Functioning Endocrine Tumors in Pregnancy: Diagnostic and Therapeutic Challenges

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Abstract

The occurrence of endocrine tumors in pregnancy poses several diagnostic and therapeutic challenges. Although rare, functioning tumors involving the pituitary, thyroid, adrenal, and pancreas are reported in the literature. Timely diagnosis and management of these tumors are essential as they might lead to adverse maternal and fetal outcomes if left untreated. This review is an attempt to characterize various functioning tumors that could occur in pregnancy, their clinical features, diagnosis, and management.

Keywords: Adrenal gland, endocrine tumors, pituitary, pregnancy, thyroid

Introduction

Functioning endocrine tumors are not commonly encountered during pregnancy. Several physiological changes occur in the mother during pregnancy to support the growth and development of the fetus. As a result of these adaptive hormonal changes, functioning tumors may present with different characteristics and biological behavior. It is imperative that these tumors be identified early; as some of them could lead to adverse maternal and fetal outcomes if left undiagnosed and untreated. The management of such individuals may be challenging and need to consider the risks and benefits of surgery versus expectant management. In this review, we attempt to describe the presentation of various functioning endocrine tumors in pregnancy, their clinicopathological implications, and management.

Pituitary gland

An intact pituitary function is essential for the normal induction and maintenance of female fertility and pregnancy.[1] Lactotroph hyperplasia that occurs due to high estrogen levels is responsible for pituitary enlargement during pregnancy. Although pituitary tumors may present with infertility, the advances in the management of these tumors have made it possible for several women in the reproductive age group to conceive.[2] Nevertheless, the occurrence of functioning pituitary tumors in pregnancy is beset with both diagnostic and therapeutic challenges. Common functioning pituitary tumors include prolactinoma, Cushing's disease, acromegaly, and rarely a TSH secreting pituitary adenoma.

a. **Prolactinoma:** The majority of pituitary tumors in pregnant women are macroprolactinomas. Macroprolactinomas are less common, and the exact incidence of these tumors in pregnant women is not accurately known.[3] The risk of tumor enlargement during pregnancy depends on the tumor size around the time of conception. Although the risk of tumor enlargement is about 3% in microprolactinoma, it is much higher in macroprolactinoma, and is reported to be about 30%.[4] In women with prolactinomas, an MRI should be done before conception, and this will serve as a baseline to compare tumor size during pregnancy, and to distinguish between enlargement of tumor or hemorrhage into the tumor.

Microprolactinoma: Although macroprolactinomas tend to follow a benign course in nonpregnant women, during pregnancy, the risk of symptomatic tumor growth

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is <2%, and the development of neurological sequelae like headache and optic chiasmal compression with new onset of visual field defects which are seen in about 1.6–5.5% of those affected.[4] Prolactin levels increase during pregnancy, and hence prolactin measurement does not serve as a useful biochemical marker to monitor tumor growth. The very low risk of enlargement of microprolactinomas during pregnancy provides sufficient evidence to discontinue dopamine agonists once pregnancy is confirmed, and this has been endorsed by the Endocrine Society.[5] At diagnosis of pregnancy, a baseline visual field charting is done and should be followed up every 2–3 months. Serial MRI assessment is not mandatory. However, if the patient becomes symptomatic with severe visual field defects and progressive headaches, an MRI of the pituitary gland is done to assess for change in tumor size. If substantial growth is demonstrable, the patient is initiated on cabergoline. For patients who have remained symptom-free throughout pregnancy, prolactin levels should be reassessed 2 months after delivery or cessation of lactation. If prolactin levels are elevated, treatment with a dopamine agonist is resumed. For women who wish to continue breastfeeding, an MRI of the pituitary gland is repeated to establish stability in the size of the tumor, as the initiation of dopamine agonists may impair lactation.[4]

Macroprolactinoma: Ideally, women with macroprolactinoma should be treated before conception. The risk of tumor growth falls to less than 5% in those who have been treated with prior radiation or surgery. In selected cases, where the macroprolactinoma is invasive or abuts the optic chiasm, it is prudent to continue dopamine agonists throughout pregnancy.[5] Women with macroprolactinoma who have stopped dopamine agonists should have formal visual field charting in every trimester. They should be warned of symptoms suggesting enlargement of the tumor and pituitary apoplexy; an MRI of the pituitary is repeated in case of worsening of vision or progressive headache. If initiation of dopamine agonists does not bring down the tumor size significantly, they are advised to undergo trans-sphenoidal surgery in the second trimester.

b. **Adrenocorticotropic hormone (ACTH)-dependent Cushing's disease:** The diagnosis of Cushing's syndrome in pregnancy is often difficult due to considerable overlap in symptomatology with pregnancy. The occurrence of bruising, hypertension, glucose intolerance, acne, and hirsutism should be regarded with a high degree of suspicion. Cushing's syndrome during pregnancy is associated with a high incidence of pre-eclampsia and the Haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome.[6]

Laboratory diagnosis of Cushing's syndrome may be challenging during pregnancy. As there is an increase in serum levels of total cortisol caused by estrogen-mediated synthesis of cortisol binding globulin, this might result in abnormal results on dynamic testing of serum cortisol. Cushing's syndrome is diagnosed in pregnancy by demonstrating disruption of circadian rhythm of cortisol, and by urinary-free cortisol estimation, which is elevated to more than three times the upper limit of normal. Besides these tests, a recent study showed that late-night salivary cortisol cutoffs of ≥0.25 μg/dL, 0.26 μg/dL, and 0.33 μg/dL in the first, second, and third trimester, respectively, were diagnostic of hypercortisolism.[7] When Cushing's syndrome due to an adrenal adenoma is encountered in pregnancy, corticotrophin levels are often unsuppressed, due to stimulation of pituitary corticotrophs by placental corticotropin releasing hormone (CRH) or direct stimulation of adrenal receptors by placental ACTH. Women with Cushing's disease; however, have elevated ACTH levels or are in the high normal reference range.[7]

The treatment of choice to control hypercortisolism during pregnancy is surgical excision of the pituitary or adrenal adenoma. Ideally, surgery should be performed in the second trimester, before 24 weeks of gestation. Surgery performed beyond 32 weeks is associated with a higher risk of preterm delivery. Following surgery, patients are initiated on hydrocortisone, the dose of which is similar to that used in nonpregnant adults in the first two trimesters, with a higher dose required in the third trimester.[8]

Medical management is an option in a subset of patients detected in late pregnancy, the experience with its use is limited. Metyrapone, an 11-beta hydroxylase inhibitor has been used to achieve control of hypercortisolism, although there is an increased risk of worsening hypertension due to accumulation of deoxycorticosterone. Dopamine agonist cabergoline may also be used in cases of Cushing's disease. The use of mitotane and ketoconazole is contraindicated during pregnancy, due to the potential risk of teratogenicity.[8] The use of Mifepristone to treat Cushing's syndrome in pregnancy is contraindicated as it may induce abortion and fetal loss.[9]

c. **Acromegaly:** Growth hormone (GH) producing pituitary adenoma is usually associated with infertility. However, with successful medical and surgical treatment of the adenoma, and with advances in *in vitro* fertilization techniques, pregnancy rates in women with acromegaly have increased.[10] During the first trimester, because of estrogen-mediated hepatic resistance to GH, there is a fall in serum levels of IGF1 and a transient improvement in symptoms of acromegaly. However, with the progression of pregnancy, there is increased placental production of GH-Variant (GH-V) and IGF-1 levels increase by two-three fold.[11] Acromegaly results in the development of diabetes and hypertension in pregnancy, and the risk of symptomatic tumor growth is less than 10%.[12]

At baseline, a formal visual field evaluation, followed by an MRI of the sellar region is obtained. Visual field changes should be assessed throughout pregnancy. Changes in visual acuity and visual field deficits may also occur due

to pituitary apoplexy. A distinction between hemorrhagic infarction of the tumor or proliferative growth should be made based on the patient's clinical symptoms and changes on MRI of the sellar region. Pituitary apoplexy is often managed conservatively; surgery is indicated in patients with deteriorating vision or neurological status. For symptomatic overgrowth of the tumor, the patient may be initiated on dopamine agonists. Failure to respond may warrant the use of somatostatin analogs. The decision for surgical intervention is reserved for patients who show clinical worsening despite medical therapy.[12]

Thyroid gland

Several physiological alterations in thyroid function are encountered in normal pregnancy. The estrogen-mediated increase in thyroid-binding globulin, increased urinary iodine clearance, increased placental degradation of maternal thyroxine and the agonistic action of beta-hCG on the TSH receptor can contribute to changes in thyroid hormone levels during pregnancy.[13]

a. **Hyperthyroidism in pregnancy:** Autonomous thyroid nodules causing hyperthyroidism usually occur in women above the age of 40 years, particularly in areas of iodine deficiency.[14] Anti-thyroid drugs are the agents of choice to treat hyperthyroidism during pregnancy. Women who conceive while on anti-thyroid drugs are switched over to an agent with lesser risk of teratogenicity such as propylthiouracil in the first trimester and are maintained at the lowest possible dose, with regular monitoring of thyroid function tests. A block and replace regimen is not recommended as this is likely to lead to blocking of thyroid hormone synthesis by the fetal thyroid. Women whose hyperthyroidism is well controlled before conception may opt to stop the medication, and periodically monitor their thyroid function tests, and restart the drug, if indicated by biochemical results.[13] Adverse effects associated with anti-thyroid drugs include maternal hepatic dysfunction and pre-auricular sinus in the newborn with propylthiouracil use. Carbimazole, on the other hand, could lead to agranulocytosis, fetal choanal atresia, and aplasia cutis. Beta-blocking agents may be used to control the adrenergic symptoms; however, their use should be limited to a few weeks as it may lead to intrauterine growth retardation, neonatal hypoglycemia, apnea, and bradycardia.[15] Rarely, hyperthyroidism may be encountered in cases of molar pregnancy, which is one of the components of gestational trophoblastic disease (GTD). Thyrotoxicosis occurs because elevated levels of β hCG acting on the TSH receptor, resulting in increased production and release of thyroid hormones in circulation. Patients with clinically evident hyperthyroidism may present with weight loss, palpitation, easy fatiguability, and tremors. Surgical evacuation is the mainstay of treatment for a hydatidiform mole. Previously undetected hyperthyroidism may result in life-threatening high output cardiac failure and considerable perioperative morbidity and mortality. Hyperplacentosis is another condition of increased trophoblastic activity characterized by elevated circulating hCG secondary to higher placental weight in comparison to normal pregnancy.[16] It is thus essential to routinely check thyroid function tests in all women diagnosed to have a molar pregnancy.[17,18]

Parathyroid gland

With the development of sensitive two-site immuno-assays that accurately determine intact parathormone (PTH) levels, studies have demonstrated that PTH is suppressed to low-normal levels in the first trimester of pregnancy and gradually increases to the mid-normal range as pregnancy progresses. In late pregnancy, PTH levels tend to exceed the normal range and the levels of total and ionized calcium slightly decrease.[19] Besides these changes, there is a 1, 25 di-hydroxy vitamin D driven doubling of intestinal absorption of calcium and phosphorus, through which women meet their mineral demands during pregnancy.[20] Additionally, parathyroid hormone-related protein is an important regulator of fetal blood calcium and placental calcium transport.[21]

a. **Primary hyperparathyroidism (PHPT):** Hyperparathyroidism in pregnancy may occur in about 0.5–1.4% of cases. It is essential to make an early diagnosis, as the symptoms associated with PHPT such as malaise, lethargy, and proximal muscle weakness may be confused with symptoms of normal pregnancy.[22] Syndromic associations such as multiple endocrine neoplasias (MEN)-1 and MEN-2 should be considered in those with a significant family history of the same.[23] The symptoms of nausea, dehydration, and altered mental status may herald an impending hypercalcemic crisis. Symptomatic disease is still commonly encountered in many Indian settings.[24] Hypercalcemia has also been shown to worsen preeclampsia. A hypercalcemic crisis may occur anytime during pregnancy or following delivery, once the placental transfer of calcium halts abruptly. Maternal complications include nephrolithiasis, pancreatitis, bone disease, hyperemesis gravidarum, and spontaneous abortion. Fetal complications include intrauterine growth retardation, intrauterine demise, low birth weight, preterm delivery, and neonatal hypocalcemia caused by suppression of the fetal parathyroid glands.[25] Conventional localization techniques such as sestamibi scans and CT scans are contraindicated in pregnancy. Sonogram of the neck is the preferred modality used for localization of a parathyroid lesion in pregnancy. Surgery is recommended when the serum calcium is 1 mg/dL above the upper limit of normal, and is preferred to be performed in the second trimester. In the asymptomatic patient with serum calcium levels that are less than 11 mg/dL, conservative medical management with adequate hydration and forced diuresis with a loop diuretic is

recommended. Calcitonin and Cinacalcet are Category "C" drugs in pregnancy.[25]

Adrenal gland

During pregnancy there is an increase in activity of both the hypothalamic-pituitary-adrenal (HPA) axis as well as the renin-angiotensin-aldosterone system. Although the size and weight of the adrenal gland remain the same in pregnancy, there is a considerable increase in the size of the cortisol producing zona fasciculata.[26]

a. **Adrenal adenoma:** Adrenal adenomas may present with Cushing's syndrome in pregnancy and are more commonly encountered than Cushing's disease. Cushing's syndrome in pregnancy is more commonly encountered with an adrenal adenoma, accounting for about 40–60% of cases as compared with pituitary Cushing's syndrome. This discrepancy is due to better ovum quality and improved fertility caused by suppression of adrenal androgens, as compared with pituitary Cushing's syndrome wherein the adrenal androgens are elevated due to increased ACTH drive. Laboratory diagnosis of Cushing's syndrome in pregnancy has been detailed above. The treatment of choice is a laparoscopic resection of the tumor in the second trimester, and this has led to an increase in the live birth rate.[26] Rarely aberrant LH/hCG receptor expression on the adrenal may result in Cushing's syndrome in pregnancy, which resolves spontaneously following delivery.[27]

b. **Adrenocortical carcinoma (ACC):** These tumors may manifest as a result of hormonal excess due to excessive cortisol and androgen secretion from the tumor or due to the mass effect on surrounding organs. It presents as muscle weakness, hypertension, diabetes, depression, varying features of virilization, and local or systemic effects caused by the tumor and its metastases. The diagnosis is made by demonstrating adrenocortical hormonal excess and localizing the tumor on MRI scans in which ACC appears as heterogeneous masses on both T1 and T2 weighted imaging.[26] The treatment options for ACC in pregnancy are limited. The treatment should be individualized and involves a multi-disciplinary team approach. The best time for surgical intervention is the second trimester.[28] Although women have successfully conceived on mitotane therapy, the potential for teratogenicity limits the use of this drug during pregnancy.[8]

c. **Primary hyperaldosteronism:** Primary hyperaldosteronism (PA) occurs in about 0.6–0.8% of all pregnancies. The course of hypertension due to PA is variable and unpredictable during pregnancy. Case reports have shown both worsening of hypertension and hypokalemia as well as spontaneous resolution. The variable course in pregnancy is attributed to progesterone. It has also been hypothesized that symptoms manifest only if the amount of progesterone is unable to compensate for the magnitude of aldosterone excess.[29] Maternal and fetal outcomes depend on the prevailing blood pressure. Uneventful pregnancies have been reported; complications include preterm delivery, end-organ damage, and placental abruption. The diagnosis of PA in pregnancy is challenging as renin and aldosterone levels are elevated in normal pregnancies. In case of suspicion of PA, as evidenced by the presence of hypertension before 20 weeks of gestation and hypokalemia, screening is done by measuring the renin levels, which are usually suppressed in PA. MRI of the abdomen is recommended for imaging the adrenal gland. Once a diagnosis of PA is made, medical treatment is initiated. Although the drug of choice in healthy individuals is the group of mineralocorticoid antagonists, spironolactone is described as a pregnancy category "C" drug. Cases describing healthy newborn babies in women treated with spironolactone have been reported; nevertheless, treatment must be individualized weighing the benefits of control of hypertension and hypokalemia and the risks of undervirilization of a male fetus in early gestation. Eplerenone, a selective mineralocorticoid antagonist has no anti-androgenic effects, and based on current data is recommended for use in pregnancy and during breastfeeding. Hypertension and hypokalemia that are uncontrolled on medical management warrants surgery; laparoscopic adrenalectomy in case of an aldosterone-producing adenoma may be safely performed in the second trimester.[30]

d. **Pheochromocytoma**: The early diagnosis of a catecholamine secreting tumor in pregnancy may be complicated due to overlap in symptoms with other conditions that occur in pregnancy such as idiopathic hypertension, pre-eclampsia, eclampsia, and gestational diabetes. The classic triad of headache, tachycardia, and diaphoresis may be absent; however, an increase in intra-abdominal pressure due to fetal movements and compression of the tumor by the enlarging uterus may provoke paroxysms classical of pheochromocytoma. A thorough family history should be sought as pheochromocytoma may be encountered in von Hippel Lindau syndrome, familial paraganglioma syndrome involving the *SDH* gene mutations, and in association with MEN2.[31]

A fatal complication that is to be dreaded during pregnancy is catecholamine-induced cardiomyopathy, which may present as acute heart failure, acute coronary syndrome, or cardiogenic shock. Although the fetus is not exposed to catecholamines due to the expression of placental catechol o-methyl transferase, chronic hypertension may cause constriction of the placental blood vessels and lead to uteroplacental insufficiency. Diagnosis is made by measurement of urinary 24-h urine metanephrine and normetanephrine as the sensitivity and specificity of these tests are similar to that of the non-pregnant state. The use of the MRI abdomen is the diagnostic modality of choice in imaging pheochromocytoma in pregnancy as it does not involve the use of ionizing radiation. Once the diagnosis

of pheochromocytoma is confirmed, preoperative management includes graded dosing of alpha-blockers for a period of 10–14 days followed by the subsequent addition of a beta-blocker. Phenoxybenzamine may be used as a nonselective alpha-receptor blocking agent, although neonates born to treated patients should be monitored for neonatal hypotension and respiratory depression. Other agents that may be used include doxazosin and prazosin. Labetalol may be added subsequent to the adequate alpha blockade to counter reflex tachycardia induced by alpha blockade and catecholamine-induced tachyarrhythmias. In cases of pheochromocytoma diagnosed early in gestation, laparoscopic adrenalectomy may be performed safely in the early part of the second trimester. If however, the diagnosis is delayed to beyond 23-24 weeks of gestation, laparoscopic surgery may be precluded by the enlarged gravid uterus. Here, it is recommended to initiate medical management, wait for sufficient fetal maturity, conduct the delivery by cesarean section and plan on tumor removal as a concurrent procedure or after 2-6 weeks of delivery with adequate hydration and salt intake.[32]

Pancreatico-duodenal neuroendocrine tumors

The common functioning pancreatic neuroendocrine tumors include insulinoma, glucagonoma,[33-35] gastrinoma, and VIP-oma.[36] These have been rarely reported in pregnancy. Some of them behave indolently and it may be possible to wait until after delivery to treat them. Surgical excision should; however, be attempted if they cause significant symptoms, intrauterine growth restriction, or problems because of mass effect.[37]

Ovarian tumors

Functioning ovarian tumors in pregnancy are uncommonly encountered and may pose a diagnostic and management challenge. While most ovarian tumors are benign and resolve spontaneously, there are others that persist and may warrant surgery. Ovarian torsion is a complication for adnexal tumors in pregnancy.[38,39] Ovarian hyperandrogenism seen in pregnancy may be due to theca lutein cysts and luteomas of the ovary. Early identification and treatment of these conditions are crucial as persistent maternal hyperandrogenism may alter the fetal developmental trajectory.[40]

Other rare functioning tumors in pregnancy

a. **Carcinoid during pregnancy:** Carcinoid tumors are slow-growing tumors that arise from the neuroendocrine cells. Common sites of origin of carcinoid tumors include the gastrointestinal tract and the pulmonary system. Rarely, they may present with carcinoid syndrome with features of flushing, diarrhea, and shortness of breath. The diagnosis in these cases may be challenging as some of these symptoms may be attributed to the physiological state of pregnancy. Decisions regarding imaging and biopsy are influenced by pregnancy, with a desire to minimize the risk of ionizing radiation and procedural risk. Surgical resection is the treatment of choice; surgery and anesthesia are not reported to cause fetal malformations but may be associated with increased fetal loss. The data on the safety of somatostatin analogs in pregnancy is conflicting. Hepatic artery embolization and radiofrequency ablation (RFA) may be performed for liver lesions although it is better to avoid RFA during the period of organogenesis.[41]

b. **FGF23 mediated oncogenic osteomalacia:** Reports on tumor-induced osteomalacia presenting during pregnancy are limited in the literature.[42] The options of management include phosphate supplements and calcitriol during pregnancy with an elective cesarean section to avoid the trauma of bearing down during labor. Tumor localization by somatostatin scintigraphy may be undertaken postpartum followed by surgical excision of the tumor.

Conclusion

Thus, functioning endocrine tumors though rare, may occur in pregnancy. Often, typical manifestations of these tumors may be masked by the nonspecific symptoms that are seen in normal gestation. Surgical management if warranted may be safely undertaken in the second trimester. A high index of suspicion is required in diagnosing these tumors which if untreated may result in adverse maternal and fetal outcomes.

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