26 Adrenal Tumors and Pregnancy

M. Nicole Lamb, David R. Farley

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26.1 Introduction

Adrenal tumors identified during pregnancy are extraordinarily rare. While incidentalomas (adrenalomas) are commonly identified with abdominal computed tomography (CT) imaging (1–4%) or autopsy (5–17%), pregnant women should undergo neither CT scanning nor autopsy! [8]. Therefore, identifying those rare, functioning adrenal tumors during pregnancy is uncommon. The most widely reported of this unique combination is with pheochromocytomas. Its prevalence in full-term pregnancies is 1/50,000–54,000 [12]. Other adrenal tumors found during pregnancy are even more unusual; in fact, the English medical literature uncovers only 18 pregnant women with aldosteronomas and 97 with cortisol producing tumors [11, 13]. Such rarity should not be surprising: uncovering inherently very rare retroperitoneal tumors that may affect weight gain, swelling, hypertension, headache, malaise, and the like during a 9-month gestational period in young women is difficult (Fig. 1). Clearly, to identify such rare lesions, one must have serendipity, a high index of suspicion, or the adrenal tumor must be "functional" (hormonally active).

At the Mayo Clinic in Rochester, Minnesota, only 4 cases of adrenal tumors were reported in 30,246 pregnant patients between 1975–1996 [5]. These four patients, plus a recent fifth case, showcase, and well represent, the rare patients surgeons may encounter and highlight truisms for their treatment.

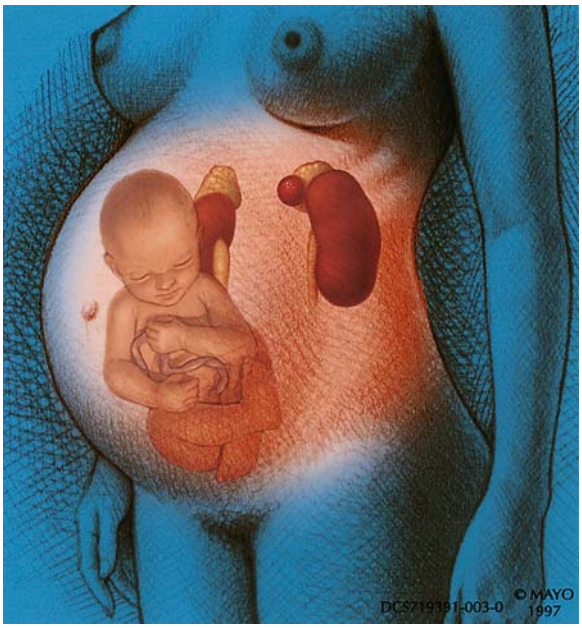

Fig. 1. The retroperitoneal location of the adrenal glands and the hormonal milieu of pregnancy make detection difficult

Patient 1: A 36-year-old woman at 27 weeks' gestation (gravida 2, para 1) presented to the emergency room with intractable emesis and dyspnea. She suffered a myocardial infarction (Fig. 2) resulting in her death and that of her fetus. At autopsy an unsuspected right-sided pheochromocytoma measuring 13×10×10 cm was found. In retrospect, during her previous pregnancy she had experienced symptoms (palpitations, flushing, headache, and emesis) of catecholamine excess. Unfortunately most adrenal tumors will be masked by the "symptoms" of a normal pregnancy – and most adrenal tumors will, therefore, go undiagnosed.

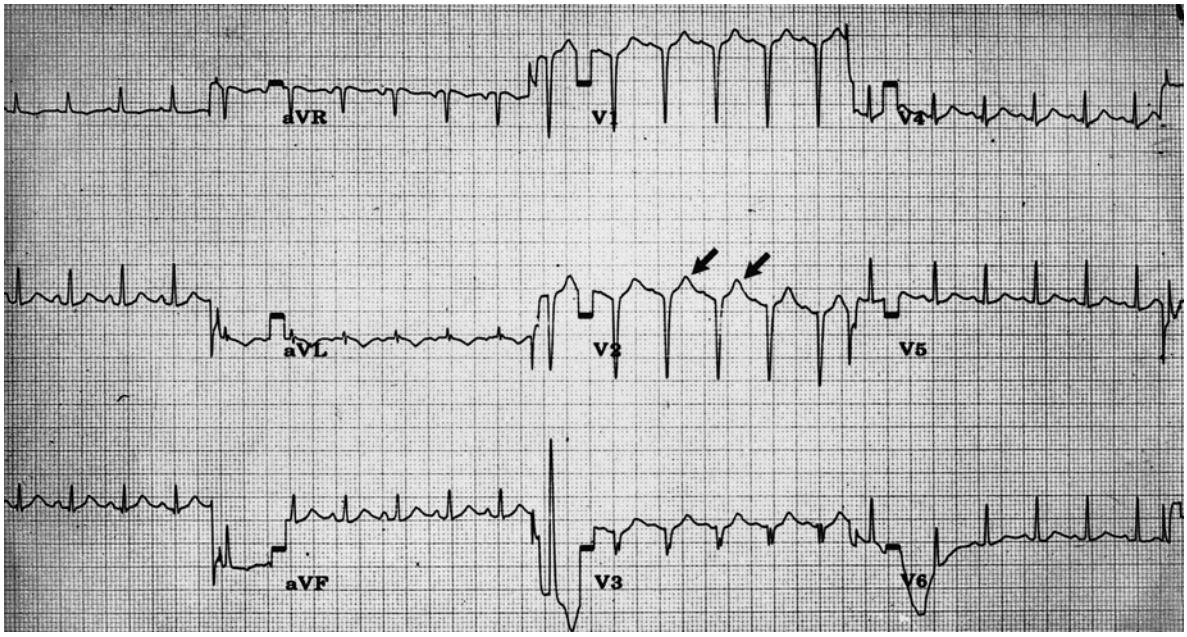

Fig. 2. An electrocardiogram showing evidence of ST segment elevation compatible with myocardial infarction

Truism #1 One needs a high index of suspicion to diagnose adrenal tumors!

Truism #2 Most pregnant women with symptomatic adrenal masses have pheochromocytomas.

Truism #3 Untreated pheochromocytomas are lethal.

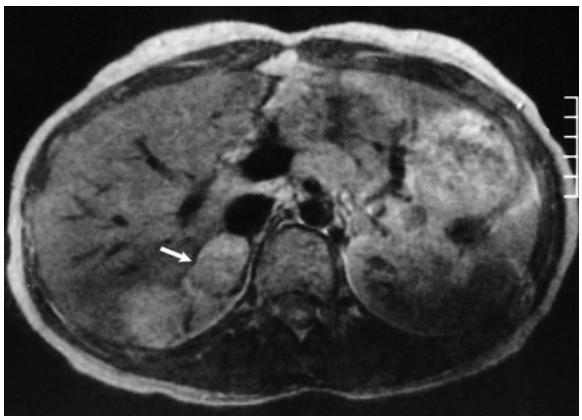

Fig. 3. Magnetic resonance imaging reveals a right-sided adrenal mass in a young woman with von Hippel-Lindau disease. (From Harrington et al. [5]. Reprinted with permission of Springer-Verlag)

Patient 2: A 29-year-old woman (gravida 2, para 1) with a family history of von Hippel-Lindau (vHL) disease was found to have a 3-cm right adrenal mass (Fig. 3), a 6-cm pancreatic mass, and an unsuspected pregnancy while undergoing routine screening for vHL disease. Early in the second trimester (17 weeks), she underwent an open right adrenalectomy, distal pancreatectomy, and an elective suction and curettage with bilateral tubal ligation. She died 3 years later due to metastatic pancreatic islet cell cancer.

Truism #4 Most adrenal tumors – whether in pregnant or non-pregnant patients – are found serendipitously.

Truism #5 Familial endocrine syndromes (multiple endocrine neoplasia [MEN], vHL, etc.) should lower thresholds to evaluate possible adrenal abnormalities.

Truism #6 If surgical intervention is advisable during pregnancy, the second trimester is best.

Patient 3: A 22-year-old woman (gravida 2, para 1) was seen at 12 weeks' gestation with increasing weakness and fatigue. Identification of hypertension and hypokalemia led to documentation of hyperaldosteronism and suppressed renin levels. An abdominal magnetic resonance imaging (MRI) study showed a 3×2×2-cm right-sided adrenal mass (Fig. 4). She had induced labor at 32 weeks' gestation for superimposed preeclampsia. The infant had respiratory distress syndrome for 15 days but eventually recovered. Two months postpartum the mother underwent a right-sided posterior adrenalectomy without complication.

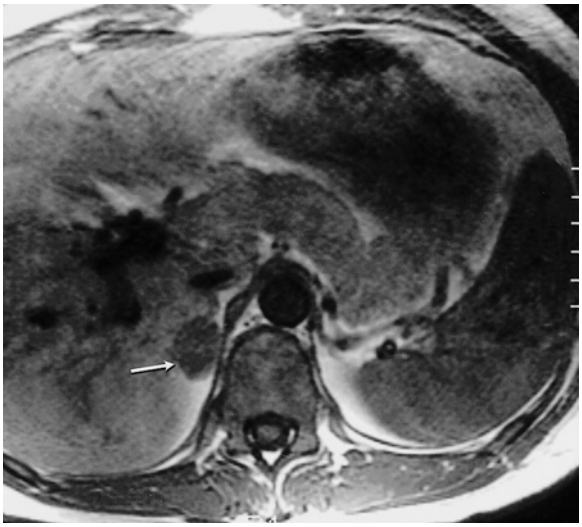

Fig. 4. Magnetic resonance imaging identifying a right-sided aldosteronoma. (From Harrington et al. [5]. Reprinted with permission of Springer-Verlag)

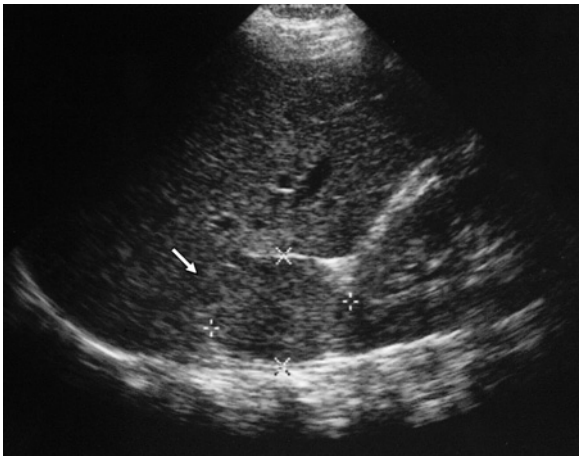

Fig. 6. Ultrasonography identifies a 6-cm right adrenal mass. (From Harrington et al. [5]. Reprinted with permission of Springer-Verlag)

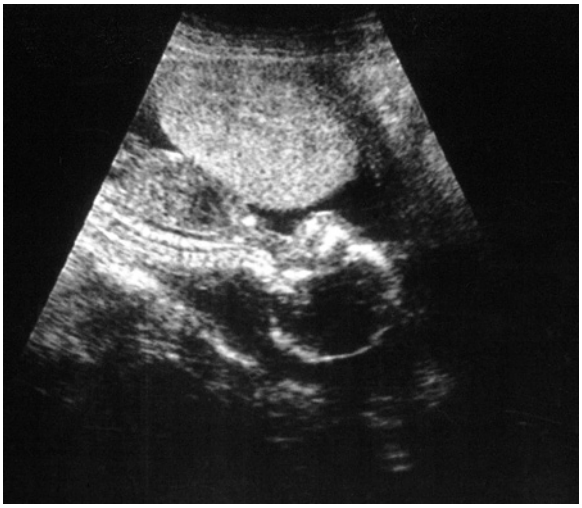

Fig. 5. Ultrasonography depicts a healthy fetus

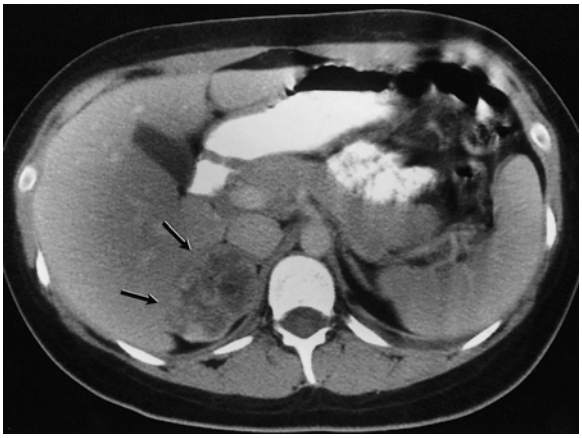

Fig. 7. Postpartum computerized tomographic scan showing a heterogeneous right adrenal mass

Truism #7 MRI is the best imaging modality to visualize adrenal glands during pregnancy.

Truism #8 Most adrenal masses found during pregnancy do not require immediate resection.

Truism #9 Functional adrenal tumors carry morbidity to the mother *and* the fetus.

Patient 4: A 21-year old woman (gravida 2, para 1) presented at 30 weeks' gestation complaining of intermittent right upper quadrant abdominal and back pain. Abdominal ultrasonography (US) revealed a healthy fetus (Fig. 5) and a 6×5×4-cm solid right-sided adrenal mass (Fig. 6). An exhaustive endocrine work-up found no laboratory abnormalities. The patient delivered a healthy baby at 39 weeks' gestation. A postpartum CT scan showed a heterogeneous mass (Fig. 7). The mass was resected laparoscopically and found to be a benign adrenal adenoma with central hemorrhage (Fig. 8).

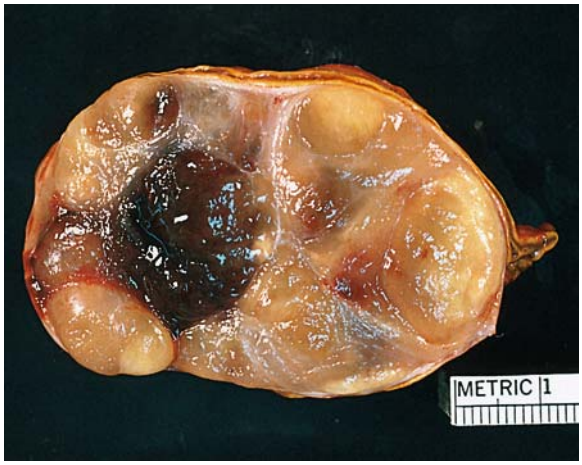

Fig. 8. Benign adrenal adenoma with central hemorrhage

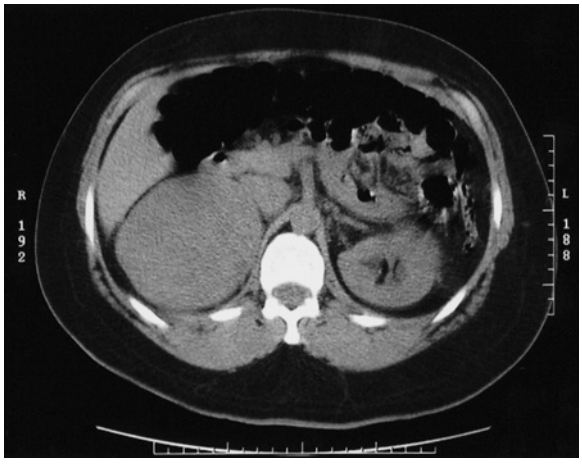

Fig. 9. Preoperative computerized tomographic scan showing what turned out to be an adrenal cortical cancer

Truism #10 Most adrenal masses are benign.
Truism #11 Laparoscopic adrenalectomy is the gold standard procedure for all patients unless hemodynamic instability or tumor size compromise surgical technique.
Truism #12 Laboratory testing during pregnancy is an inexact science.

Patient 5: A previously healthy 38-year-old woman developed difficulties during early pregnancy. Extended work-up led to identification of a large adrenal mass (Fig. 9). Concern for malignancy arose, surgical consultation was obtained, and an open adrenalectomy was performed. Histologic analysis revealed adrenal cortical carcinoma (ACC). The patient is fit and well now 9 months later.

Truism #13 Although rare, physicians must worry about adrenal masses being malignant.
Truism #14 Most adrenal masses occur in women.
Truism #15 Adrenalectomy is the only treatment for ACC.

26.2 Diagnosis and Risk

Early diagnosis and expedient treatment facilitate fetal and maternal survival in most pregnant patients with adrenal tumors. Unfortunately, in the undiagnosed mother with a pheochromocytoma, the mortality rate is 17–48% [12]. When the tumor is diagnosed in the antenatal period, maternal mortality rates are 2–4% [10]. Diagnosis intrapartum or after delivery carries a maternal mortality of 14–25% [10]. Diagnosis before delivery has a fetal mortality of 11–15%. In delayed diagnosis, fetal mortality is a staggering 26–54%. While it is important to diagnose adrenal abnormalities, the accuracy is clearly suboptimal in the pregnant patient. In fact, the sensitivity is 89% and specificity 67% for diagnosing pheochromocytomas in pregnancy [10].

The maternal mortality in undiagnosed pregnant women with cortisol-producing tumors with 5 years of follow-up is 50% [3]. The complications of being hypercortisolemic during pregnancy are hypertension (65%), superimposed preeclampsia (32%), diabetes (32%), congestive heart failure (11%), wound break down (8%), and death (5%). Although no comprehensive data exists for pregnancy and aldosteronomas, diagnosis and treatment of a cortisol- or catecholamine-producing tumor appears crucial to the survival of both the mother and the fetus.

There are several key signs and symptoms that should prompt further investigation of a possible functioning adrenal mass (especially when these features are present in the first trimester). One must remember that pheochromocytomas are, in fact, responsible for 1/200 cases of hypertension in all patients [2]. Even in pregnancy, pheochromocytoma is rarely associated with proteinuria (<20%) or thrombocytopenia as is commonly seen in women with preeclampsia or eclampsia. The primary symptoms of a pheochromocytoma are indeed: hypertension (98%), headaches (80%), hyperhidrosis (65%), and heart palpitations (60%). The symptoms of pregnant women with Cushing's syndrome are the same as in the non-pregnant state: truncal obesity, abdominal striae, moon facies, and glucose intolerance. As such, they are often masked by pregnancy. Signs specific for cortisol-producing tumors include hyper-

tension, hypokalemia, muscle weakness, or paralysis. The diagnosis of an adrenal tumor will therefore only occur if the physician is actively looking for such signs and thinking about them. The presence of such foreshadowing signs raises suspicion for the presence of an adrenal mass; serologic, urine, and imaging studies should then be considered.

26.3 Hormone Levels and Lab Analysis

Laboratory studies can be difficult to interpret due to the biochemical changes that a woman's body undergoes during pregnancy. While pregnancy causes many hormone levels to be elevated, most hormone levels remain the same as when a woman is not pregnant. Importantly, catecholamine levels remain normal in pregnancy, but do become elevated in the presence of a pheochromocytoma. Therefore, changes in catecholamine levels can be measured accurately without considering the effect of pregnancy. In order to diagnose a pheochromocytoma, a 24-h urine specimen should be obtained. Although several groups now tout plasma catecholamine analysis, we prefer the greater accuracy of 24-h urinary studies. Urinary-free catecholamines (epinephrine, norepinephrine, and dopamine) levels should be measured (Table 1). Breakdown products of metanephrines (M) and vanillylmandelic acid (VMA) should also be checked. While the sensitivity for urinary M (67–91%) or VMA (28–56%) is low, the specificity for both M (83–100%) and VMA (98–100%) urinary levels are excellent. If normal levels of urine catecholamines are obtained on two separate occasions, then a diagnosis of pheochromocytoma can be excluded.

In normal pregnancy both aldosterone and renin levels are increased. By 8 weeks' gestation there is a fourfold increase in aldosterone levels, which continues to rise to a maximum of ten times the normal level at delivery. Progesterone is markedly increased in pregnancy and acts as a competitive inhibitor of aldosterone in the distal tubules; therefore, the physiological effects of increased aldosterone are tempered in pregnancy [6]. Consequently, measuring aldosterone is inherently inaccurate during pregnancy. There is sparse literature on the biochemical diagnosis of aldosterone-producing tumors during pregnancy. When attempting to assess aldosterone levels, hypokalemia should be corrected because a low potassium level will suppress aldosterone. Urine potassium levels must be measured to confirm potassium wasting. Plasma renin levels can be checked, but levels are usually higher in pregnancy. While virtually all pregnant women will have "physiologic" hyperaldosteronism, coupling low potassium levels and lower than normal (typically high) renin levels should prompt imaging for an aldosteronoma.

There are no definitive criteria for hypercortisolemia in pregnancy; normally, urinary-free cortisol and plasma cortisol levels are elevated (68–252 μg/dl) at least three times as high as in the non-pregnant state (11–83 μg/dl). Diurnal rhythms are normally maintained in pregnancy but are typically blunted in Cushing's syndrome [9]. Hence the plasma cortisol levels of pregnant women remain elevated but on a normal cycle. Having stated that, making the diagnosis and identifying the source of hypercortisolism in pregnancy is difficult. A dexamethasone suppression test is not accurate in the estrogen excess state of pregnancy because of the elevation of total serum cortisol. In preg-

Table 1. Measurement of urinary-free catecholamine levels

	Normal pregnancy values	Non-pregnancy values
Epinephrine (μg/24 h)	0.5–20	0.5–20
Norepinephrine (μg/24 h)	10–70	10–70
Metanephrine (μg/24 h)	<1.3	<1.3
Vanillylmandelic acid (μg/24 h)	<6.5	<6.5
Dopamine (nmol/24 h)	300–3,900	300–3,900
Aldosterone	4–10× increase	1–21 ng/dl
Renin	Elevated	?
Serum cortisol	?	7–25 μg/dl AM 2–14 μg/dl PM
Urine-free cortisol	68–252 μg/dl	24–108 μg/24 h

nancy there will effectively be a lack of suppression by dexamethasone. It has been suggested that a 24-h urine-free cortisol level in multiple samples and serum cortisol measurements at 0800 and 2300 hours (assessing the diurnal rhythm) be drawn. If these results suggest an unusually elevated cortisol, plasma ACTH levels should be measured in order to differentiate the tumor as ACTH dependent or independent.

26.4 Adrenal Imaging During Pregnancy

Imaging studies should follow a confirmed biochemical diagnosis (especially in the case of a pheochromocytoma). MRI is the preferred modality to use in the pregnant patient because it will produce high quality images but will not expose the fetus to harmful radiation or toxic contrast dye. Pheochromocytomas often appear as bright masses on T2-weighted images, allowing one to distinguish a pheochromocytoma from the asymptomatic or incidental adrenal adenoma found in as many as 5% of such studies [10]. More recent literature suggests that abdominal US can be helpful in detecting pheochromocytomas [12]. Given both ionizing radiation and contrast dye are teratogenic to the fetus, both CT and angiography are contraindicated in pregnancy. While metaiodobenzylguanidine (MIBG) is selectively taken up by adrenergic tissues, MIBG scans are similarly contraindicated in pregnancy (Table 2) [2, 6].

26.5 Treatment

Total eradication of an offending adrenal mass involves surgical resection. However, depending on the stage of pregnancy and the type of tumor, medical management may be more appropriate therapy … at least initially. While most functioning adrenal tumors should be removed sooner rather than later, adding a fetus to the equation alters "best management". Surgical resection in the first trimester is controversial because of the increased risk of fetal morbidity and mortality. Surgical intervention in the third trimester carries a high risk of spontaneous delivery, and adrenalectomy during this late stage is usually deferred until delivery or postpartum. The safest time for adrenal resection is the second trimester: less teratogenicity, less fetal morbidity and mortality, and less likely to induce premature delivery.

As described elsewhere in this text, after the diagnosis of pheochromocytoma has been confirmed and the tumor localized, the first line of therapy is pharmacologic. Alpha-blockade is performed preferably with phenoxybenzamine, as there is no evidence that this drug is teratogenic to the fetus. If symptoms continue and are not well controlled with this alpha-blocker, then a beta-blocker may be added, but this is controversial during pregnancy. Propranolol is commonly used but can cause intrauterine growth retardation (IUGR) (Table 2); therefore, its use should be very temporary (<72 h) or fetal monitoring must occur frequently.

Operative resection is the only curative treatment for pheochromocytoma. However, urgent surgical intervention must be weighed against the potential morbidity and/or mortality of the fetus and mother versus the risk of medically managing blood pressure through delivery. In early pregnancy, before 24 weeks' gestation, adrenalectomy carries more risk: 44% risk of fetal demise. A 22% risk of fetal death occurs if resection is performed after 24 weeks [6]. Despite these statistics an operation may need to be performed within the first 24 weeks if the mother and fetus are deteriorating or in an attempt to protect both from labile blood pressures. Delaying operation on the other hand creates an increased risk of stroke, myocardial infarction, or hemorrhage into the tumor [10]. If surgical delay is chosen, then it is best to treat the patient med-

Table 2. Contraindications in pregnancy

Imaging study	Complications
Computerized tomography	Teratogenic to fetus
Metaiodobenzylguanidine	Teratogenic to fetus
Medications	**Complications**
Spironolactone	Feminizing affect on male fetuses
ACE inhibitor (angiotensin-converting enzyme)	Oligohydramnios and neonatal renal failure
Propranolol (beta-blockers)	Intrauterine growth retardation (IUGR)

ically until the fetus is viable and ready for cesarean section. Vaginal birth and concomitant adrenalectomy is contraindicated because of the 31% risk of maternal mortality for such a practice; unfortunately a 19% risk of maternal mortality is associated with a planned C-section [6]. Detection of the pheochromocytoma during the third trimester is cause to postpone operation until a pre-planned C-section delivery of a mature fetus can occur [12]. In the interim medical management is usually sufficient.

Although timing of intervention is difficult for pheochromocytomas, such is not the case for cortisol-producing tumors. Resection should be performed immediately, as early as 12 weeks' gestation, due to the proven detrimental affects of extreme hypercortisolemia on the fetus. According to a report of 60 women with 69 pregnancies, fetuses growing in the presence of cortisol-producing tumors are at an increased risk to be delivered stillborn (12%), or prematurely (52%), spontaneously abort (12%), or are born with IUGR (25%) [15]. While it is better for the fetus to have the mother receive surgical treatment, at least one study (n=43) suggests there are significant risks associated with adrenalectomy: premature birth (47%), IUGR (35%), neonatal death (12%), and perinatal death (12%) [3]. Additional studies find that if the patient delays operation until after the delivery, the risk is great for: premature birth (72%), IUGR (26%), neonatal death (7%), stillbirth (12%), and perinatal death (19%) [10].

Medical treatment remains controversial as to its effectiveness in the case of Cushing's syndrome. Prebtani et al. [13] suggest that in the first trimester medical therapy should be used and operation can wait until the second semester. In the third trimester medical therapy is advised until fetal development is complete. Part of the dispute is due to the limited number of reported cases and data. If the tumor is discovered in the third trimester, there are three published cases where ketoconazole was successfully used despite its known teratogenic association and its ability to cause transplacental passage and reduction of fetal steroid production [13]. Lo has suggested the usage of metyrapone to treat the hypercortisolism. Metyrapone is an inhibitor of 11-beta-hydroxylase and leads to a reduction of cortisol levels. This treatment could be used to stabilize patients prior to operation or as an alternative for poor surgical candidates. While metyrapone has the potential to cross the placenta and affect fetal adrenal steroid synthesis, there have been no identifiable adverse effects reported [9]. Prior to elective operation, hypertension and diabetes should be controlled as well.

With primary aldosteronism in pregnancy, surgical intervention is preferred but medical management is a viable option. Hypokalemia must be corrected immediately because of its detrimental affect on fetal energy supply resulting in IUGR [4]. Operation, if selected, should be performed in the early second trimester. After resection, potassium levels and hypertension immediately improve. If the adenoma is detected in the third trimester, medical management is suggested, using potassium supplementation and anti-hypertensives, such as methyldopa, beta-blockers, calcium channel blockers, or hydralazine. Spironolactone and angiotensin converting enzyme (ACE) inhibitors are contraindicated in pregnancy. Spironolactone has feminizing affects on male fetuses. ACE inhibitors cause oligohydramnios and neonatal renal failure.

26.6 Operative Strategy

The rarity of these tumors is such that most of the literature on adrenal tumors during pregnancy focuses on the removal of pheochromocytomas. A pheochromocytoma may be removed by open or laparoscopic techniques without interfering with the gravid uterus, but the risk of spontaneous abortion is increased with laparotomy [2]. Regardless of the technique, the patient must be carefully positioned. Facilitating exposure for the surgeon is paramount, but keeping the gravid uterus off the inferior vena cava (IVC) to maintain venous return to the heart is important. Left lateral decubitus positioning for a right adrenalectomy (Fig. 10) and use of the reverse Trendelenburg

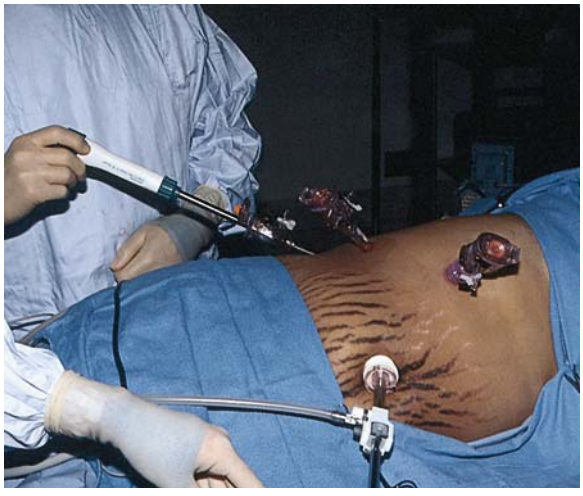

Fig. 10. Preoperative view depicting left lateral decubitus positioning for a right adrenalectomy

position for resecting either gland minimizes IVC compression.

There are laparoscopic considerations to be aware of. The unknown effects of the carbon dioxide (CO_2) pneumoperitoneum on the fetus, possible risk of uterine damage during trocar placement, premature labor due to increased intra-abdominal pressure, and fetal acidosis are all possible harms to the fetus [12]. Given thousands of pregnant women have safely undergone laparoscopic cholecystectomy, laparoscopic adrenalectomy during pregnancy should similarly be safe and efficacious. Two well documented adrenalectomies in pregnant women showed no maternal hypotension, hypoxia, increased end-tidal carbon dioxide, or decreased fetal heart rate during laparoscopic operations [1]. With the use of laparoscopy during pregnancy there is less fetal depression secondary to the decreased use of narcotics, a lower rate of maternal wound complications, diminished postoperative maternal hypoventilation, and more rapid return to a full diet for the mother which decreases nutritional stress on the fetus [12].

If the surgeon decides that adrenalectomy will not occur intrapartum, then tumor removal may occur at delivery or postpartum. This decision depends on the ability to locate the tumor at the time of the C-section. It is suggested that a longer longitudinal incision be made to facilitate easier localization and removal. During an open adrenalectomy, control of excess catecholamine release is maintained via deep anesthesia and adrenergic blocking medications. Magnesium sulfate has been shown to inhibit catecholamine release, block catecholamine receptors directly, and have a direct dilator affect on vessel walls. Once the tumor is removed the mother's symptoms are relieved and postpartum complications are minimal, assuming the patient is well hydrated.

In patients with cortisol-producing tumors, the collective literature suggests the frequency of maternal and fetal complications in patients undergoing adrenalectomy *during* pregnancy is lower than those having adrenalectomy *postpartum* [1]. Nonetheless, debate continues as to whether or not surgical intervention can be postponed until after the delivery. Pricolo et al. [14] found that in a study which included 19 women with 26 pregnancies involving cortisol-producing adrenal adenomas, that fetal and neonatal complications, when adrenalectomy was performed intrapartum, compared favorably (1 in 7, 14%) to operations performed postpartum (12 complications in 19 patients, 63%). Similarly, resection during pregnancy generated fewer maternal complications (7%) than postpartum adrenalectomy (84%). Early surgical resection to correct hypercortisolism appears safer for both mother and child. The general consensus is that surgical intervention depends on the severity of hypercortisolism and the gestational age of the fetus [13]. If adrenalectomy is postponed until after the delivery, vaginal delivery is preferred over C-section because of the mother's poor tissue healing and potential for wound breakdown [3].

26.7 Summary

Adrenal tumors causing problems during pregnancy are rare. Having such lesions diagnosed before childbirth is extraordinarily uncommon and typically serendipitous. Most *functional* adrenal tumors require surgical resection or medical intervention to prevent IUGR or fetal death. Therefore, when a pregnant woman presents with hypertension without proteinuria and/or without thrombocytopenia (typical for preeclampsia), the physician *must* begin to explore the possibility of pheochromocytoma. Primary hyperaldosteronism and cortisol-producing adenomas are even more difficult to detect, but clinical suspicion with confirmatory laboratory analysis and imaging studies (MRI is best choice) allow physicians the opportunity to intervene earlier. While most patients can undergo delayed resection following childbirth (Fig. 11), surgeons should opt for adrenalectomy in the second trimester for most cortisol-producing tumors and those pheochromocytomas and aldosteronomas that remain refractory to pharmacologic therapy.

Fig. 11. Healthy mother and child following adrenalectomy at 39 weeks' gestation

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