotherapy before surgery. Chemotherapy during pregnancy should be carried out after weighing up the pros and cons. Due to teratogenicity, it should be avoided in the first trimester. It is reported in the literature that chemotherapy in the middle and late stages of pregnancy is relatively safe and has no obvious adverse effects on the mother and child in the short term. Possible complications include fetal growth restriction and premature delivery. When the condition permits, most researchers recommend postpartum chemotherapy (9,10). For advanced and metastatic CRC, FOLFOX [oxaliplatin, leucovorin, and 5-fluorouracil (5-FU)] regimen chemotherapy is recommended.. Application of 5-FU in early pregnancy can cause fetal malformations, with a rate of 14–19%. When 5-FU chemotherapy is applied in middle and late pregnancy, the incidence of fetal malformations is reduced to 1.3% (3). Gensheimer *et al.* (11-13) reported that the FOLFOX regimen was used to treat 3 cases of CRC during pregnancy at gestational weeks 13–24. The follow-up period was 11.75 months to 3.5 years. All the children's heights, weights, and nervous system development were within the normal range. Cisplatin and its derivatives are also often used in the treatment of CRC, but are not recommended for pregnant and lactating women, and oxaliplatin is not a first-line drug due to neurotoxicity (14). Pelvic radiotherapy during pregnancy is often fatal to the fetus. During embryonic organ formation, radiotherapy is contraindicated. Radiotherapy can be considered for tumors far away from the uterus. When the tumor is located in the pelvic cavity, radiotherapy can cause serious or even fatal damage to the fetus. At this time, radiotherapy is recommended after delivery or termination of pregnancy. In recent years, some researchers have used angiogenesis inhibitors for the treatment of advanced metastatic CRC. Bevacizumab is a human monoclonal antibody against vascular endothelial growth factor (VEGF), and is the first Food and Drug Administration (FDA) approved angiogenesis inhibitor. Bevacizumab combination chemotherapy for advanced metastatic CRC has achieved a good therapeutic effect in clinical research results, but its safety and effectiveness in pregnant patients require further evaluation (15,16).

The overall prognosis of CRC during pregnancy is poor. Chan *et al.* (17) followed up 42 CRC patients, who had a median survival time of less than 5 months, and most patients died within 1 year of diagnosis. Khodaverdi *et al.* reported a pregnant patient with CRC who underwent partial bowel resection 40 days after cesarean section. The postoperative pathology was Dukes' stage IIa, and the patient underwent adjuvant chemotherapy after surgery. The patient was followed up for 7 months and was found to have survived (2). Gensheimer *et al.* reported a case of CRC found at 12 weeks of gestation. Due to early detection, the tumor did not spread. The mother had a good outcome, and had no remission after 1 year follow-up (11). Therefore, patients with early tumors can have a good prognosis. The patient in this case study was diagnosed at 38 weeks of gestation. She was diagnosed with advanced sigmoid colon cancer, with extensive liver and abdominal metastasis. During the puerperium, acute massive blood in stool was occurred 11 days after cesarean section. So emergency interventional hemostasis surgery was carried out and radical sigmoid colectomy was performed subsequently. The patient was weak. The general condition of the patient postoperatively was poor, with fever and significantly elevated white blood cells. She died of multiple organ failure 32 days after surgery (43 days after childbirth).

Conclusions

In summary, the clinical manifestations of CRC during pregnancy are not specific, and diagnosis and treatment pose a significant challenge. Patients are often found to have advanced tumors, and have a poor prognosis. Therefore, clinicians should strive for early diagnosis to improve patient prognosis. For high-risk groups with predisposing factors and family history, tumor screening is feasible before planning a pregnancy.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/jgo-21-31

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-21-31). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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