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# Carcionoid of the appendix in pregnant woman – case report and literature review

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**Abstract**

Neuroendocrine neoplasms are detected very rarely in pregnant women. The following is a case report of carcinoid tumor of the appendix diagnosed in 28 year-old woman at 25th week of gestation. The woman delivered spontaneously a healthy baby at the 38th week of gestation. She did not require adjuvant therapy with somatostatin analogues. The patient remained in remission. There are not established standards of care due to the very rare incidence of carcinoid tumors in pregnancy. A review of the literature related to management and prognosis in such cases was done.

**Abbreviations:**

| | |
|---|---|
| NET | - Neuroendocrine tumor |
| 5-HIAA | - 5-Hydroxyindoleacetic acid |
| CRP | - C-reactive protein |
| MRI | - Magnetic resonance imaging |
| Ca-19.9 | - Cancer antigen 19.9 |
| CEA | - Carcinoembryonic antigen |
| LDH | - Lactate dehydrogenase |
| TGF-alpha | - Transforming growth factor-alpha |
| ICU | - Intensive care unit |
| Anti-TPO | - Anti-thyroperoxidase antibodies |
| Anti-TG | - Anti-thyroglobulin antibodies |
| PET/CT | - Positron emission tomography–computed tomography |
| SPECT | - Single-photon emission computed tomography |
| SRS | - Somatostatin receptor scintigraphy |

## INTRODUCTION

The incidence of malignant neoplasms during pregnancy is estimated at 1:1000–1:2000 (Williams & Turnbull 1964; Pavlidis 2002; Smith *et al.* 2003). Cervical and breast cancers are the most commonly diagnosed malignancies in pregnant women (Pavlidis 2002). Due to the fact that gastrointestinal tumors affect mostly elderly women, the incidence of these tumors during pregnancy is decidedly lower. Colorectal cancer, the most common gastrointestinal malignancy in women, occurs in 1/13,000 pregnancies (Pavlidis 2002). There is no data in the literature on the incidence of appendiceal malignancies during pregnancy.

Appendiceal malignancies constitute approximately 0.5% of all gastrointestinal neoplasms (Hesketh 1963). Approximately 50% of malignant appendiceal lesions are neuroendocrine tumors (NETs), which derive from cells of the neuroendocrine system diffusely distributed in the digestive system and lungs. The prevalence of NETs in resected vermiform appendices is estimated at 0.3–0.9% (Moertel *et al.* 1968; Goede et. al. 2003; Iwuagwu *et al.* 2005), with carcinoid of the appen-

CASE REPORT

dix being the most commonly diagnosed tumor, typically well differentiated and benign. Active hormonal changes may lead to clinical manifestations, which are mainly due to high serotonin levels. The most common manifestations of carcinoid syndrome include hot flushes, diarrhea, abdominal pain, and transient bronchospasm, with its most common complication: right heart valvular fibrosis (carcinoid heart valve disease or Hedinger's syndrome), which leads to right heart failure. Carcinoid syndrome itself, as long as the patient does not develop heart failure, does not affect the patient's prognosis. One malignant tumor associated with poor prognosis is goblet-cell carcinoid or goblet-cell carcinoma, which is hormonally inert, and most commonly metastasizes to the ovaries, liver, and peritoneum.

The key blood chemistry parameter in NET diagnostics is chromogranin A, as this is a sensitive, though nonspecific, marker. One specific marker of NET is the level of the serotonin metabolite 5-hydroxyinoloacetic acid (5-HIAA) in a 24-hour urine collection sample. This assessment is conducted twice.

Surgery is the treatment of choice in the case of appendiceal NETs. Tumors measuring <2 cm in diameter, with no mesenteric infiltration, can be successfully treated with a simple appendectomy. In the case of uncertainty as to the necessary extent of the procedure, the presence of deep infiltration, tumors exceeding 2cm in diameter, poorly differentiated tumors, or regional lymph node involvement – right hemicolectomy is the established procedure.

Below, we presented the case of a 28-year-old woman diagnosed with appendiceal carcinoid during her pregnancy. The case report includes patient management following histopathological diagnosis. We also reviewed the relevant literature to help present the issue of management in pregnant women with such a rare diagnosis.

## CASE REPORT

A 28-year-old woman (gravida 2, para 2) presented to the emergency department at 25$^{th}$ week of pregnancy with nausea and abdominal pain in the right lower quadrant. Physical examination findings: 2-cm-long cervix, fundal height 1 fingerbreadth above the navel, fetal heart rate approx. 140 bpm, and slight tenderness in the right lower quadrant. There were no peritoneal signs; bowel sounds were normal. An abdominal ultrasound examination revealed no abnormalities; the uterine cavity contained a live fetus. The vermiform appendix was not visualized. Laboratory test findings: CRP 11.9 mg/L, complete blood count – within normal limits. The patient was admitted to a surgery department for observation. Fluid therapy and spasmolytics were initiated. The patient's symptoms aggravated on the second day of hospitalization. Follow-up blood tests showed elevated inflammatory markers and slight anemization. Due to suspected acute appendicitis, the patient was qualified to undergo surgical treatment. The appendix was excised in a typical fashion. There were no complications in the mother or the fetus during the procedure or in the postoperative period.

A postoperative histopathological examination revealed evidence of acute gangrenous appendicitis and the presence of a pale yellow lesion measuring 12×18 mm in the middle appendiceal section, which was consistent with well differentiated (G1) pT1b carcinoid. Tumor cells showed expression of chromogranin A and synaptophysin. Mitotic index Ki 67 was <1%. The tumor infiltrated the whole thickness of the appendiceal wall, but did not exceed the serosa. The surgical margin was negative.

In the 29$^{th}$ week of pregnancy, the patient presented to the Gynecological Oncology Outpatient clinic of 1$^{st}$ Department of Obstetrics and Gynecology, Medical University of Warsaw to receive a consultation and plan further treatment. Physical examination revealed the patient to be in good general condition, with no symptoms typical for carcinoid syndrome; the cervix was not effaced, 2 cm thick, fundal height at four fingerbreadths above the navel, fetal heart rate approx. 140 bpm. The previous histopathological samples were sent for re-examination at a reference center, which led to a confirmation of the earlier diagnosis. The patient was scheduled to undergo magnetic resonance imaging (MRI) of the abdomen and lesser pelvis. The MRI scans showed no abnormalities. The right ureter was shown to be dilated due to its compression by the pregnant uterus. The patient was referred to the Endocrinology Department for further diagnostics. Laboratory tests showed normal levels of serum chromogranin A and normal levels of 5-HIAA in 24-hour urine collection. An ultrasound examination of the thyroid gland and abdomen revealed no abnormalities. Due to negative laboratory test findings, a lack of clinical manifestations, and normal imaging study results, the patient did not qualify to receive somatostatin analogs.

Spontaneous, regular uterine contractions occurred in the 38$^{th}$ week of pregnancy. The patient gave birth via vaginal delivery to a live female newborn weighing 3,500 g, with the Apgar score of 10. A pelvic examination conducted during a follow-up visit six weeks after delivery revealed no abnormalities. Three months after delivery, the woman was re-admitted to the Endocrinology Department to undergo total body scan and SPECT scans of the head, chest, abdomen, and lesser pelvis. No foci of abnormally increased radiotracer uptake were detected, which would have indicated the presence of somatostatin receptors. Moreover, serum TSH, anti-TPO and anti-TG antibody levels were normal. An ultrasound examination of the thyroid and the abdominal cavity revealed no abnormalities either.

A year later, a PET/CT scan was conducted to detect somatostatin receptors. The scans revealed tracer accumulation at the level of the head of the pancreas, which was consistent with a variation of the physiological uptake pattern. The levels of cancer markers

were normal: CA-19.9 at 1.8 IU/mL, CEA at 2.23 ng/mL, and LDH at 143 U/L. The patient remained under follow-up.

## DISCUSSION

Neuroendocrine tumors during pregnancy are a rare clinical occurrence. The most common location of carcinoids in pregnant women is the vermiform appendix. The co-occurrence of appendiceal carcinoid and pregnancy was first described by Banner *et al.* (1945). Two pregnant women underwent appendectomy due to acute appendicitis. Microscopic examination of the resected appendices revealed carcinoid. The subsequent course of both pregnancies was unremarkable; they both ended in vaginal deliveries.

The most common location of carcinoid in the general population is the gastrointestinal tract (54.5%) and the respiratory system (30.1%). Much less common locations include the pancreas (2.3%), ovaries (1.2%), and bile ducts (1.1%). Gastrointestinal tract carcinoids are most common in the small intestine (44.7%). They have been also detected in the rectum (19.6%), appendix (16.7%), colon (16.7%), and stomach (7.2%) (Maggard *et al.* 2004).

One out of ten people diagnosed with carcinoid, irrespective of its location, exhibits carcinoid syndrome manifestations (Godwin 1975; Moertel *et al.* 1961). At the time of diagnosis, our patient had no such manifestations; albeit, they tend to be decidedly more common in the case of carcinoids with an unfavorable course and the presence of metastases. In such situations, approximately 20–30% patients exhibit manifestations. Metastases to the liver are unquestionably the most common cause of manifestations characteristic for carcinoid syndrome (Ahmed *et al.* 2009; Pape *et al.* 2004) . In the case of appendiceal carcinoids metastases are very rare (Goede *et al.* 2003; Druce *et al.* 2010; Groth *et al.* 2011). Although non-specific abdominal pain is the most common symptom of gastrointestinal tract carcinoids, in the case of our patient it was most likely due to acute inflammation. Appendiceal carcinoid tumors are characterized by their ability to produce TGF-alpha, which stimulates proliferation of myocytes and S-100 nerve cells. As a result of increased cellular proliferation the wall of the appendix thickens, which leads to appendiceal obstruction, and – ultimately – inflammation.

Like in the general population, the second most common carcinoid location in pregnant women is the respiratory system. Those carcinoids are characterized by a rapid clinical course. Massive hemoptysis requiring urgent bronchoscopy and hospitalization at an ICU has been reported in three pregnant women with bronchial carcinoid (Binesh *et al.* 2013; Chhajed *et al.* 2011; Cornell *et al.* 2010).

There have been 5 cases of ovarian carcinoid during pregnancy reported in the literature (Hoch *et al.* 1971; Dombrowski *et al.* 1986; Strittmatter *et al.* 1992; Basham *et al.* 2000; Yamaguchi *et al.* 2013). Primary ovarian carcinoid constitutes approximately 0.3% of all carcinoid cases and only approximately 0.1% of all ovarian neoplasms. It is a component of 3 out of 4 mature teratomas, typically with a benign course and good prognosis. Of note is the fact that approximately 1/4–1/3 of those patients develop carcinoid syndrome. One of the 5 reports mentioned above described a pregnant woman diagnosed with a mixed type of the disease – adenocarcinoid – composed of carcinoid and adenocarcinoma tissue. The four remaining patients had benign carcinoids.

Primary ovarian carcinoids are often detected incidentally during routine sonographic examinations during pregnancy. They may have similar presentation to that of other ovarian tumors, which may be due to endocrine function of those tumors. Unlike typical gastrointestinal carcinoid tumors which derive from the midgut, strumal carcinoids derive from the foregut and hindgut. This has pertinent clinical implications, since carcinoid syndrome manifestations are typical for tumors that derive from the midgut. In other cases, different substances may be secreted, e.g. neuropeptide Y, which may lead to a dissimilar presentation than that of a typical carcinoid syndrome. It is exactly this substance that caused severe constipation in one of the reported cases of ovarian carcinoid. That patient underwent laparoscopic adnexectomy, including the tumor. The subsequent course of the pregnancy was unremarkable and a healthy baby was born. Studies in mice demonstrated that neuropeptide Y may cause neural tube defects. However, this was not the case in the patient described above.

In the case of the patient with adenocarcinoid, the tumor was detected in the left adnexa in the first weeks of pregnancy. Due to tumor enlargement, the patient was qualified for surgical resection. The left adnexa were excised via laparotomy at week 20 of pregnancy. Intraoperative examination revealed ovarian adenocarcinoma and, consequently, the extent of surgery was increased to include lymph node removal, omentectomy, and peritoneal biopsy. It was only in the final examination of tissue samples that the diagnosis of ovarian adenocarcinoid was established. The anatomical changes in the lesser pelvis and abdominal cavity associated with uterine enlargement during pregnancy considerably limit both physical examinations and imaging studies conducted in pregnant women. A transposed and compressed tumor-affected appendix may be inaccessible via rectal exam and invisible in an ultrasound examination. In up to 97% of cases the appendix cannot be visualized via ultrasound examination in women in their second and third trimester of pregnancy. Nonetheless, due to their high safety profile, ultrasound examinations are the only routine imaging studies conducted during pregnancy. Apart from the challenge mentioned above, another considerable limitation of ultrasound examination is inability to differ-

entiate between appendicitis and appendiceal tumor as well as to visualize a tumor in an inflamed appendix. According to American College of Radiology any discrepancies between a pregnant patient's clinical presentation and sonographic findings in the case of suspected appendicitis/appendiceal tumor are an indication for magnetic resonance imaging (Smith *et al.* 2013).

After the end of pregnancy, our patient was evaluated for neoplastic disease via total body scan, SPECT, and PET/CT scans. No pathological radiotracer accumulation was detected. NETs are characterized by somatostatin receptor overexpression. Somatostatin receptor scintigraphy (SRS) involving the use of radiolabeled somatostatin analogs to identify the relevant receptors is a standard imaging study in this type of tumors and is the fundamental diagnostic assessment for diagnosis and staging (Caplin *et al.* 1998; Plöckinger *et al.* 2004; Ramage *et al.* 2005; Cwikla *et al.* 2007). Somatostatin receptor mapping is also the objective of PET/CT scanning, a technique characterized by a higher resolution due to the use of somatostatin analogs labeled with positron-emitting radionuclides.

In the case presented here, the appendix was excised with a standard technique and this was a sufficient extent of surgery. In the case of appendiceal tumors exceeding 20 mm, the extent of surgery should be increased (Pape *et al.* 2012). There have been three case reports of pregnant women whose surgery had to be expanded due to the size of the carcinoid tumor. Two of those patients underwent right hemicolectomy (Korkontzelos *et al.* 2005; Louzi *et al.* 2006) and one underwent ilieocecal resection (Syracuse *et al.* 1979). However, in most cases the removal of the affected appendix alone was a sufficient treatment. Moreover, there have been three cases of appendiceal carcinoid diagnosed in an appendix resected during a Cesarean section due to its abnormal appearance. Because of a characteristic macroscopic appearance of carcinoid, with its dense texture, yellowish color, and irregular shape caused by desmoplastic reaction of the mesentery, routine inspection of the appendix during a Cesarean section has been recommended (Syracuse *et al.* 1979; Gökaslan *et al.* 2002).

Since carcinoids in pregnant women are very rare, it is difficult to assess the effect of the tumor on the course of pregnancy. It is not necessary to perform a Cesarean section in a pregnant woman who underwent surgery during her pregnancy due to carcinoid. Our patient gave birth via a spontaneous, term, vaginal delivery. In all cases of pregnant women diagnosed with carcinoid reported in the literature, Cesarean sections were performed only due to obstetric indications.

Apart from one child, who was diagnosed with a genetic syndrome after its birth, all newborns were in good general condition. No definitely unfavorable effects of carcinoid on fetal development have been observed. Although such effects may occur in pregnant women with disseminated disease, a vast majority of appendiceal carcinoid tumors in pregnant women are small, localized lesions.

Studies in various animal models demonstrated unfavorable effects of high serotonin levels on fetal development. This may be due to the effects of serotonin on uterine arteries, the placenta, and myometrium. Serotonin causes vascular constriction and myometrial contraction, which leads to reduced oxygen and nutrient supply to the fetus. This may result in fetal death, intrauterine growth restriction, or severe congenital defects involving primarily the eyes and limbs (Poulson *et al.* 1963).

It is disadvantageous to have a woman in labor with concomitant carcinoid who exhibits symptoms of carcinoid syndrome. Both anesthetic agent administration and Cesarean section are associated with the risk of carcinoid crisis, which is life-threatening both for the mother and the fetus. In the case of carcinoid crisis, the treatment of choice is octreotide, a synthetic somatostatin analog.

Octreotide crosses the placental barrier via passive diffusion. There is very limited data on the safety of its use in pregnant women. Octreotide may, theoretically, cause pituitary hypoplasia in the fetus; however, follow-up studies in the children of women who received this drug over the course of their pregnancies show no abnormalities. Detailed guidelines on octreotide treatment can be found in the Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system (Oberg *et al.* 2004). Main indications for treatment initiation are clinical manifestations of carcinoid or the presence of metastases despite a lack of symptoms. Our patient did not meet these criteria and, thus, was not qualified to receive octreotide treatment.

The available literature contains three case reports on deliveries by pregnant women with carcinoid syndrome. These patients gave birth under epidural anesthesia, with continuous intra-arterial blood pressure monitoring. One of the women received a continuous intravenous octreotide infusion (Woo *et al.* 2009; Le *et al.* 2009).

In summary, appendiceal carcinoid, which is a type of a NET, is a rare diagnosis in pregnant women. The case of carcinoid during pregnancy presented here is the 29$^{th}$ report published in the literature. Anatomical changes occurring during pregnancy and the nonspecific nature of carcinoid symptoms make diagnosing these tumors difficult. Like in the case presented here, most of the appendiceal carcinoid tumors described in the literature were small, with no metastases, and required no extensive intestinal resection, and had no adverse effects on the fetus, course of pregnancy, or delivery.

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