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Surgical treatment of adrenal tumors during pregnancy

Marisa A. Bartz-Kurycki[1] · **Sophie Dream**[1] · **Tracy S. Wang**[1]

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Abstract
While most adrenal tumors are identified incidentally and are non-functional, hormone-secreting tumors can cause morbidity and mortality. Hemodynamic lability and hypertension in pregnancy are associated with worse maternal and fetal outcomes. Achieving a diagnosis of hormone excess due to adrenal tumors can be clinically more difficult in the gravid patient due to normal physiologic alterations in hormones and symptoms related to pregnancy. This review focuses on some nuances of the diagnostic work-up, perioperative care, and surgical management of adrenally-mediated cortisol excess, primary aldosteronism, and pheochromocytoma and paraganglioma in the pregnant patient.

Keywords Adrenalectomy · Pregnancy · Pheochromocytoma · Adrenal tumors

Abbreviations

ACC	Adrenocortical carcinoma
ACTH	Adrenocorticotrophic hormone
ARR	Aldosterone-renin ratio
AVS	Adrenal vein sampling
BAH	Bilateral adrenal hyperplasia
CRH	Corticotropin-releasing hormone
CT	Computed tomography
DST	Dexamethasone suppression testing
DVT	Deep venous thrombosis
HU	Hounsfield units
IV	Intravenous
IVC	Inferior vena cava
LNSC	Late-night salivary cortisol
MACE	Mild autonomous cortisol excess
MRA	Mineralocorticoid receptor antagonists
MRI	Magnetic resonance imaging
PA	Primary aldosteronism
PASO	Primary Aldosteronism Surgical Outcome
PPGL	Pheochromocytoma and paraganglioma
PRA	Posterior retroperitoneoscopic approach
RAV	Right adrenal vein
TA	Transabdominal adrenalectomy
UFC	Urinary free cortisol

1 Introduction

Adrenal nodules are incidentally identified in 5–7% of patients, primarily as a result of increased use of abdominal imaging.[1, 2] Though adrenal nodules are more prevalent in older patients, approximately 2–10% of adults will have adrenal neoplasms.[3, 4] Amongst incidentally-found nodules, most are benign and non-functional (50–60%).[2, 5] Functional tumors can secrete cortisol, aldosterone, catecholamines, and/or androgens. Adrenocortical carcinoma (ACC), is an aggressive malignant neoplasm that accounts for 2–12% of adrenal masses, which can only be cured with surgical resection.[2, 5].

Adrenal tumors are exceedingly rare in pregnancy, but functional adrenal tumors can have serious effects on maternal and fetal outcomes, related to the type of hormone and degree of excess hormone production. Appropriate workup involves imaging and laboratory studies to evaluate for ACC and functional tumors (Fig. 1). This review discusses diagnostic challenges, indications for surgery, perioperative management, surgical approaches, and outcomes for gravid patients with adrenal tumors.

✉ Tracy S. Wang
tswang@mcw.edu

[1] Department of Surgery, Medical College of Wisconsin, Milwaukee, WI, USA

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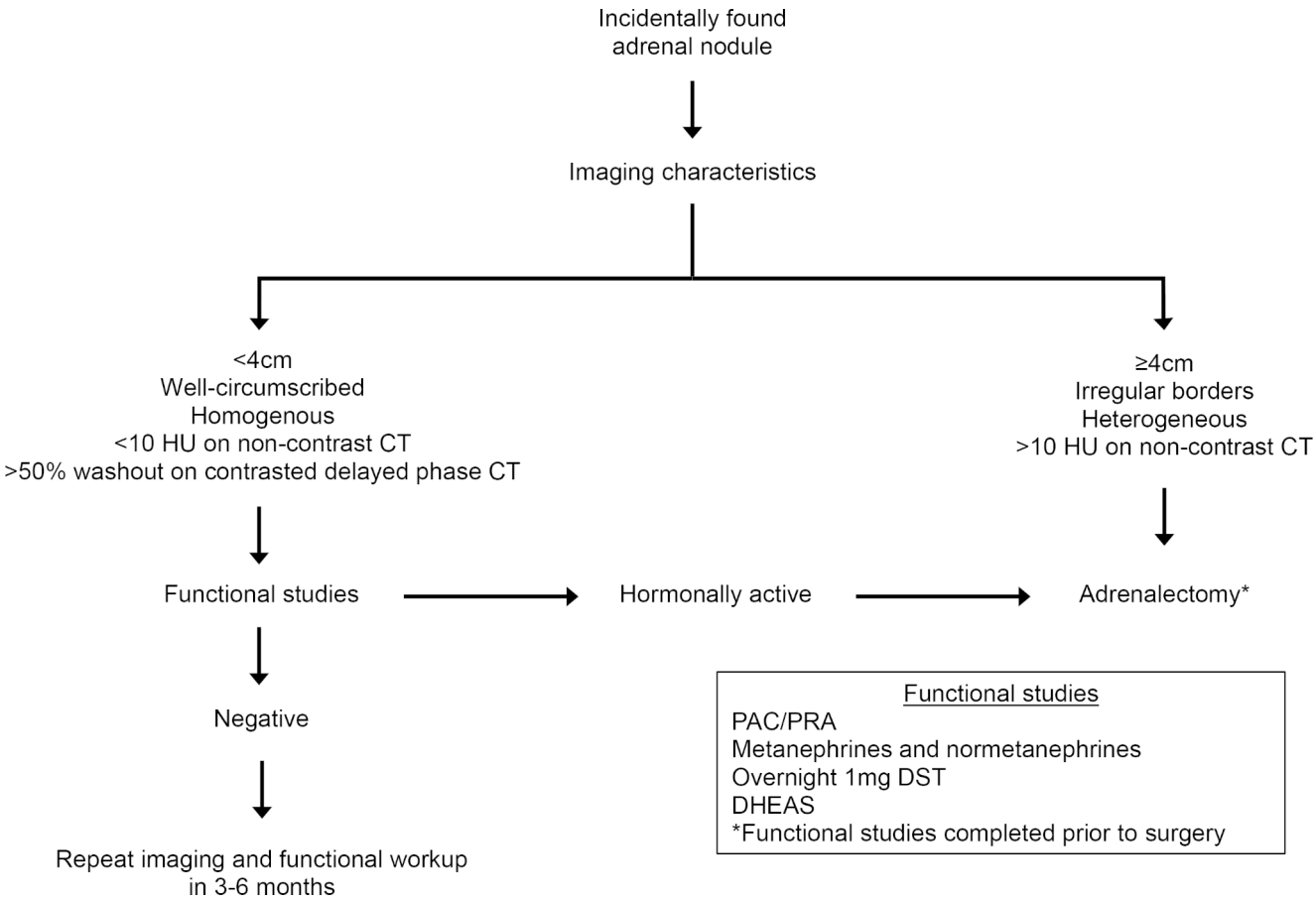

Fig. 1 Stepwise assessment and management of incidentally-found adrenal nodules. Abbrev: HU = Hounsfield units. CT = computed tomography. PAC = plasma aldosterone concentration. ARR = plasma renin activity. DST = dexamethasone suppression test. Adapted from Zeiger M et al. American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons Medical Guidelines for the Management of Adrenal Incidentalomas. Endocr Pract. 2009;15 Suppl 1:1–20

2 Imaging

For patients being evaluated for symptoms concerning for a functional primary adrenal tumor, such as hemodynamic lability, headaches, recalcitrant hypertension, and/or symptoms of cortisol excess, imaging of the abdomen may be necessary. Cost, speed, and lack of radiation are advantages of ultrasound. However, due to the anatomic location of the adrenal glands, adequate evaluation can be challenging. The quality of the study depends on patient body habitus as well as the experience and skill of the ultrasound technician.[6].

Magnetic resonance imaging (MRI) is the preferred imaging modality in pregnant patients due to the risks to the fetus associated with ionizing radiation in computed tomography (CT).[7, 8] Typically, adrenal adenomas will have reduced signal intensity on out-of-phase images and augmented signal intensity on in-phase images. In contrast, signal intensity in malignant lesions, pheochromocytomas, and lipid-poor adenomas will not change phase-to-phase. [9, 10] Low-dose CT protocols may be considered if initial MRI is indeterminate or if availability to obtain a MRI is limited. Non-contrast CT scans that demonstrate a mass with Hounsfield units (HU) less than 10 are suggestive of an adenoma.[11] Lipid-poor adenomas may display values of 20–40 HU, and in these cases contrasted imaging is necessary to further characterize the lesion. On contrasted triple phase CT scans, adenomas will enhance with values up to 80–90 HU and exhibit washout of contrast more than 50% on delayed phase images.[3, 9, 12] Characteristics such as irregular borders, size ≥ 4 cm, growth > 1 cm, and internal heterogeneity raise concern for ACC, pheochromocytoma, or metastases to the adrenal gland. Contrast agents for imaging, both iodinated and gadolinium, have not been shown to have teratogenic effects. Iodinated contrast has the potential to suppress neonatal thyroid function. If administered during pregnancy, it is recommended that the infant be screened for hypothyroidism during the first week of life.[13].

3 Hypercortisolism

3.1 Diagnosis

Hypercortisolism of adrenal origin is quite rare in the pregnant population (0.07 patients per 100,000), but is also more difficult to diagnose in the setting of pregnancy.[14] Cortisol production increases throughout pregnancy as a result of placental secretion of corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH). Normal diurnal variation is maintained in pregnancy, however, serum cortisol levels are increased without diurnal variation in patients with hypercortisolism. [15] The 2008 Endocrine Society guidelines for the diagnosis of hypercortisolism recommend the use of urinary free cortisol (UFC) as first line testing in non-pregnant patients.[16] However, increased levels of UFC are observed in pregnancy and therefore, less reliable, especially in the first trimester. Low-dose dexamethasone suppression testing (DST) has greater potential for false-positive results in gravid patients due to the increased cortisol levels, therefore DST is not recommended for first line evaluation in pregnant patients. [16] More recent studies have suggested that late-night salivary cortisol (LNSC) levels may be helpful in the diagnostic work-up of pregnant women. Prospective evaluation of LNSC in pregnant patients identified the following upper limits of reference ranges by trimester: first trimester 0.25 lg/dL (6.9 nmol/L), second trimester 0.26 lg/dL (7.2 nmol/L), and third trimester 0.33 lg/dL (9.1 nmol/L). [17] Clinically, hypercortisolism may also be more difficult to diagnose in the gravid patient as many of the signs overlap with normal physiologic changes in pregnancy. Despite these challenges, diagnosis of hypercortisolism should be suspected when the UFC is three times greater than the upper limit of the reference range.[18].

3.2 Management

Overt hypercortisolism is associated with maternal morbidity and adverse fetal outcomes; adrenalectomy is first-line treatment for gravid patients who can otherwise tolerate surgery given the potential adverse effects of medications that inhibit steroidogenesis.[15, 18, 19] Medical management is considered in patients for whom the risks of surgery outweigh potential benefits.[15] Metyrapone, which inhibits steroidogenesis at the adrenal gland via CYPB11B1, is the most commonly used medical treatment for hypercortisolism in pregnancy because it does not have adverse effects on the liver and does not affect fetal development.[20] Frequent monitoring is necessary as metyrapone may worsen hypertension and preeclampsia secondary to salt retention. Ketoconazole, mitotane, and aminoglutethimide are other medications used for the treatment of hypercortisolism; however, these drugs are contraindicated in pregnancy due to their teratogenic potential on the fetus. Ketoconazole also may have anti-androgenic effects on the fetus, while mitotane and aminoglutethimide may result in virilization.[15, 18, 20].

The diagnosis of mild autonomous cortisol excess (MACE) can be controversial, but is generally considered to be present in patients with a cortisol level > 1.8 μg/dL and < 5.0 μg/dL in response to 1 mg overnight DST or LNSC ≥ 3 nmol/L in the absence of overt symptoms of hypercortisolism, although patients may have associated comorbidities of hypertension, diabetes, obesity, and dyslipidemia. [9, 21–23] Limited data is available regarding the effects of MACE in pregnant patients. A multidisciplinary discussion regarding adrenalectomy in these patients during pregnancy is advised.[24].

3.3 Perioperative Considerations

Patients with hypercortisolism have a greater risk of deep venous thrombosis (DVT).[25] Pregnancy is a hypercoagulable state that already carries an increased risk of DVT related to venous compression and alterations in levels of coagulation factors. Consideration should be given to DVT prophylaxis prior to surgery. If the patient develops a DVT or pulmonary embolism while gravid, low molecular weight heparin or unfractionated heparin are the recommended anticoagulants.[26].

Due to the risk of adrenal insufficiency following unilateral adrenalectomy, particularly in patients with overt hypercortisolism, a discussion between the surgeon, anesthesiologist, and obstetrician should take place prior to surgery regarding the perioperative use of glucocorticoid replacement.[3, 21].

3.4 Postoperative management

Adrenal insufficiency following adrenalectomy for hypercortisolism in gravid patients is possible and should be anticipated. Symptoms of adrenal insufficiency include fatigue and generalized weakness. Patients may also experience nausea, vomiting and abdominal pain. Hypotension, hyponatremia, and hyperkalemia are signs of adrenal insufficiency. Prior studies have demonstrated that approximately half of patients undergoing adrenalectomy for hypercortisolism, MACE, and PA will require glucocorticoid supplementation postoperatively.[22, 23] There is insufficient evidence to recommend for or against routine glucocorticoid replacement in pregnant patients undergoing adrenalectomy for hypercortisolism. Small case series of gravid patients who underwent adrenalectomy for hypercortisolism have

demonstrated glucocorticoid replacement in 75% of patients for a duration of 1 week to 60 months.[27] Other series do not report glucocorticoid replacement at all.[20] The decision to start glucocorticoid replacement should be individualized and based on the judgment of the multidisciplinary team of endocrinology, surgeon, and maternal-fetal medicine. At our institution, we favor selective glucocorticoid replacement, as described below.

In the non-pregnant patient, the authors do not routinely start glucocorticoid replacement, except for patients with severe hypercortisolism preoperatively. At our institution, IV glucocorticoid replacement is reserved for patients with signs of adrenal insufficiency (hypotension, hyponatremia, hypokalemia, gastrointestinal upset, weakness and/or fatigue). Our institutional protocol involves cosyntropin stimulation testing for most patients with overt hypercortisolism, MACE, and PA (if preoperative evaluation for hypercortisolism was not performed).[22, 23, 25] As part of this assessment, ACTH, basic chemistry panel, and cortisol are obtained prior to cosyntropin administration. Cortisol levels are drawn again 30 and 60 min after cosyntropin administration. If the baseline cortisol level is < 5 µg/dL or stimulated cortisol levels are < 14 µg/dL, we will begin glucocorticoid replacement (GR) with oral hydrocortisone 20 mg in the morning and 10 mg in the evening. After postoperative follow up, care is transitioned to the patient's endocrinologist as GR replacement often continues for 1–2 years after surgery.[23] This is in line with the Endocrine Society clinical practice guidelines.[25] Some institutions routinely utilize glucocorticoid replacement following unilateral adrenalectomy for hypercortisolism.[28, 29] If glucocorticoid replacement is utilized, the hypothalamic-pituitary-adrenal axis should be reassessed every 3–6 months.[16].

4 Pheochromocytoma and paraganglioma (PPGL)

4.1 Diagnosis

Pheochromocytoma is exceedingly rare in pregnancy, affecting less than 0.01% of patients.[14, 30, 31] Most patients with functioning PPGL present with hypertension, palpitations, headaches, and diaphoresis. The presentation of PPGL can be difficult to differentiate from pregnancy-induced hypertension; however, patients with PPGL typically do not exhibit proteinuria or edema.[15, 32] Plasma-free metanephrines and/or 24-hour urine metanephrines should be obtained to evaluate for PPGL. Plasma free metanephrines are usually the first line test as it is more feasible and has higher sensitivity.[3, 33] False-positive rates of up to 20% have been reported.[34] Thus positive tests should be followed by a confirmatory test, such as 24-hour urine fractionated metanephrines. Plasma-free metanephrines should be drawn after the patient has been resting in the supine position for at least 20 min. Laboratory values drawn with insufficient rest period may result in values that are up to 30% greater due to postural sympathetic activation.[35, 36] In the second and third trimesters, it is advised that gravid patients should not lay supine due to increased pressure of the uterus on the IVC, which may affect the results.

A recent study of PPGL in pregnant patients demonstrated catecholamine secretion in 95% of patients, and more than 80% with catecholamine levels more than 5 times the upper limit of normal.[37] Unfortunately, there is a paucity of data regarding normal and abnormal plasma and urine metanephrine levels in the pregnant population. Given the lack of data and that complications are associated with the degree of catecholamine excess, we recommend using the cutoff of 2 times greater than the upper limit of normal for screening and 3 times greater than the upper limit of normal for confirmation for plasma free metanephrines.[2, 3] For 24 h urinary metanephrines, a total level > 1800 µg is often consistent with PPGL.[3] Antihypertensives, such as alpha-methyl dopa and labetalol, can interfere with liquid chromatography-electrochemical detection assays, but usually do not affect liquid chromatography tandem mass spectrometry assays. Additionally, it is important to note whether the patient is taking any tricyclic antidepressants, decongestants, and phenoxybenzamine which can result in a false positive test. Genetic counseling and testing should be offered to the patient as a heritable mutation will be identified in up 30–66% of patients.[15, 33, 37].

4.2 Management

Patients with PPGL should also be referred for surgical consultation, as the effects of excessive catecholamine release can lead to maternal cardiovascular morbidity, such as stroke, cardiomyopathy, and myocardial infarction, and mortality.[37] Additionally, the hemodynamic lability associated with PPGL can have adverse consequences on placental circulation.[30, 38] Hypertension, both sustained and paroxysmal, are associated with end-organ damage in the mother and adverse effects on the fetus, including growth restriction and fetal demise.[39] Medical management with alpha blockade may be sufficient; however, adrenalectomy is recommended for patients with refractory hypertension despite medical management as well as for patients who cannot tolerate the medication side effects.[37, 38].

A recent study by Bancos et al. demonstrated that early diagnosis and treatment of PPGL is critical in pregnancy to reduce complications. In patients with PPGL diagnosed before pregnancy, there were no maternal complication,

while complications or death occurred in 36% and 64% of patients who were diagnosed during or after pregnancy, respectively. Preterm delivery was also associated with a higher rate of complications.[37] Compared to previously published data which demonstrated a maternal mortality rate of 8%, this series demonstrated improved maternal mortality, at a rate of 1%.[37, 40] In the same study, fetal loss was observed in 9% of pregnancies, compared to 17% in prior studies.[37, 40] These improved outcomes are associated with early detection and treatment of PPGL.[37].

4.3 Perioperative considerations

Patients diagnosed with a PPGL during or after pregnancy have a higher rate of maternal and fetal complications compared to those who were diagnosed before pregnancy. Among women who were diagnosed before or during pregnancy, those who did not undergo alpha-adrenergic blockade had three times greater odds of complications compared to patients who were treated with alpha blockade during pregnancy. [37] Alpha blockade should begin at least 2 weeks prior to surgery.

Doxazosin (alpha-1 antagonist) and phenoxybenzamine (non-selective, irreversible alpha antagonist) are the most commonly used agents for functional PPGL. While both medications are Class C medication per the FDA and cross the placenta, doxazosin is associated with reduced risk of reflex tachycardia and post-operative hypotension.[38] Phenoxybenzamine may be more useful for patients with severely elevated levels of metanephrines, multifocal, and/or large tumors, though respiratory depression and hypotension has been reported in neonates.[38, 41] Effects on the fetus are not well known for these medications. Animal studies of doxazosin have not demonstrated teratogenic effects and it is felt that the risks associated with hypertension may outweigh the risks of doxazosin.[42] Calcium-channel blockers can also be considered for refractory hypertension. Metyrosine is also a class C medication and should be used with extreme caution in pregnant patients.[43].

4.4 Postoperative management

Postoperatively, patients must be monitored for hypotension, although admission to intensive care is often not necessary. Factors contributing to postoperative hypotension include hypovolemia from preoperative vasoconstriction and volume contraction, residual alpha blockade in the setting of sudden decline in catecholamines after resection, effects from other antihypertensive agents, and intraoperative blood loss. Most patients will be managed successfully with IV fluid resuscitation, though approximately 10% of patients may require transient vasopressor support.[33, 44, 45] There is insufficient data to determine whether vasopressor support is increased in pregnant patients compared to non-pregnant patients undergoing adrenalectomy.

Rarely, patients can also exhibit hypoglycemia after PPGL resection due to insulin resistance and liver glycogenolysis related to the effects of catecholamine excess on pancreatic islet cells.[44, 46] Without a surplus of catecholamines, liver glycogenolysis declines and sensitivity to insulin improves. When observed, it is usually within 24 h of resection.[46] Insulin resistance has been observed due to hormonal changes in pregnancy, thus there is even greater potential for hypoglycemia in these patients.[47] Postoperatively, we recommend routine monitoring for hypoglycemia and use of IV fluids containing 5% dextrose as indicated.

Resection of PPGL is associated with improvements in hypertension, diabetes, and cardiovascular risk.[33] The risk of recurrence depends on the pathology of the tumor. Patients with benign tumors have a low risk of 5-year recurrence (2.0-6.5%).[44, 48] Lifelong surveillance for recurrence is recommended for patients with PPGL with high-risk features (genetic mutation, young age at diagnosis, paraganglioma, and large tumor).[33, 44, 49] For average risk patients, surveillance is recommended for at least 10 years.[49] Surveillance should include plasma metanephrines 2–6 weeks following resection and annually thereafter.[33, 49] Imaging should be performed every 1–2 years in patients without catecholamine-secreting PPGL and when plasma metanephrines are elevated.[33, 44, 49].

5 Primary Aldosteronism

5.1 Diagnosis

Primary aldosteronism (PA) is a group of conditions characterized by secondary hypertension due to excess secretion of aldosterone by one or more of the adrenal glands; hypokalemia may also be present.[50] Increases in estrogen and progesterone during pregnancy lead to increased secretion of renin, angiotensinogen, and angiotensin-converting enzyme. As a result, angiotensin II secretion is also increased and incites the zona glomerulosa of the adrenal cortex to secrete more aldosterone. By the end of pregnancy, aldosterone levels can reach levels that are 10-fold greater than baseline.[51] Aldosterone acts to reduce sodium excretion and augment potassium losses at the kidney. Increases in physiologic levels of aldosterone in pregnancy are countered by the competitive inhibition of progesterone in the distal convoluted tubule. These physiologic effects lead to hypervolemia during the first trimester, however, patients who do not have PA are typically normotensive.

Hypertension complicates 6–8% of pregnancies, and with the above described physiologic changes in the renin-angiotensin system, diagnosis of PA can be difficult.[51] Estimates of rates of PA within the pregnant population range from 0.01–0.8%.[14, 15, 31, 51–54] Only a minority of patients with PA exhibit spontaneous hypokalemia (9–37%).[50, 53] Workup for PA should be considered in patients with hypertension, especially if on multiple antihypertensive agents (Table 1). In patients with an adrenal nodule and hypertension, PA should be ruled out. Suspicion of PA should be high in patients with a plasma aldosterone level > 15 ng/dL and a suppressed plasma renin level, resulting in an elevated aldosterone-renin ratio (ARR > 20). In patients with spontaneous hypokalemia, plasma aldosterone level > 20 ng/dL, and an undetectable plasma renin, no additional confirmatory biochemical testing is needed. For patients who do not meet those criteria in whom PA is suspected, confirmatory testing should be pursued.[50] There are fewer than 50 gravid patients with PA described in the literature, which makes it difficult to provide clear cutoffs for laboratory values in this population.[51, 55].

Abdominal imaging should be performed in patients with a biochemical diagnosis of PA. Because aldosterone-secreting adenomas tend to be smaller tumors, adrenal vein sampling (AVS) is recommended in most patients to differentiate between a unilateral aldosterone-producing adenoma and bilateral adrenal hyperplasia (BAH).[50, 56] Whereas unilateral adrenalectomy is curative for patients with an aldosterone-producing adenoma, BAH is medically managed with mineralocorticoid receptor antagonists (MRA). Patients in which AVS may be omitted include patients < 35 years of age with spontaneous hypokalemia, significant aldosterone excess, and imaging that demonstrates a unilateral cortical adrenal adenoma.[50] In AVS, cannulation of the inferior vena cava (IVC), left, and right adrenal veins is essential. Because the right adrenal vein (RAV) tends to be short in length, this can be a technically difficult procedure. Cosyntropin stimulation allows for calculation of the cortisol ratio between each of the adrenal veins and IVC; if greater than 3:1, cannulation of the adrenal vein is confirmed.[57, 58] AVS is considered to lateralize to a particular adrenal gland when the aldosterone/cortisol ratio is greater than 3:1 or 4:1; lower ratios are likely indicative of BAH.[50, 56, 57, 59] The use of AVS in pregnancy provides additional challenges since it utilizes fluoroscopy, which risks radiation exposure to the fetus. Positioning may also increase the difficulty of the procedure as patients in the second or third trimester will require modified positioning to offload pressure from the uterus on the IVC.

Table 1 Biochemical workup for PA indicated if

BP > 150/100mmHg on 3 measurements on 3 separate days
BP > 140/90mmHg on 3 antihypertensives (including diuretic)
BP < 140/90mmHg on 4 or more antihypertensives
Hypertension and hypokalemia
Hypertension and adrenal incidentaloma
Hypertension and sleep apnea
Hypertension and family history of hypertension or stroke < 40 years
Hypertension and 1st degree relative with PA

5.2 Management

In contrast to patients with overt hypercortisolism or a PPGL, medical management with antihypertensive medications, particularly MRAs such as spironolactone and eplerenone, which are potassium-sparing, can be considered in patients with PA, although those with refractory hypokalemia and/or hypertension should also be referred for adrenalectomy during pregnancy. In patients for whom AVS would generally be recommended (based on age and/or the presence of bilateral adrenal nodules), a discussion regarding the risks and benefits of AVS will be needed.

Refractory hypertension is the most common sign of PA with hypokalemia observed in 9–37% of patients with PA.[50] Although MRAs such as spironolactone and eplerenone are the preferred antihypertensive agents in patients given the potassium-sparing and antihypertensive effects, spironolactone is not recommended in pregnancy due to its anti-androgenic effects (class C). Eplerenone has been used safely for the treatment of PA in pregnancy, though it remains a class B medication.[15] Monitoring for hypokalemia is essential and oral potassium supplementation should be started in patients with hypokalemia, especially if hypertension is being managed without an MRA. Hypokalemia can be exacerbated in patients with hyperemesis gravidarum, and intravenous (IV) potassium supplementation may be required.

Alpha methyl dopa is considered the first line medication for hypertension in the gravid patient. Beta blockers may be associated with various congenital malformations (cardiovascular, neural tube defects, cleft lip and palate); however, use of labetalol during the second and third trimesters has been described without adverse effects. If additional medications are required for control of hypertension, thiazide diuretics and eplerenone can be considered based on whether the patient has hypokalemia.[51].

5.3 Postoperative management

Cure of PA is assessed using the Primary Aldosteronism Surgical Outcome (PASO) study criteria, which assesses biochemical cure as well as clinical improvement. Correction of hypokalemia without potassium supplementation should be observed within three months of adrenalectomy

and is typically the first abnormality to resolve. Improvement in hypertension is assess six months to one year after surgery and annually thereafter. More than 90% of patients will achieve biochemical cure; however, complete clinical cure is highly variable (17–62%).[60].

The authors routinely stop potassium supplementation after adrenalectomy and obtain a basic chemistry panel and serum aldosterone level on postoperative day 1. Antihypertensive medications are tapered based on postoperative blood pressure, though typically we will attempt to stop any potassium-sparing medications first. This is performed with the aid of the patient's endocrinologist given the often-delayed improvement in hypertension.

6 Indications for surgery

Patients with non-functional, incidentally identified adrenal nodules that appear benign and measure < 4 cm in size can generally be observed in the general population as well as in pregnant patients.[3, 7] ACC is an aggressive malignant lesion with a poor prognosis for which surgical resection is the only cure; adrenalectomy should be considered, irrespective of the stage of gestation.

If performing adrenalectomy during pregnancy, the possibility of emergency delivery should be discussed and ideally, the patient will have provided informed consent for emergency cesarean delivery if indicated. Prophylactic tocolytics are not recommended in the absence of preterm labor.[8, 61] Corticosteroid administration is recommended in pregnant patients with premature fetuses of viable gestational ages (24–37 weeks) and should be considered for fetuses 22–23 weeks gestational age.[62].

7 Perioperative Management

7.1 Timing

Historically, recommendations on timing of when to perform surgical procedures in pregnant patients were limited to the second trimester given the increased risk of spontaneous abortion in the first trimester and risk of preterm labor in the third trimester. However, the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice and Society of American Gastrointestinal and Endoscopic Surgeons advise against delaying medically necessary surgical treatment in pregnant patients.[8, 63] Laparoscopic surgery can be performed safely during any trimester, if necessary, although it is imperative to adjust incisions according to gestational age and fundal height (Fig. 2).[8] At 20 weeks gestation, the top of the fundus reaches the level of the umbilicus, shifting intraabdominal viscera cephalad. The uterus can grow to the level of the xiphoid process around 36 weeks.[64].

Existing studies have demonstrated successful adrenalectomy in pregnant women with gestational ages ranging from 5 to 35 weeks, though not without risks.[19, 37, 51, 65–67] A recent meta-analysis of non-obstetric abdominopelvic surgeries in pregnant patients demonstrated the highest risk of fetal loss when operations were performed in the first and early second trimesters (T1/T2 2.9% (IQR 0.0, 4.7%) vs. T3 0.1% (IQR 0.0, 0.0%). Preterm birth, however, was most frequently observed in patients in the third trimester (T1/T2 5.6% (IQR 1.8, 10.0%) vs. T3 13.8% (IQR 7.8, 18.8%). Maternal death is rare regardless of trimester (0.04% (IQR 0.0, 0.0%).[68] In a separate study by Bancos et al., fetal loss was observed in 0.9% and maternal cardiovascular events occurred in 0.5% of patients undergoing adrenalectomy for PPGL during pregnancy.[37].

7.2 Obstetric/Fetal monitoring

Medically necessary surgery should not be delayed in pregnancy as this can have adverse effects on the mother and fetus.[8, 63] Monitoring of the fetus should be performed in conjunction with an obstetric physician who has privileges to perform obstetric surgery in case urgent caesarean section is indicated. Fetal monitoring should include fetal heart rate with doppler in all fetuses regardless of gestational age. In viable fetuses (minimum of 22 weeks gestation), fetal

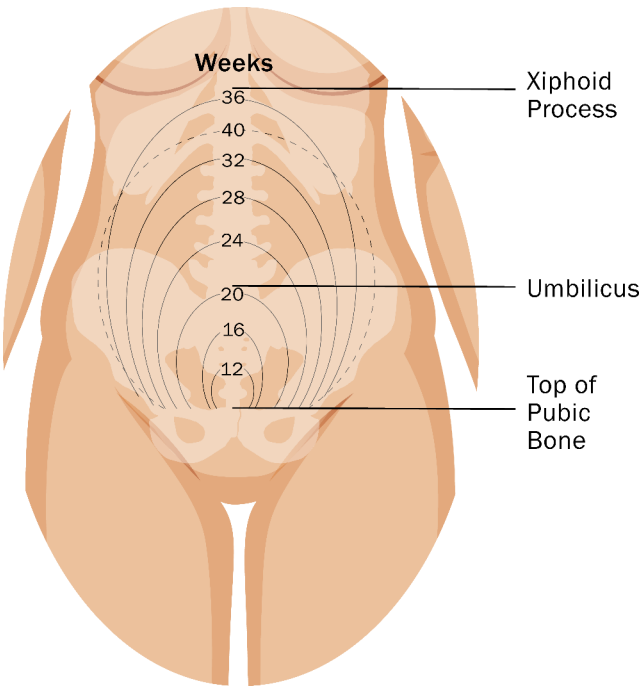

Fig. 2 Estimated fundal height by gestational age of the fetus. Illustrations by Elizabeth Chen

monitoring should include tocometry and fetal heart rate monitoring preoperatively and postoperatively.[8, 63].

Intraoperative fetal monitoring should be considered when the fetus is viable, an obstetric provider is available, and it is physically possible.[63] However, continuous fetal monitoring has not been shown to alter fetal outcomes during labor and is associated with a higher rate of caesarean Sect. [69] The two approaches to adrenalectomy, transabdominal and retroperitoneal, will be discussed in detail in subsequent sections. Fetal monitoring is limited to the perioperative setting in the transabdominal approach so not to violate the sterile field. However, modified prone positioning for the retroperitoneal approach would allow for easier continuous fetal monitoring, with less potential interference in the operative field. Recent use of prone positioning in pregnant patients with COVID-19 pneumonia and acute respiratory distress has demonstrated that this positioning is safe, though continuous fetal monitoring is advised.[66, 70, 71].

7.3 Postoperative course

Postoperatively, patients should undergo fetal monitoring by an obstetrical physician. Maternal care will otherwise resemble that of the general population who undergoes adrenalectomy for the same indication. Intraoperative transversus abdominis plane block has been associated with improved pain control and reduced use of opioids.[72] Postoperative pain control is achieved with scheduled acetaminophen to achieve baseline pain control. Other NSAIDs, such as ibuprofen, are contraindicated in pregnancy. Narcotics can be safely used postoperatively in pregnant patients. The literature on postoperative opioid use in adrenalectomy suggests that the majority of patients will require some narcotic pain medication after adrenalectomy.[73, 74].

8 Surgical Considerations

8.1 Approaches

The options for adrenalectomy include open and minimally invasive approaches, with minimally invasive adrenalectomy (either laparoscopic or robotic-assisted) being the standard for most patients with adrenal tumors. Open adrenalectomy is the preferred approach for patients in whom there is a concern for malignancy, based on tumor size or imaging characteristics. Laparoscopic transabdominal adrenalectomy (TA) was introduced in 1992, and has since become the standard of care for most adrenal tumors, particularly for benign tumors < 8–10 cm in greatest dimension.[3, 7, 75] In 1996, the posterior retroperitoneoscopic approach (PRA) was described.[76] Differences between the TA and PRA approaches include the anatomy encountered, positioning, and insufflation pressures.

TA is more commonly performed, likely related to surgeons' extensive training and familiarity with abdominal anatomy. For left adrenal pathology, mobilization of the colon, spleen, and pancreas is required to adequately expose the adrenal gland. On the right, the triangular ligament of the liver and the colon are mobilized to expose the adrenal gland. Positioning for this approach is lateral decubitus. For gravid patients with left adrenal pathology, this may place pressure on the intraabdominal IVC, while for patients with right adrenal pathology this positioning will help offload pressure from the IVC. Typical insufflation pressures for laparoscopic surgery (10–15 mmHg) have been shown to be safe in pregnant patients.[77–79].

PRA was introduced as an alternative approach to minimally invasive transabdominal adrenalectomy, with the potential benefit of not requiring mobilization and retraction of other organs to gain access to the adrenal gland, which is especially advantageous in patients with prior abdominal surgery. However, the learning curve for this approach may be steeper due to "backdoor" view of the retroperitoneal structures, which can be disorienting as there are fewer landmarks.[80] This approach may be advantageous in the gravid patient as the modified prone positioning of the patient for this technique alleviates compression of the uterus on the vena cava and is associated with improvements in oxygenation and systolic blood pressure.[66, 70, 71, 81] However, this benefit must be balanced with the higher insufflation pressures that are required for adequate exposure (20-28mmHg), which effectively compresses the IVC. These insufflation pressures have been shown to be safe without significant hemodynamic effects in the general population undergoing right-sided PRA.[82–84] Only a few cases of PRA in gravid patients have been described and no hemodynamic instability secondary to insufflation was observed.[66, 67].

Robotic-assisted adrenalectomy was first performed in the early 2000s using a transabdominal approach, and is currently utilized for both anterior and posterior approaches. [85] Multiple studies have compared laparoscopic and robotic-assisted adrenalectomy in non-gravid patients, and have found both techniques to be safe and effective for experienced adrenal surgeons.[86, 87] Limited data is available regarding robotic-assisted adrenalectomy in pregnant patients, though successful operations have been reported. [88–90].

8.2 Positioning

For the open technique, the patient is positioned supine on the operating room table with or without a roll under the side of the tumor. For patients in the second or third trimester, it is recommended that the patient be placed in partial lateral decubitus position. The gravid uterus can compress the inferior vena cava when the patient is supine. This places the patient at risk for reduced venous return to the heart, reduced cardiac output, and result in hypotension and reduced perfusion of the placenta.[8] Midline, unilateral or bilateral subcostal incision is typically used for an open approach. Arms may be tucked or extended laterally depending on the patient's body habitus. The authors utilize a self-retaining retractor system, such as the Thompson retractor, to aid in adequate exposure.

With the minimally invasive transabdominal approach, patients are initially placed supine on the operating table. A beanbag is used to aid in positioning. Following induction of general anesthesia and intubation, the patient is then transitioned to a lateral decubitus position. (Fig. 3). The patient should be positioned such that the breakpoint on the operating room table is just cephalad to the superior iliac spine. Flexing the bed will augment the distance between the ribs and the iliac spine to increase the working space. It is imperative that all pressure points are padded to avoid nerve injury and pressure ulcers. The arm on the ipsilateral side of the tumor is elevated and secured on an arm board; the contralateral arm should be padded and supported with an axillary roll. The lower leg should be flexed, and the upper leg should be straight with pillows between the legs. Foam padding is used to cushion the ankles and heels.

For the posterior approach, the patient is positioned supine on the transportation gurney for induction of anesthesia and intubation. A Cloward table (Surgical Equipment International, Honolulu, Hawaii) is used to place the patient in a modified prone position (Fig. 4). This table supports the patient's hips while providing an open space for the abdomen to hang ventrally. The patient's hips and knees should be flexed at a 90-degree angle. Appropriate padding is needed to support the gravid uterus. Fetal monitors should be placed during positioning. The arms are extended cephalad with the elbows flexed at a 90-degree angle and adequately padded.

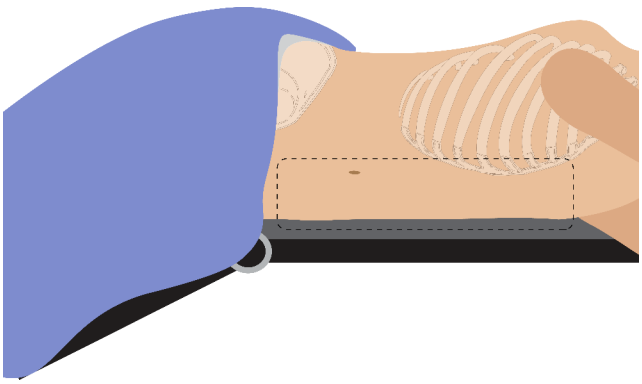

Fig. 3 Left lateral decubitus positioning for minimally invasive right transabdominal adrenalectomy. Dashed lines represent positioning roll used as an alternative to a bean bag. Illustrations by Elizabeth Chen

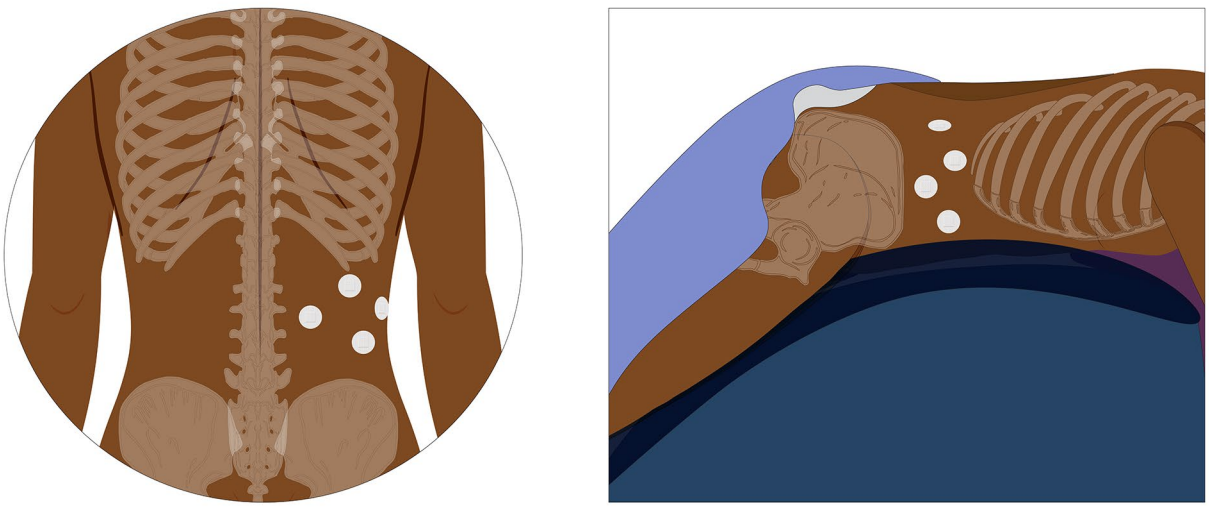

Fig. 4 (a) Anterior view of incisions for minimally invasive right PRA. (b) Right lateral view of prone-jackknife positioning and incisions for minimally invasive right PRA. Illustrations by Elizabeth Chen

8.3 Minimally Invasive Access

As pregnancy progresses to the second and third trimester, the fundal height increases shifting intra-abdominal contents cephalad. (Fig. 2) Options for accessing the abdominal cavity include open (Hasson) or closed techniques (Veress needle and/or optical trocar). Access to the abdomen can be safely accomplished using open or closed techniques.[8] A subcostal approach is advised to avoid iatrogenic injury to the uterus. An additional measure that may help avoid injury to the gravid uterus is ultrasound-guided trocar placement. [91].

9 Surgical technique

9.1 Minimally invasive Transabdominal Left Adrenalectomy

The initial incision is made in the midclavicular line on the side of the nodule. Additional trocars are placed in the upper midline at the inferior aspect of the falciform ligament, as well as caudal to the midline trocar, and lateral and inferior to the subcostal midclavicular trocar (Fig. 5). The location of the trocars are modified slightly if performing a robotic-assisted adrenalectomy so that they are farther from the targeted adrenal gland.

The splenic flexure of the colon is mobilized along the white line of Toldt. The colon is then retracted inferomedially to expose Gerota's fascia. Next, the spleen is mobilized from its attachments to the kidney and diaphragm. Careful medial retraction of the spleen exposes the pancreas and left kidney. As the plane between the kidney and pancreas is developed using a combination of blunt dissection and ligation with an ultrasonic or bipolar energy device, the left adrenal gland is exposed at the superior and medial aspect of the kidney. A paddle retractor may be used to retract the spleen and tail of the pancreas. The renal vein should be identified inferiorly and followed cephalad to the left adrenal vein. Careful blunt dissection of the left adrenal vein will allow for ligation with clips or a vascular stapler. Additional blunt dissection should be used to evaluate for the inferior phrenic vein, which may require ligation. The authors use the ligated adrenal vein on the adrenal gland to facilitate retraction. Starting inferiorly, the attachments to the adrenal gland are ligated circumferentially. Care should be taken to identify the posterior-most aspect of the adrenal gland so that none is left behind. Once free of its attachments, the gland is placed in a specimen bag for extraction from the abdomen.

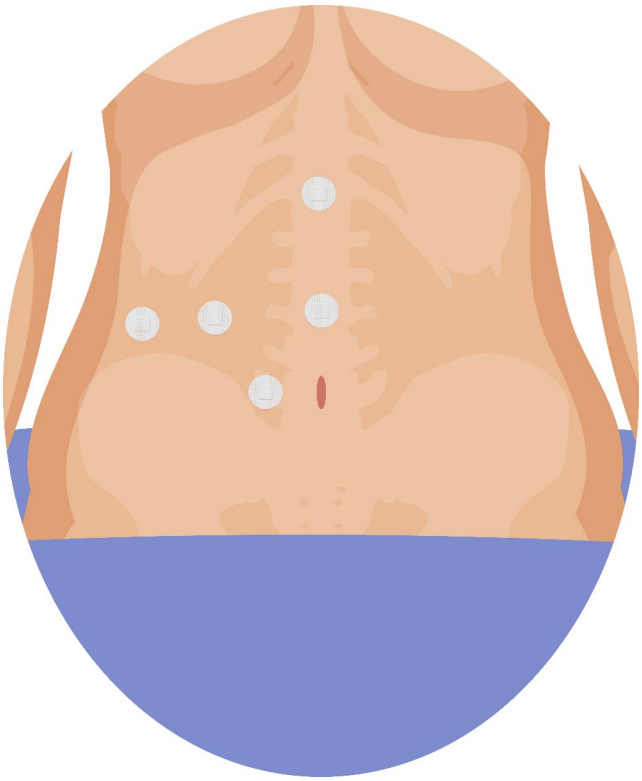

Fig. 5 Anterior view of incisions for minimally invasive right transabdominal adrenalectomy. Illustrations by Elizabeth Chen

9.2 Minimally invasive Transabdominal Right Adrenalectomy

Trocar placement for right transabdominal adrenalectomy mirrors that of left adrenalectomy. The right triangular ligament of the liver is dissected first to the level of the diaphragm. The liver should then be retracted anteromedially using a soft paddle or fan retractor to allow for adequate exposure of the adrenal gland and IVC. Once the IVC is identified, gentle cephalad dissection should identify the right adrenal vein. The right adrenal vein should be ligated with clips or a vascular stapler. Grasping the remainder of the right adrenal vein on the adrenal gland for retraction then allows for dissection of the medial and inferomedial attachments. We recommend dissection with an ultrasonic or bipolar device to achieve adequate hemostasis. The gland is an elevated to achieve adequate exposure of remaining attachments. Once free, the adrenal gland is placed in a specimen bag and removed from the abdominal cavity.

9.3 Minimally invasive retroperitoneoscopic adrenalectomy

The first incision is made below the tip of the 12th rib. The retroperitoneal space is entered and dissected bluntly.

Additional trocars are placed at the lateral border of the paraspinous muscle and at least 5 cm lateral to the initial incision, both using direct palpation (Fig. 4). A trocar is then inserted through the initial incision and the retroperitoneal space is insufflated to 20mmHg. The retroperitoneal space is developed using a combination of blunt dissection using laparoscopic Kittner dissectors and ligation of smaller veins with an energy device. For robotic-assisted adrenalectomy, the camera remains in the middle port, while with retroperitoneoscopic adrenalectomy the laparoscope is then moved to the most medial port, and the lateral to trocars are used by the surgeon.

It is important to identify the superior pole of the kidney inferiorly as a landmark. The kidney should be retracted inferiorly with a laparoscopic Kittner dissector, and the adrenal gland should be elevated superiorly. An energy device should be used to divide the tissue at the superior aspect of the kidney. The adrenal vein will be identified medial to the adrenal gland. The RAV empties directly into the IVC and tends to be short and wide, while the left adrenal vein drains into the renal vein. Care is taken not to avulse the RAV from the IVC. The adrenal vein is carefully dissected circumferentially and is grasped on the adrenal side with a Walz grasper or Cadiere forceps for laparoscopic or robotic approaches respectively. It is then carefully ligated doubly on the proximal side and divided toward the adrenal gland. If the inferior phrenic vein drains into the adrenal vein, it will also require ligation. An energy device is then used to dissect the attachments to the adrenal gland and a counterclockwise fashion. Once free of its attachments, a specimen bag is inserted through the middle port. We recommend lowering the insufflation pressure to 8 to 12 mmHg to assess for any venous bleeding.

10 Conclusions

Adrenal nodules require comprehensive workup, especially in pregnant patients. Hormone-secreting tumors can contribute to hypertension and diabetes which can have serious consequences in pregnancy for both the patient and fetus. Adrenalectomy is safe and effective in pregnancy and is first line treatment for overt hypercortisolism and PPGL. Patients with PPGL should be offered genetic counseling and testing. A multidisciplinary team (endocrinology, obstetrics, endocrine surgery) is essential for successful care of these patients.

Statements and Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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