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A Multidisciplinary Approach to Managing Carcinoid Syndrome in Pregnant Women: Ensuring Maternal and Fetal Safety Trough Interdisciplinary Collaboration

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Abstract

Neuroendocrine tumors (NET) are rare, but their incidence is on the rise, especially among young patients, notably women of reproductive age. These tumors can be localized in various areas and can be grouped as gastrointestinal (GEP) (48%), pulmonary (25%), pancreatic (9%), bronchial, thymic, pituitary, renal, and ovarian NETs, and other localizations. This paper presents the case of a 40-year-old pregnant woman diagnosed with NET NET G1 right lower lobe lung neuroendocrine tumor (typical carcinoid, Ki 67 1%), with bronchiectasis and area of atelectasis and secondary hepatic, pulmonary, and possibly lymph node determinations. The diagnosis was initially established seven years ago upon detection of secondary hepatic lesions. The patient received treatment with somatostatin analog every 4 weeks during pregnancy, starting at 28 weeks of gestation. She gave birth by elective cesarean section in week 37 to a healthy baby. The safety profile of SSAs during pregnancy is still controversial. By presenting this case, we underscore the crucial role of a multidisciplinary team, such as endocrinology, obstetrics-gynecology, surgery, and oncology, in ensuring appropriate therapeutic management based on tumor localization, staging, and grade, the severity of symptoms, and selecting treatment options that minimally impact pregnancy.

Keywords: neuroendocrine tumor, pregnancy, octreotide, somatostatin analogue, carcinoid syndrome

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INTRODUCTION

Neuroendocrine tumors (NET) are rare, but their incidence is on the rise, especially among young patients, notably women of reproductive age. (1) This increasing prevalence is a significant trend that medical professionals must be aware of, including oncologists, obstetricians, and endocrinologists.

NETs are a heterogeneous group of tumors originating in the diffuse neuroendocrine system. (1, 2) They are uncommon during pregnancy.[1,2] These tumors can be localized in various areas and can be grouped as gastrointestinal (GEP) (48%), pulmonary (25%), pancreatic (9%), bronchial, thymic, pituitary, renal, and ovarian NETs, and other localizations.[1,3,4,5] They can be classified into functional tumors, which secrete hormones associated with specific syndromes, and non-functional tumors, which do not secrete hormones and lack an associated syndrome.[1,3,4]

According to the World Health Organization (WHO) classifications from 2017 and 2019, NETs are divided into well-/moderately differentiated and poorly differentiated/anaplastic tumors. Well-differentiated NETs are categorized into grades G1, G2, and G3 based on their mitotic activity number and Ki67 proliferative index. Understanding the grade of the tumor is crucial because higher-grade tumors (G2 and G3) have a significantly increased likelihood of metastasis.[1,3,6.7]

Diagnosing NET in younger populations (under 50 years of age), particularly women of reproductive age, is becoming increasingly challenging. The trend of women delaying pregnancy has led to a rise in the number of cancer diagnoses during pregnancy, including NETs. It is estimated that 1 in 1000 pregnant women is diagnosed with cancer for the first time during pregnancy, highlighting the complexity and importance of this issue.[1,3,7]

Neuroendocrine tumors may be discovered incidentally or suspected due to clinical symptoms. When these tumors cause symptoms due to the specific hormones they secrete, they are referred to as "functional". In contrast, the majority of NETs are "non-functional", meaning they do not produce biologically active hormones.[4,8,9,10-13] Both functional and non-functional NETs often present with late, non-specific symptoms that may be misattributed to other conditions.[4] In an international study of patients with confirmed NETs, the most common initial diagnoses provided to patients included gastritis, irritable bowel syndrome, anxiety, inflammatory bowel disease, asthma, and menopause.[4,14]

Monitoring a pregnant woman diagnosed with NET can be challenging due to symptoms that may mimic typical physiological changes during pregnancy.[2]

The symptoms associated with NETs vary based on tumor localization and the secretion of bioactive peptides or vasoactive factors, such as serotonin or bradykinin, into the bloodstream.[1,3] Diagnostic markers like chromogranin A levels (with sensitivity ranging from 71.3% to 83% and specificity from 71% to 85%) and newer transcriptomic biomarkers such as NETest (sensitivity of 94.4% and specificity of 95.4%, though not widely available yet) can assist in diagnosing NETs.[1,3]

Carcinoid syndrome, which includes symptoms such as flushing (typically affecting the face, neck, and chest), chronic diarrhea, bronchial obstruction, and valvular heart disease, occurs when NET-produced hormones reach the systemic circulation and elevate systemic levels of serotonin or its metabolite, 5-hydroxyindoleacetic acid (5-HIAA). This syndrome usually arises after liver metastases, which allow these hormones to bypass liver metabolism, which would typically inactivate them. Retrospective cohort studies suggest that carcinoid syndrome occurs in 6% to 13% of patients with pathologically confirmed gastrointestinal NETs but in less than 1% of those with bronchopulmonary NETs.[4,11,12,15-17,18]

Diagnostic imaging techniques, including cross-sectional imaging (MRI and CT) and functional imaging (PET/CT with 68Gallium-DOTATATE), are utilized to diagnose, monitor treatment response, and track disease progression.[1,3]

However, the evidence base for diagnostic and therapeutic strategies specifically for pregnant women is limited, as they are often excluded from clinical trials.[1,3,19] There are concerns about the unnecessary exposure of both mother and fetus to ionizing radiation, in addition to the rarity of NETs in this population, which results in limited experience at most treatment centers.[1,3,20]

Managing NETs during pregnancy poses challenges in terms of the safety and efficacy of various treatments, as well as their effects on the fetus.[1] Guidelines for diagnosing and treating this heterogeneous group of tumors, particularly gastropancreatic and pulmonary NETs (both functional and non-functional), are outlined in the ENTS guidelines.[1,2 20-29]

A multidisciplinary approach involving endocrinologists, obstetricians, oncologists, anesthesiologists, and surgeons is essential. Surgery may be considered for pregnant women diagnosed with NET when tumor

progression or hormonal activity poses a significant threat to the mother.[1,4]

Treatment with somatostatin analogs (Lantreotide, Octreotide) is the first line of therapy and is generally well tolerated during pregnancy. Somatostatin analogs (SSA) are characterized by a wide range of inhibitory functions, including inhibition of hypothalamic hormones, regulation of gastrin and gastric acid secretion, the release of insulin, glucagon, pancreatic amylase and other hormones in the gastrointestinal tract, such as cholecystokinin, vasoactive peptide, and intestinal secretion.[1,30-35] In addition, it may exert inhibitory effects on cell proliferation.[30,36-39]

Even anti-inflammatory and anti-nociceptor effects have been described.[30,40] The effect of somatostatin analogs on different cells in different tissues is determined by the types of somatostatin receptors (SSTR) expressed on their surface.[30] In 1992, the first two somatostatin receptors, SSTR1 and SSTR2, were discovered.[30,41] There are five SST receptors, SSTR1 through 5, which are encoded by five different genes, each on a separate chromosome.[30] The safety profile of SSA during pregnancy is still controversial.[18]

This article presents a case report of a pregnant patient diagnosed with NET before pregnancy.

CASE REPORT

A 40-year-old woman presents with a 7-week ongoing pregnancy, spontaneously conceived, at The University Emergency Hospital Bucharest Outpatient Department for monitoring and assistance during childbirth.

Obstetric History

- Last menstrual period (LMP): 16.06.2024 (patient cannot confirm the exact date).
- Gravida III:
- One spontaneous birth in 2016, female, 3800 g.
- One spontaneous miscarriage (twin pregnancy) at 17 weeks with spontaneous membrane rupture. During this period, 03.2019 - 07.2019, the patient discontinued Sandostatin therapy.

Medical History

The patient's meticulous medical history reveals a diagnosis in 2018 (at 34 years old) with a neuroendocrine tumor (NET G1), likely of pulmonary origin - right lower lung lobe (typical carcinoid, Ki-67 1%). The initial diagnosis was made by detecting hepatic metastases, the largest measuring 10 cm.

Imaging evolution (CT, 12.2023) shows that NET G1 remains stable, with pulmonary metastases, bronchiectasis, atelectasis, and hepatic metastases in regression compared to 02.2023 and stable lymph node involvement.

Treatment History

She received Peptide Receptor Radionuclide Therapy (PRRT): 3 cycles of Lu-177-DOTATOC (last one on 02.08.2020 in Basel, Switzerland), chemotherapy: Capecitabine and Temozolomide (30.09.2021 - 12.2023). Carcinoid Syndrome was treated with somatostatin analogs (Sandostatin LAR 30 mg/28 days from 04-07.2018, then increased to 60 mg/28 days from 07.2018 - 03.2019 and 07.2019 - 06.2024). The patient also has bilateral thyroid microcysts and splenic cystic formations.

Treatment with chemotherapy was voluntarily stopped in 12.2023, and also somatostatin analog therapy ceased in 06.2024 during the first and second trimesters of pregnancy.

Pregnancy Course

Initial Consultations: The patient was informed about the risks associated with her underlying condition and possible pregnancy complications. She was advised to consult oncology and endocrinology specialists for multidisciplinary management but declined, as documented in her medical records. This decision posed challenges in managing her care and required careful monitoring and coordination among the medical team.

The patient was managed at The University Emergency Hospital Bucharest Obstetrics and Gynecology Clinic during her pregnancy. Non-invasive prenatal test (NIPT, PANORAMA) was performed at 11 weeks: Low-risk result. Fetal medicine specialists did periodic ultrasounds for fetal growth and anomaly detection. The first-trimester morphology scan (13w4d) showed no anomalies, and the estimated due date (EDD) was 14.03.2025. The second-trimester morphology scan (20w2d) revealed no anomalies, EDD maintained, and bilateral uterine artery resistance increased. The patient had a hematology consult, during which anticoagulant therapy (Clexane 0.6 ml) was indicated. The third-trimester morphology scan (30w5d) was without detectable anomalies, so the EDD was revised to 27.02.2025.

Additional pregnancy ultrasounds were performed at 16 and 24 weeks, and bi-weekly fetal biometrics and Doppler velocimetry (middle cerebral artery and umbilical artery PI) were conducted from 26 weeks onwards. There was normal growth with an apparent growth velocity from 28 weeks, 2 weeks ahead.

There were no obstetric Complications such as hypertensive disorders or preeclampsia, and the routine screening showed no gestational diabetes.

The maternal symptoms, including fatigue, epigastric pain, and episodes of paroxysmal dyspnea (possibly bronchospasm) at 10 and 28 weeks, were successfully managed, providing reassurance and hope for the patient's well-being.

Laboratory results:

- At 10 weeks: The patient presented with a mild normochromic anemia, and slightly elevated liver enzymes: TGP 40.03 U/L, (0-34 U/L), alkaline phosphatase 280.99 U/L (30-12 U/L), GGT 140.29 U/L.
- At 14-17 weeks: The patient's condition showed significant improvement with the normalization of transaminases, GGT 82 U/L, 65 U/L and alkaline phosphatase 187 U/L, 199 U/L.
- At 22-26 weeks: It's important to note the mild fluctuations in alkaline phosphatase 230 U/L and GGT 110 U/L, despite normal transaminases.

The patient undergoes endocrinological evaluation (28 Weeks) within the Endocrinology Clinical Section of the National Institute of Endocrinology C.I. Parhon. The results revealed elevated Chromogranin A (CgA): 2217 ng/ml, elevated serotonin: 389.50 ng/ml, normal ENS, GGT 84 U/L, alkaline phosphatase 306 U/L.

An interdisciplinary examination was performed, involving oncology, gastroenterology, anesthesiology, and general surgery. This comprehensive approach was taken to assess the patient's biological status in the context of NET and establish a thorough therapeutic plan.

Management

The treatment was initiated with 40 mg of Octreotide every 4 weeks (per national protocol).

Liver Ultrasound showed hepatic metastases (largest 69 mm in segments V-VIII), hepatosplenomegaly, cirrhotic liver configuration, and signs of early portal hypertension. (Figure 1)

The gastroenterology consult recommended initiating Carvedilol 6.25 mg BID and postpartum upper GI endoscopy. The effect of treatment was the stabilization of CgA and serotonin but increased alkaline phosphatase and GGT levels.

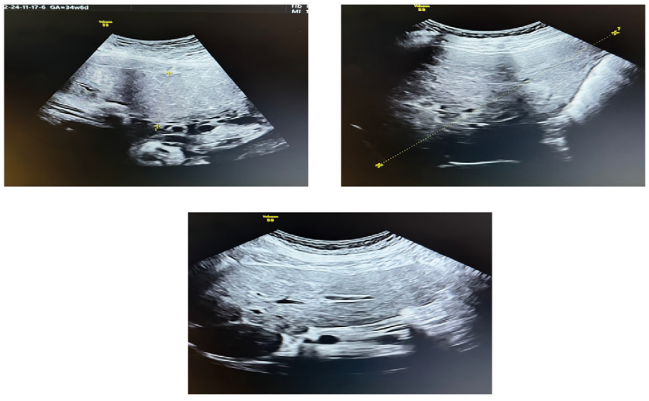

Figure 1. Liver Ultrasound: hepatic metastases (largest 69 mm in segments V-VIII), cirrhotic liver configuration, and signs of early portal hypertension

Corticotherapy for fetal lung maturation is given at 32 weeks: Dexamethasone: 4 doses of 6 mg at a 12-hour interval.

Clinical symptoms improve following the initiation of treatment with SSA, and paraclinical tests are maintained within constant limits.

In the 35-36th week of pregnancy, the patient complained of increased fatigue and epigastric pain. Laboratory tests reveal worsening of the liver cytolysis syndrome (GGT = 339 U/L FA =570 U/L). (Figure 2)

The physicians indicated preoperative prophylaxis with 100 mcg of Sandostatin SC every eight hours, 3-5 days preoperatively and 3 days postoperatively.

Delivery and Neonatal Outcome

The patient gave birth by elective cesarean section (36w1d, February 2025). The main indication was worsening maternal hepatic cytolysis syndrome. Postpartum treatment for ablactomy is given.

Neonatal Outcomes

The newborn Male appeared normal, with a birth weight of 3880 g and an APGAR of 8. The neonatology team evaluated the baby. The initial postnatal course included serial blood glucose monitoring (to assess maternal Sandostatin effects). The baby needed oxygen therapy via mask but was intubated 18 hours later for congenital pneumonia, a favorable response to antibiotic therapy.

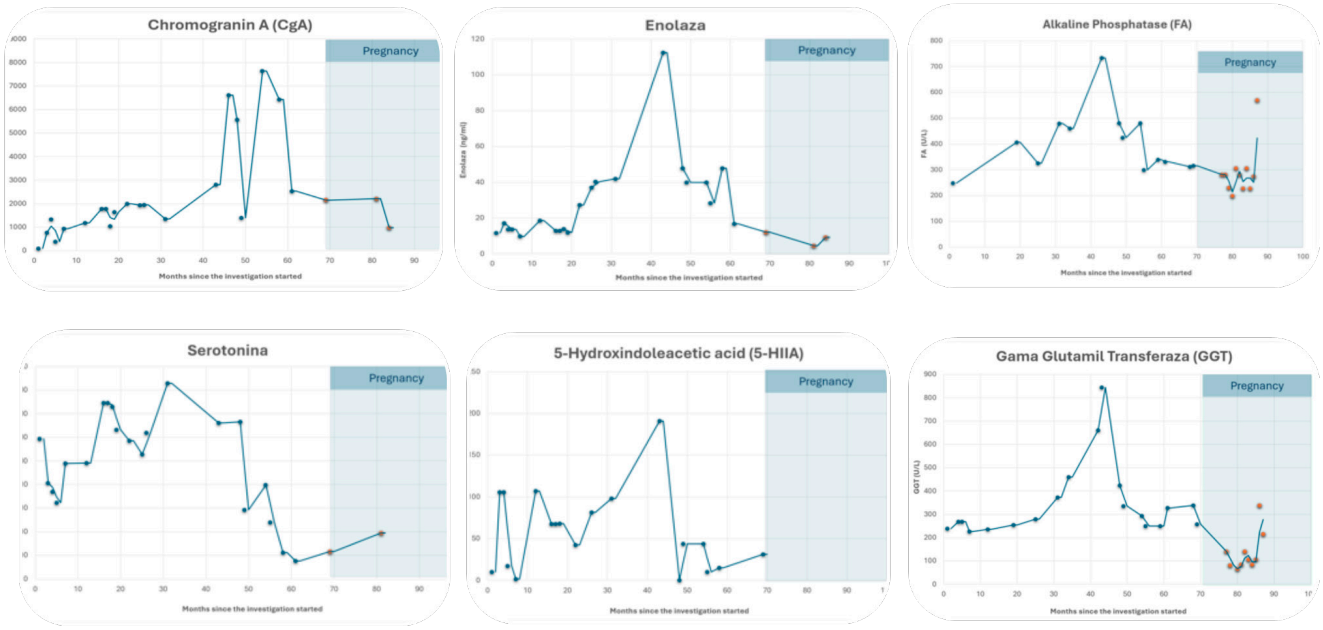

Figure 2. The figure shows the changes in laboratory tests before and during pregnancy

Maternal Postpartum evolution was favorable. The patient had a complete set of blood tests two weeks after the birth. Paraclinical findings included worsening hepatic cytolysis syndrome, elevated alkaline phosphatase, and GGT.

Postoperative CT scan (chest, abdomen, pelvis) showed pulmonary: Right hilar lymphadenopathy (15/11 mm), nodular ground-glass opacities in left and right lungs, bronchiectasis, hepatic: Nodular lesion (73.63 mm, segment VIII). (Figure 2.1, Figure 2.2)

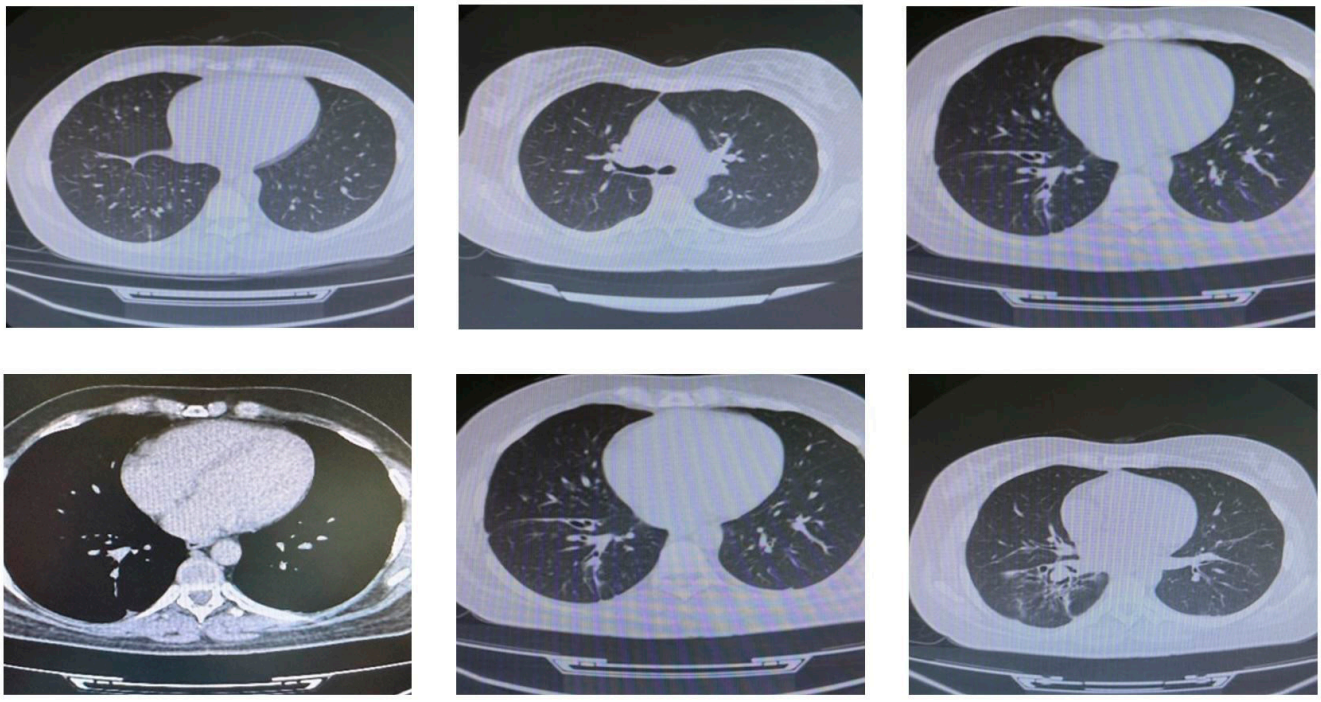

Figure 2.1 Postoperative CT scan: Right hilar lymphadenopathy (15/11 mm), nodular ground-glass opacities in left and right lungs, bronchiectasis

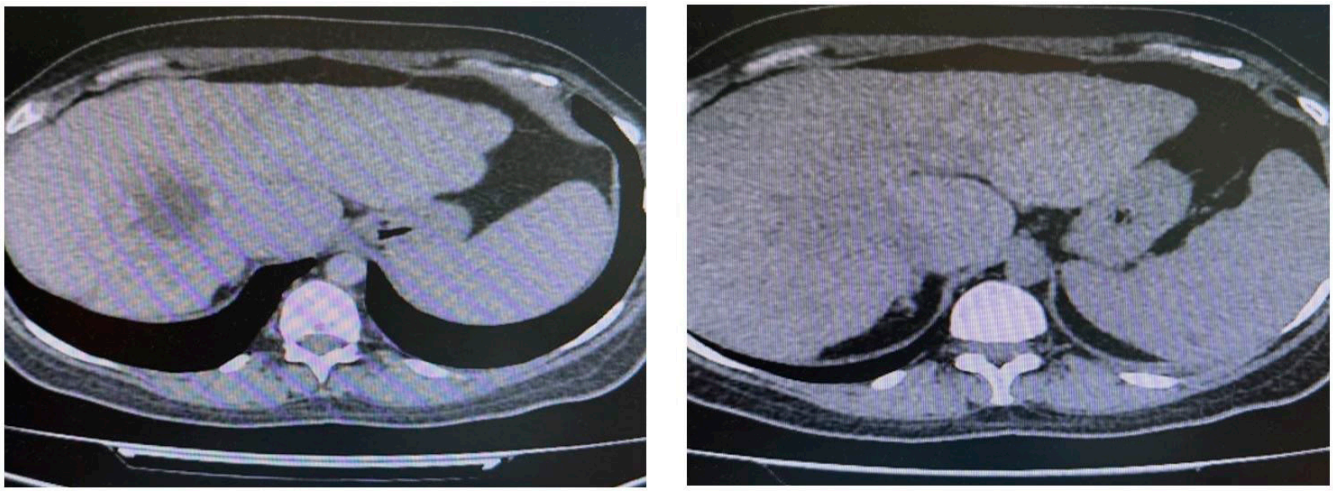

Figure 2.2 Postoperative CT scan: Nodular lesion (73.63 mm, segment VIII)

The patient was discharged with the following recommendations:

- Endocrinology consult for an adjustment treatment plan for somatostatin analog therapy.
- Oncology consult: Postpartum reassessment (1 month) for potential chemotherapy resumption (Capecitabine & Temozolomide).
- Pulmonology & Thoracic Surgery: Evaluate potential pulmonary tumor resection.

This case highlights the complexities of managing pregnancy in a patient with metastatic NET, balancing oncologic therapy with fetal and maternal outcomes.

DISCUSSIONS

In specialized literature, cases of pulmonary NETs diagnosed before or during pregnancy are rare. Bronchopulmonary NETs are characterized by central lesions, which may cause bronchial obstruction, recurrent pneumonia, cough, and hemoptysis. (1,11-13) Monitoring these cases is challenging because non-specific symptoms, such as fatigue, vomiting, dyspnea, and cough, are often attributed to physiological changes during pregnancy.[2]

This paper presents the case of a 40-year-old pregnant woman diagnosed with NET NET G1 right lower lobe lung neuroendocrine tumor (typical carcinoid, Ki 67 1%), with bronchiectasis and area of atelectasis and secondary hepatic, pulmonary, and possibly lymph node determinations. The diagnosis was initially established seven years ago upon detection of secondary hepatic lesions. By presenting this case, we underscore the crucial role of a multidisciplinary team in ensuring appropriate therapeutic management based on tumor localization, staging, and grade, the severity of symptoms, and selecting treatment options that minimally impact pregnancy.[1,19,42]

One contributing factor in this case was the patient's poor compliance with neuroendocrine tumor treatment; she discontinued on her initiative a few months before becoming pregnant. Her refusal to undergo interdisciplinary consultations with endocrinologists and oncologists at the beginning of her pregnancy further complicated the establishment of a suitable therapeutic plan. Additionally, the patient did not undergo any preconception investigations for NET staging within the year leading up to her pregnancy, meaning that the symptoms she presented might have been interpreted solely in the context of her pregnancy rather than being related to a possible progression of her underlying disease.

Referring to our case, in which we are talking about a pregnant woman with pulmonary NET and secondary metastatic disease, in order to have a correct picture regarding a possible progression of the underlying disease during pregnancy, we must take into account the physiologic changes that occurred in the context of pregnancy in the maternal body. The impact of pregnancy on carcinoid tumor progression is not entirely elucidated.

Studies have indicated that 30% of patients diagnosed with NETs express progesterone receptors (often found in pancreatic NETs) and estrogen receptors

(mainly in non-pancreatic NETs).[1,43.44] Pregnancy involves elevated levels of estrogen and progesterone, which could potentially explain disease progression in some cases.[45]

During normal pregnancy, the chromogranin A (CgA) level increases as it is secreted at the placental level. Moreover, under physiologic conditions, 5-Hydroxyindoleacetic acid (5-HIAA) values rise progressively and return to normal after delivery. Therefore, if significant clinical symptoms do not accompany changes in these parameters among pregnant women with carcinoid syndrome, then they should be interpreted with caution because they may be attributed to pregnancy-induced changes. Notably, the Cg A value is limited (30-60% in metastatic stages), and 5-HIAA are not specific markers during pregnancy; however, they can be used as follow-up markers postpartum.[29,46,47]

Managing carcinoid syndrome during pregnancy and labor poses challenges, making long-acting somatostatin analog (SSA) therapy a viable treatment option. Since their introduction, multiple phase II trials (e.g., the CLARINET Study) and case series have demonstrated high rates of disease stabilization following SSA treatment and suggested that this treatment may prolong overall survival and progression-free survival in NET patients. (30) Recent research regarding the safety profile of SSA administration during pregnancy remains controversial, as there is a lack of clear evidence regarding teratogenic effects and long-term outcomes for children born to mothers who received treatment. However, the majority of cases support the safety of such treatments.

Literature reports indicate that both mothers and their children generally tolerate the treatment well.[18] All types of somatostatin receptors (SSTR) are expressed in the placenta and umbilical cord.[1,48]

Octreotide and lanreotide can cross the placenta through passive diffusion, leading to low concentrations in newborns' amniotic fluid and blood, compared to maternal blood. Additionally, it has been observed that the half-life of octreotide in newborns is longer than in adults.[1,48] Jesu and colleagues have indicated that administering SSA to pregnant women diagnosed with acromegaly may be associated with possible intrauterine growth restriction due to an acute reversible reduction in uterine artery blood flow.[49]

Hachmi et al. suggested in their paper that administering somatostatin analogs (SSA) during pregnancy may pose a risk of fetal neurotoxicity. They noted that the process of neurogenesis in experimental models, specifically mice, appears to be influenced by maternal serotonin levels.[50]

A study conducted by Ratnayake et al. included six pregnant women diagnosed with neuroendocrine tumors (NETs) in various locations; of these, five patients were treated with SSA, and four of them continued treatment throughout their pregnancies. Five women delivered at term without any maternal or fetal complications. However, one woman delivered prematurely, and her newborn experienced ventriculomegaly and complications due to prematurity. Although some guidelines and publications recommend discontinuing SSA treatment before conception or during pregnancy, this study demonstrated that SSA treatment during pregnancy, after careful evaluation of risks and benefits, can be beneficial due to its antiproliferative and antisecretory effects.[1,51,52]

Following a literature search, we identified three case reports of patients with metastatic NETs who received SSA treatment. Hummelshaj et al. described a case involving a 32-year-old pregnant woman diagnosed with a neuroendocrine small bowel tumor with liver metastases at age 25. She received SSA every four weeks, which was interrupted in the first trimester and restarted in the second trimester. The woman's pregnancy progressed favorably, with stable chromogranin A levels, and she delivered a healthy baby via elective cesarean section at 37 weeks. Follow-up at 10 months postpartum revealed no disease progression.[53]

Meoni et al. reported on two cases of pregnant women diagnosed with metastatic NETs who were treated during pregnancy. One was a 37-year-old woman from Japan with a diagnosis of G2 pancreatic neuroendocrine tumor (Ki67 11%) and liver and bone metastases; she delivered a healthy baby via elective cesarean section at 39 weeks. The other was a 41-year-old Nigerian woman with pre-existing pregnancy hypertension who was diagnosed with a non-functioning ileal NET (Ki67 4%) and metastases in the breast, axillary lymph nodes, and liver. She underwent a cesarean section at 35 weeks due to preeclampsia and also delivered a healthy baby.[18]

Carcinoid crisis is an acute manifestation of carcinoid syndrome caused by the sudden release of elevated levels of serotonin and other vasoactive substances (such histamine and serotonin) into the circulation.[22] It is characterized by deep flushing, bronchospasm, and fluctuating blood pressure values.[4] Therefore, as in our

case, these patients are often administered somatostatin analogs both preoperatively and postoperatively.[4]

The presence of liver metastases ranges from 87% to 100% among patients with carcinoid syndrome and can lead to severe complications like hepatic encephalopathy.[18, 22] The right hypochondrium pain experienced by our patient after starting SSA treatment at three weeks may also be considered a side effect of the therapy, as patients receiving these agents are at a higher risk of developing gallstones and biliary sludge.[4]

Although survival rates vary depending on whether the disease is localized or metastatic, recent research indicates that the five-year survival rate after diagnosis is between 80% and 95%.[54]

Fahhoum et al. reported a case of a 21-year-old pregnant woman who presented to the emergency room at 13 weeks of gestation with hemoptysis. Following imaging studies and bronchoscopy with biopsy, she was diagnosed with a grade 1 pulmonary NET. The evolution of the patient was favorable; she delivered vaginally at term a healthy baby. Her condition improved, and she delivered a healthy baby vaginally at term. At three months postpartum, she underwent a right lower lobe lobectomy with healthy margins.[55] Kevat et al. discussed a 36-year-old pregnant woman diagnosed three years prior with bilateral pulmonary carcinoids due to recurrent pneumonia. Her condition improved during pregnancy, and she did not require treatment with somatostatin analogs, as she exhibited no specific symptoms of carcinoid syndrome. A five-year follow-up showed minimal disease progression, which remained asymptomatic.[54] Binesh et al. report the case of a 28-year-old patient who presented in the 34th week of pregnancy to the emergency room for massive hemoptysis; following investigations and biopsy, the diagnosis of pulmonary NET was established. She is delivered by cesarean section at 38 weeks of gestation, and later, at 2 months postpartum, pulmonary lobectomy is performed. The evolution of the patient was favorable; at 6 months postintervention, she is asymptomatic with regular pulmonary Rx.[57]

Sewpaul et al. reported a case of spontaneous regression of a pelvic carcinoid (Ki-67 low) diagnosed in a 35-year-old woman who became pregnant during her evaluation. Her pregnancy progressed without complications, and she delivered a healthy baby via cesarean section at term. Follow-up investigations conducted five months postpartum showed no diseases. The authors suggest that several factors may contribute to this spontaneous regression, including cytotoxic changes in B and T cells during pregnancy, the host's immunological response, the activation of pro-apoptotic mechanisms, and the increased cytotoxic effect of natural killer (NK) cells. Additionally, blocking the receptors for vascular endothelial growth factor (VEGF) could lead to a significant reduction in tumor vascularization and metastasis.[56]

CONCLUSIONS

Based on these studies, it appears unlikely that pulmonary neuroendocrine tumors, even in cases of metastatic disease, negatively impact pregnancy. Moreover, pregnancy seems to have minimal effects on the progression of carcinoid tumors. The mechanisms behind tumor regression and the influence of pregnancy on these processes are still being studied, and further research may provide insights that could inform future treatments.

The impact of pregnancy on NETs and their effect on the course of pregnancy are areas that require urgent attention. Limited research has led to a lack of concrete data that could be used to establish antenatal management strategies with minimal risks for both mother and fetus. This underscores the need for further studies in this area to ensure the best possible outcomes for pregnant women diagnosed with NETs.

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Patient consent
Patient consent and consent from patient's guardian is obtained.
Data Availability. The data used to support the findings of this study are included within the article.

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