REVIEW
ENDOCRINE DISORDERS IN PREGNANCY

Pheochromocytoma and pregnancy: a deceptive connection

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Abstract

A pheochromocytoma in a pregnant patient is one of the most threatening medical conditions for mother, fetus, and physician. Although extraordinarily rare with a frequency of 0.002% of all pregnancies, this tumor is notorious for its devastating consequences. As in non-pregnant patients, the signs and symptoms are quite variable but not specific, with hypertension being one of the most prominent signs. Confusion with the much more prevalent forms of pregnancy-related hypertension is the main cause of overlooking the diagnosis. If undiagnosed, maternal and fetal mortality is around 50%. Conversely, early detection and proper treatment during pregnancy decrease the maternal and fetal mortality to <5 and 15% respectively. For the biochemical diagnosis, plasma or urinary metanephrines are the tests of first choice since they have a nearly maximal negative predictive value. For reliable localization, only magnetic resonance imaging is suitable, with a sensitivity of more than 90%. When the tumor is diagnosed in the first 24 weeks of gestation, it should be removed by laparoscopic adrenalectomy after 10–14 days of medical preparation with the same drugs as in non-pregnant patients. If the tumor is diagnosed in the third trimester, the patient should be managed until the fetus is viable using the same drug regimen as for regular surgical preparation. Cesarean section with tumor removal in the same session or at a later stage is then preferred since vaginal delivery is possibly associated with higher mortality. Despite all technical diagnostic and therapeutic progress over the last decades, the key factor for further reduction of maternal and fetal mortality is early awareness and recognition of the potential presence of a pheochromocytoma in a pregnant patient with hypertension.

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Introduction

Pheochromocytoma, a treacherous catecholamine-producing endocrine tumor, occurs in one or both adrenal glands (85%) or in the sympathetic ganglia (15%) (1). Classically, physicians search for the tumor in hypertensive patients presenting with paroxysmal symptoms such as headache, sweating or palpitations. The prevalence of pheochromocytoma in patients with hypertension is only 0.1–0.6%. Despite a high level of awareness among physicians about its catastrophic potential, the tumor is still missed during life (2, 3). This can be ascribed to the wide variability and non-specificity of its clinical signs and symptoms.

During pregnancy, the occurrence of a pheochromocytoma is even more rare and has been estimated to be present in one in 54 000 pregnancies (4, 5). Yet, despite being an uncommon condition in pregnancy, recognizing it timely in a pregnant hypertensive woman is extremely important since if it remains undiagnosed and untreated, maternal and fetal mortality amounts to 40–50% (6, 7). In contrast, after early diagnosis and proper treatment, maternal mortality has declined substantially to $<5\%$ and fetal mortality to $<15\%$ (8–11). However, the ongoing publication of case reports of pregnant patients in whom the diagnosis of a pheochromocytoma was delayed or missed indicates clearly that there is still room for improvement in terms of earlier diagnosis and treatment. In about 20% of the patients, the diagnosis is not made antepartum (5, 8) and this is considered to be unfavorable for the final outcome. In addition to the variable and non-specific signs and symptoms, the most important reason for overlooking a pheochromocytoma during pregnancy is the much higher prevalence of pregnancy-related hypertension such as gestational hypertension and (pre)eclampsia. (NICE Guideline 107: hypertension in pregnancy, www.nice.org.uk/guidance/CG107).

The initial but crucial key for early consideration of a potential pheochromocytoma during pregnancy is in the hands of the caregivers of pregnant women such as midwives and obstetricians. In any hypertensive pregnant woman, they should utilize a low threshold of suspicion. If suspected, an internist/endocrinologist

should help out with excluding or confirming the presence of tumoral catecholamine excess. In case the patient has a confirmed pheochromocytoma, from that stage, it demands a close multidisciplinary collaboration between obstetrician, internist/endocrinologist, anesthesiologist, and surgeon in a specialized center so that the prospect for both mother and fetus is optimized.

In this review, we will address the following practical questions: what do catecholamines do during pregnancy? What are the clinical signs and symptoms during pregnancy and what are the risks of catecholamine surges for fetus and mother? How should the tumor be diagnosed and localized during pregnancy? How to prepare the patient for surgery? Finally, the questions that will be answered are as follows: what is the optimal time to remove the tumor and what is the preferred mode of delivery?

What do catecholamines do during pregnancy?

As strong vasoactive compounds, catecholamines such as noradrenaline and adrenaline have a plethora of physiological functions, even far beyond cardiovascular homeostasis. As hormone and neurotransmitter, their plasma concentrations reflect global sympatho-adrenomedullary function and that is the reason why plasma catecholamines are elevated in many clinical conditions in which sympathoadrenomedullary activity is enhanced. Although they have salutary effects that are beneficial for survival in many of these conditions, their excessive release into the circulation may also jeopardize organ function. Differentiating increased plasma catecholamines in these conditions of increased sympathoadrenomedullary activity from those that are the consequence of a pheochromocytoma is a particularly challenging task for physicians in daily clinical patient care.

In healthy pregnant women, plasma and urinary catecholamine levels are not or only slightly increased (12–16). Even in pre-eclampsia, plasma catecholamine levels are only slightly elevated. Maternal catecholamines hardly cross the placental barrier, and even in patients with pheochromocytoma, the umbilical cord blood contains <10% of the maternal catecholamine concentrations (17, 18). Noradrenaline transporters, expressed in placental cells, enable the intracellular uptake of catecholamines. In addition, placental cells contain catecholamine-metabolizing enzymes such as monoamine oxidase and catechol-*O*-methyltransferase, thus serving as a protective barrier for the fetus against excessive catecholamine exposure. The fetus itself has a high basal catecholamine secretion rate but circulating concentrations of catecholamines are low due to a high clearance (19). This high secretion rate facilitates and protects the fetus during its stressful journey through the parturient birth canal during which extremely high fetal plasma catecholamine concentrations are attained (20).

During pregnancy, transient excessive maternal levels of catecholamines, as in patients with pheochromocytoma, may have deleterious effects on the uteroplacental circulation. Extreme vasoconstriction of this specific and vulnerable vascular bed may be responsible for the occurrence of placental abruption and intrauterine hypoxia, thus imposing a serious risk to the fetus.

What are the clinical signs and symptoms during pregnancy?

Some patients with pheochromocytoma are asymptomatic, particularly those who have an unknown genetic predisposition. At the other end of the spectrum, patients may present as a life-threatening emergency. In contrast, most pregnant patients harboring the tumor present with some of the well-known typical paroxysmal symptoms such as hypertension, headache, sweating, and palpitations. The prevalence of these symptoms is probably slightly lower than in non-pregnant patients (8). Most patients become symptomatic before delivery (90%), but unfortunately at that stage, the diagnosis is not made in all of them. Even nowadays, in some patients, the diagnosis is made only *postmortem*, although this has declined to <10% (8).

Many patients become increasingly symptomatic along with further evolvement of pregnancy. This may be due to the growing uterus, movements of the fetus, uterine contractions, and abdominal palpation (21). These factors may also account for a sudden precipitation of a pheochromocytoma crisis, often evolving into a real cardiovascular emergency.

Because of the similarity of some signs and symptoms, such as nausea and hypertension, in both patients with pregnancy-related hypertension and patients with pheochromocytoma, the diagnosis of the tumor may be overlooked if no close attention is paid to other symptoms. Therefore, a meticulous medical history and physical examination are mandatory in a pregnant patient that has hypertension. This also includes a careful family history since pheochromocytoma may be part of a hereditary syndrome. To date, mutations in ten tumor susceptibility genes have been identified, and this variety of genetic syndromes contributes partly to the highly variable presentation of the tumors. These syndromes include multiple endocrine neoplasia type 2, von Hippel–Lindau disease, neurofibromatosis type 1 (NF1), the familial paraganglioma syndromes (SDHA, SDHB, SDHC, SDHD, and SDHAF2) and the syndromes caused by the transmembrane protein 127 gene mutation (TMEM127) and the recently discovered MYC-associated factor X gene mutation (1, 22–25).

It should be noted that there are several signs and symptoms that may be of some help in differentiating pheochromocytoma from pre-eclampsia. The first

feature to be considered is the hypertension itself. In pregnancy-related hypertension (gestational hypertension and pre-eclampsia), the hypertension is very unlikely to be paroxysmal as is often the case in pheochromocytoma. In addition, pregnancy-related hypertension develops after 20 weeks. In contrast, hypertension in the context of pheochromocytoma can develop during any gestational phase. So if hypertension develops in a pregnant woman in the first 20 weeks, it should not be labeled erroneously as gestational hypertension or pre-eclampsia. Other signs of pregnancy-related hypertension, such as ankle edema, proteinuria and an elevated plasma uric acid are not compatible with pheochromocytoma. Finally, the presence of unexplained orthostatic hypotension in a pregnant hypertensive patient should arouse immediate suspicion of a pheochromocytoma since this feature is uncommon in pregnancy-related hypertension. A thorough physical examination should also uncover physical signs of NF1, such as café au lait spots, skin freckling or cutaneous fibromas.

What are the risks of catecholamine surges for fetus and mother?

The actual risks for the mother carrying both a pheochromocytoma and a fetus are mainly determined by the acute and chronic (non-)adrenoceptor-mediated noxious effects of catecholamines, by the severity and duration of hypertensive spells and by pre-existing cardiovascular disorders, although this last factor is less relevant in young pregnant patients. The cardiovascular risks are probably similar as in non-pregnant women, although no real comparative studies have been performed. The spectrum of cardiovascular risks is as wide as in non-pregnant patients and comprises mainly blood pressure (hypertensive crisis, syncope, and shock), cardiac (acute coronary syndrome, cardiomyopathy, and arrhythmias), and neurological (stroke) related risks. Rarely, the patient may present with non-cardiac pulmonary edema or aortic dissection (26–28). Patients who develop unexplained peripartum cardiomyopathy should also be examined for the existence of a pheochromocytoma (29–31). The initially reported high maternal mortality in undiagnosed and untreated patients was as high as 50% (5, 6, 8, 9). Nowadays, the mortality is much lower but depends on when the diagnosis is made: antepartum or *postpartum* (5). In a literature review, it was shown that the early antepartum recognition and appropriate treatment of the tumor was associated with a decreasing maternal mortality to < 5% over the last 50 years (8, 10). The highest risk of cardiovascular complications is in the peripartum period (6, 9). At that stage, the patient is particularly prone to cardiovascular risks due to labor, abdominal palpation, anesthesia, delivery or the use of certain medications like analgesics. Frequently used anti-emetic medications during pregnancy, such as metoclopramide, should also be avoided. All these factors may precipitate a pheochromocytoma crisis by invoking a sudden and strong tumoral release of catecholamines.

In contrast to maternal mortality, fetal mortality has decreased to < 15%, although some studies report a 34% mortality, even when diagnosed antenatally (32). The fetal risks are mainly determined by the vasoconstrictive effects of catecholamines on the uteroplacental circulation and include placental abruption and intrauterine hypoxia, ultimately leading to a high fetal mortality.

How to diagnose pheochromocytoma during pregnancy?

If medical history and physical examination suggest any sign or symptom pointing to a pheochromocytoma, immediate biochemical testing should be started to rule out or to confirm the diagnosis. If possible, biochemical testing should preferably precede the start of any antihypertensive treatment, except of course in emergency situations where immediate treatment cannot be postponed. Even in this modern era with the availability of highly sensitive and specific biochemical assays, one should still be aware of potential pharmacoanalytical and pharmacodynamic drug interference. Drug treatment is more likely to be a source of false-positive than of false-negative test results. In addition to cardiovascular drugs, tricyclic antidepressants have to be considered as interfering sources of false-positive test results (33).

The first and foremost step in the diagnostic work-up of a patient suspected to have a pheochromocytoma is the unequivocal demonstration of an excess secretion of catecholamines or of their *O*-methylated metabolites metanephrines. Of all available compounds that can be measured, fractionated metanephrines (normetanephrine and metanephrine measured separately) are the preferred metabolites for the initial test (34). An initial test should have the strongest power to exclude the tumor as reliably as possible so that no tumor is missed. Metanephrines, measured either in blood or in urine, have this power since they have the highest sensitivity and highest negative predictive value (35). This nearly maximal sensitivity is due to intra-tumoral *O*-methylation as the dominant pathway of catecholamine metabolism and to the continuous tumoral secretion of metanephrines into the circulation, independent of the episodic and variable release of catecholamines. This results in continuously increased plasma levels of metanephrines in contrast to periodically elevated plasma levels of the parent catecholamines. Presently, nine different studies with more than 300 pheochromocytoma patients have demonstrated that the sensitivity of plasma-free metanephrines varies

between 95 and 100%. This high reliability to exclude the tumor when the test result is within the normal range applies even to patients in whom the pretest probability is high. Consequently, a pheochromocytoma can be considered to be excluded if the test result of plasma-free metanephrines is negative. Urinary fractionated metanephrines, measured as the sulfate-conjugated *O*-methylated metabolites, represent the major forms of metanephrines excreted in the urine and provides a good alternative since it has a similar excellent sensitivity as plasma-free metanephrines (35, 36). Assays for measurement of urinary fractionated metanephrines are much more widely available than assays for plasma-free metanephrines but have the limitation of potential incomplete urine collections.

Diagnostic specificity of both plasma-free metanephrines and urinary fractionated metanephrines is, however, limited. False-positive test results (10–15%) are mainly due to inappropriate sampling conditions, confounding influences of medications (e.g. labetalol and α-methyldopa), and clinical conditions associated with elevated sympathetic activity. A blood sample for free metanephrines should be drawn after at least 20 min rest in the supine position. Elimination of the other confounding factors is desirable but mostly impossible, and therefore, follow-up tests are required to distinguish true- from false-positive results. The need for follow-up testing depends on the likelihood that positive results indicate a tumor. This is best assessed from the magnitude of elevation of test results.

Other tests, such as plasma catecholamines, urinary vanillylmandelic acid, or plasma chromogranin A, have less accuracy than plasma or urinary fractionated metanephrines and should not be preferably used for this purpose. Finally, there is no place anymore for pharmacodynamic testing. A glucagon stimulation test has an insufficient diagnostic accuracy and carries serious risks (37). Therefore, this test should be abandoned in clinical practice. In general, in some patients, a clonidine suppression test might be useful in case of slightly elevated plasma metanephrines, but because of potential of serious side effects, this test should not be carried out in pregnant women (38).

It should be emphasized, however, that there are no retrospective or prospective studies that have specifically established the diagnostic value of biochemical tests for pheochromocytoma in pregnant patients. There are also no data available that necessitate the use of different reference values for plasma or urinary metanephrines in pregnant women.

How to localize the tumor during pregnancy?

Imaging studies to localize the tumor are only justified after establishing clear and unequivocal biochemical evidence of pheochromocytoma. Some clinicians prefer abdominal ultrasound as an initial cheap, rapid, and patient-friendly imaging test. However, since diagnostic sensitivity for small tumors is limited, a normal test result does not exclude the presence of a pheochromocytoma. In non-pregnant patients, abdominal computed tomography (CT) scans with and without contrast are used as the initial imaging procedure. However, in pregnant women, T2-weighted magnetic resonance imaging (MRI) with gadolinium enhancement is the imaging procedure of first choice since CT scanning involves radiation exposure. The diagnostic sensitivity of MRI is similar to that of CT scanning (90–100%). Specificity of MRI is limited as is CT scanning (70–80%) (1, 34, 39). Therefore, one would opt for coupling the anatomical imaging of MRI to functional imaging with ^{123}I-metaiodobenzylguanidine scanning, but because this small molecule probably crosses the placenta, radiation exposure precludes the use of this imaging modality in pregnant women (40). Finally, other diagnostic procedures like presurgical tumor biopsy are contraindicated when one considers a pheochromocytoma because of the potential serious adverse events (41).

How to prepare the patient for tumor removal?

Proper preparation of a patient with a pheochromocytoma by timely installing α-adrenoceptor blockade is one of the main reasons why surgical mortality has decreased over the last 30 years to < 3% (42–44).

So all patients with a biochemically proven pheochromocytoma, including pregnant women, should receive appropriate preoperative medical management to block the effects of released catecholamines (34). Patients who are pretreated by α-adrenergic blockade have a lower maternal and fetal mortality than those who have no α-adrenergic blockade (45). The aim of this pretreatment is twofold: first, before undergoing surgery, blood pressure, heart rate, and volume depletion should be restored as far as possible. Secondly, the patient should be protected from the toxic cardiovascular effects of preoperative surges of catecholamines. This pertains to pregnant women with this tumor as well. The target blood pressure in pregnant women is controversial because very low blood pressure can jeopardize the uteroplacental circulation. In non-pregnant patients with a pheochromocytoma, some institutions aim at a blood pressure of < 140/90, while others claim less hemodynamic instability with a maximal presurgical blood pressure of 130/85 mmHg (46).

There are no randomized clinical trials that provide evidence about the drugs of first choice or for how long patients should be pretreated. Therefore, consensus with regard to the use and duration of the optimal preoperative drug regimen is lacking. It has been proposed that to attain a stable hemodynamic

condition, the optimal duration of medical pretreatment should be 10–14 days, but this is not backed up by data from prospective clinical studies.

Traditionally, most centers start preparation with α-adrenoceptor blockade using phenoxybenzamine or doxazosin. Phenoxybenzamine is a non-competitive α_1- and α_2-adrenoceptor antagonist and the starting dose is 10 mg twice a day. Every 2–3 days the dose is increased by 20 mg up to a final dose of 1 mg/kg per day. Usually, at that dose, blood pressure is restored and paroxysms have disappeared. Most prominent side effects include orthostatic hypotension, tachycardia, and nasal congestion. The main disadvantage of phenoxybenzamine is that its prolonged action after tumor removal predisposes to postoperative hypotension (47). Phenoxybenzamine crosses the placenta and it is therefore advised to monitor the newborn for the first few postnatal days because of the risk of hypotension and respiratory depression (48). It has been estimated that 1% of the phenoxybenzamine passes into maternal milk (49).

Doxazosin, recommended as an effective alternative for phenoxybenzamine, is a competitive adrenoceptor blocker with α_1-adrenoceptor specificity. Lack of pre-synaptical α_2-adrenoceptor blockade is held responsible for less reflex tachycardia. Its less long-lasting effect is the reason why there is presumably less postoperative hypotension than with phenoxybenzamine. The usual dose of doxazosin for this purpose is increased from 2 to 16 or even 32 mg per day. In a retrospective observational study, the patients who were pretreated by doxazosin or a similar α_1-adrenoceptor blocker showed a higher maximal systolic blood pressure than those who were pretreated by phenoxybenzamine. However, there were no significant differences in clinical outcome between both regimens (50).

To treat or to prevent tachyarrhythmias, β-adrenergic blockade is only started after some days of appropriate α-adrenergic blockade. This time lag is necessary to prevent a hypertensive crisis, which might be evoked when β_2-blockade might leave α-adrenoceptor stimulation by catecholamines unopposed (51). Both propranolol (40 mg three times daily) and atenolol (25–50 mg once daily) are suitable drugs for this purpose.

Alternative drugs that have been proposed and used for preoperative management are the combined α- and β-adrenoceptor blocker labetalol and calcium channel blockers. Labetalol administered orally has a threefold higher affinity for β-adrenoceptors than for α-adrenoceptors (52). This relatively weak α-adrenoblocking activity makes this drug less suitable for presurgical preparation (53). Calcium channel blockers are an alternative option but are frequently used as complementary treatment to α-adrenergic blockade (54). In contrast to α-blockers, they lack side effects such as orthostatic hypotension.

For more acute treatment of pregnant patients with pheochromocytoma, there are several options, depending on the kind of emergency. First, in some countries, phenoxybenzamine is available for i.v. use (55). Alternatives like phentolamine and sodium nitroprusside are more widely available, but this last drug may cause fetal cyanide toxicity, although infusion rates of < 1 μg/kg per min are supposed to be safe. There are also several reports showing beneficial effects of i.v. magnesium sulfate administration, which is an attractive option for treatment of severe hypertension during pregnancy (56). This drug inhibits catecholamine release, induces vasodilation, and reduces the sensitivity of α-adrenoceptors to catecholamines. However, there is no proof that magnesium has a better efficacy than α-adrenergic blockade. Finally, certain short-acting calcium channel blockers (e.g. nicardipine) are effective for rapid i.v. treatment of a hypertensive crisis. For tachyarrhythmias, a short-acting β-adrenoceptor blocker such as esmolol is available for i.v. use.

Finally, it is important to note that in pregnant patients, an essential part of the preparation is the increase in salt and fluid intake in this 2-week preparation period since this reduces the risk of postoperative hypotension considerably (55). Although non-pregnant patients with pheochromocytoma are managed on an outpatient basis when prepared for surgery, pregnant women deserve an in-patient approach so that blood pressure and volume status can be more closely monitored.

What is the optimal time to remove the tumor and what is the preferred mode of delivery?

In pregnant patients, the optimal time for surgical tumor removal is critical and it has been advised that the tumor is removed either before 24 weeks of gestation or after delivery (4, 8, 57). The second trimester is the safest period to do surgery during pregnancy because of the risk of spontaneous abortion in the first trimester (58). In patients in whom the tumor is diagnosed after 24 weeks of gestation, the patient can be treated for a prolonged period, using the same drugs that are used for presurgical preparation, until the fetus is viable. In those patients, the tumor can be removed simultaneously with cesarean section or separately after delivery. In the third trimester, the anatomical conditions are more critical to perform laparoscopic adrenalectomy.

The surgical approach of first choice is laparoscopic tumor removal. This is a safe procedure with a complication rate of < 8%. Its benefits, such as less intraoperative hemodynamic instability, shorter hospital stay, and less postoperative pain, outweigh the risks by far (59). In patients with bilateral disease, adrenal-cortex-sparing surgery (partial adrenalectomy) has been

advocated to prevent permanent glucocorticoid deficiency.

In the long term, hypertension might persist after surgery in nearly 50% of patients despite the removal of the source of excessive catecholamine production. The tumoral recurrence rate during follow-up has been estimated to be 14% in adrenal disease and 30% in extra-adrenal disease (60). All patients should be followed up every year for at least 10 years after surgery. Patients with extra-adrenal or familial pheochromocytoma should be followed up indefinitely. Finally, genetic screening for hereditary pheochromocytoma in young pregnant women should not be forgotten since about one-third of all patients have a hereditary predisposition.

There are no definite data to recommend the best mode of delivery: vaginal delivery or cesarean section? In a previous study, vaginal delivery had a higher maternal mortality (31%) than cesarean section (19%) (6, 9). Yet, in patients who are to deliver with a pheochromocytoma *in situ*, labor is not without risk even after appropriate presurgical medical treatment. Therefore, cesarean section is the preferred way of delivery (8). Epidural, general, or combined anesthetic techniques have been used successfully for cesarean section (61). In those patients in whom the tumor has been removed successfully by surgery before 24 weeks of gestation, delivery can be done either way.

In conclusion, over the last decades, the prognosis of pregnant patients with a pheochromocytoma has considerably improved. This is mainly due to technical progress in terms of further evolvement of surgical and anesthesiological techniques. However, the crucial factor for extra significant gain is earlier awareness and recognition of the potential presence of a pheochromocytoma in a pregnant patient with hypertension. Finally, additional prognostic benefit can be expected if these patients are treated by a multidisciplinary team with high-level expertise in this specific field.

Declaration of interest

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