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Robotic adrenalectomy for functional adenoma in second trimester treats worsening hypertension

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Case Report:

A 33-year-old G6P3023 was found to have a 4.2 cm right adrenal incidentaloma during an admission for right pyelonephritis. Computed tomography (CT) was performed to rule out perinephric abscess in the setting of worsening leukocytosis while on antibiotics (Figure 1). Initial differential diagnosis from endocrinology included pheochromocytoma and primary aldosteronism. Due to the lack of typical physical exam stigmata, Cushing syndrome was initially of low concern. Of note, her past medical history included hypertension treated with amlodipine 10 mg and hydrochlorothiazide 12.5 mg. During admission, extensive endocrine laboratory workup demonstrated an elevated aldosterone:plasma renin activity (PRA), suppressed dehydroepiandrosterone (DHEA), normal 24 hour urine metanephrine and catecholamine, and hypokalemia (Table 1). This initial biochemical workup did not provide any definitive diagnosis; however, it did convincingly rule out pheochromocytoma due to the normal catecholamine levels in the serum and urine. Eliminating this pathology was critical due to the mortality of hypertensive crisis in the perioperative period.

After discharge from the hospital, the patient was lost to endocrine and surgical follow-up, so no further endocrine diagnostic workup was performed during that time. Approximately 2 months after discharge, the patient was found to be pregnant and established care with maternal-fetal medicine, endocrinology and urology. Her obstetrical course was complicated by worsening hypertension (130/100 at 8 weeks gestation), requiring the addition of labetalol 100 mg BID. Despite this, she had worsening hypertension (160/100 and 147/97 at 14 and 17 weeks, respectively), so her labetalol dose was increased to 200 mg BID. After consultation with maternal-fetal

medicine and endocrinology, surgical resection was recommended in the second trimester due to maternal-fetal complications associated with adrenal adenomas in pregnancy. In addition, current guidelines recommend resection for adenomas greater than 4 cm due to concern for adrenocortical carcinoma.¹ Preoperative workup included magnetic resonance imaging without contrast, demonstrating an unchanged mass, and repeat endocrine lab studies. Preoperative lab testing was helpful as aldosterone was found to be within normal limits, thereby making primary aldosteronism less likely. Additionally, the patient had a suppressed ACTH of <9 pg/mL (normal range: 9-46 pg/mL) at 15 weeks gestation and on repeat testing at 17 weeks. This result, paired with the initial low DHEA finding, led to the diagnosis of subclinical Cushing syndrome. Pregnancy induced alterations in diagnostic hormonal labs, such as dexamethasone suppression test and urine free cortisol, made definitive diagnosis of subclinical Cushing syndrome more difficult. However, the suppressed ACTH on repeat testing, which is typically normal to high in pregnancy, strongly suggested a functional adrenocortical adenoma.² Based on the size of the mass, functionality and associated risk of hypertension on the pregnancy, adrenalectomy was the best option, per maternal-fetal medicine and endocrinology.

At 19 weeks gestation, the patient underwent an uncomplicated right robotic adrenalectomy with the da VinciTM Si (Figure 2), with minimal adjustment in surgical technique under general anesthesia. A Veress needle was used for abdominal access and establishing pneumoperitoneum. Port placement was mildly cephalad to account for the gravid uterus. An 8 mm planned camera port was placed in the midclavicular line

and a 30-degree camera was inserted to survey the abdomen. There was no evidence of adhesive disease. Under direct visualization, an 8 mm working port was placed just under the costal margin at the midclavicular line. Two additional 8 mm robotic ports were placed, a standard port caudal on the midclavicular line and finally a long port just off the anterior superior iliac spine for the fourth arm. A 12 mm assistant port and 5 mm liver retractor port were placed in the midline above the umbilicus. A maximum pneumoperitoneum of 12mmHg was maintained throughout the procedure. She was pre-treated with 2 mg dexamethasone for perioperative steroid coverage. The surgical duration was 118 minutes with an estimated blood loss of 50 cc. A pre- and post-op fetal ultrasound were done showing appropriate fetal heart rates. Post-operatively, she received an additional 2 mg dexamethasone. A cosyntropin stimulation test to evaluate the hypothalamic-pituitary axis was completed on the first postoperative day (POD) and found to be low, consistent with functional cortisol producing adenoma and subclinical Cushing syndrome. Patient was discharged home POD 1 on 5 mg prednisone daily for 8 weeks for replacement steroids. Pathology report showed adrenocortical neoplasm, consistent with adrenocortical adenoma with negative surgical margins (Figure 3). Her blood pressure normalized 4 weeks postoperatively and she was taken off all antihypertensive medications.

Due to compliance issues, the patient stopped the steroids three weeks postoperatively and denied any symptoms, such as orthostatic signs, dizziness, or palpitations. At 36 weeks gestation, cortisol and ACTH were abnormal, prompting endocrinology to suggest stress steroid coverage with 100 mg hydrocortisone IV during

delivery. Pregnancy progressed with no complications with an estimated fetal weight 2211 grams (37%) at 33 weeks. At 39 weeks, the patient delivered a healthy 2800 g female via cesarean section due to fetal intolerance and failure to progress in the second stage of labor. On postpartum day 3, she developed preeclampsia with severe range blood pressures up to 182/120. The patient denied any symptoms, including headache, chest pain, shortness of breath, vision changes and epigastric pain. She declined magnesium sulfate for seizure prophylaxis. The patient was given labetalol 20 mg IV and started on labetalol 200 mg BID which was up titrated to 300 mg BID. Patient was discharged on labetalol 300 mg TID, amlodipine 10 mg daily, and 5 mg prednisone daily for one month of steroid coverage.

Discussion: Presented by Huda B. Al-Kouatly, M.D.

As modern imaging continues to advance, adrenal incidentalomas are more frequently diagnosed, posing challenges to providers regarding management.³ The majority of these lesions (80%) are benign.³ Herein, we present a case of a large adrenal incidentaloma identified in a patient found to be pregnant during surgical evaluation.

The workup for adrenal incidentaloma entails identifying malignant potential or functional status using clinical, laboratory, and radiographic testing. The differential diagnosis includes adrenocortical carcinoma, pheochromocytoma, primary aldosteronism, Cushing syndrome, and benign adenoma. In this case, none of these pathologies could be initially excluded. After biochemical workup, the low DHEA and

ACTH led endocrinology to diagnose subclinical Cushing syndrome. This pathology is defined as hypercortisolemia without the apparent physical manifestations of typical Cushing syndrome.⁴ It usually presents as unilateral adrenal incidentalomas, as seen in our case. Current recommendations on treatment remain controversial, but lean towards surgery.⁴ Interestingly, hypercortisolemia can cause amenorrhea and oligomenorrhea leading to infertility, features evidently absent in our patient's case.⁵

Literature reports that untreated Cushing syndrome in pregnancy can lead to maternal hypertension, preeclampsia, impaired glucose control, and increased rates of premature birth, intrauterine growth restriction, spontaneous abortion, and stillbirth.⁶ Our patient experienced asymptomatic postpartum preeclampsia. In addition to her treated subclinical Cushing syndrome, she had additional risk factors of chronic hypertension, obesity, and African-American race.

Diagnosis of the functional status of adrenalomas is complicated by physiologic hormonal changes of pregnancy. The hypothalamic-pituitary axis is altered, resulting in increased cortisol, aldosterone, and renin levels.⁷ However, catecholamine levels are unchanged, so diagnosis of pheochromocytoma remains analogous to non-pregnant patients.⁶ In contrast, the workup for Cushing syndrome is adjusted. The dexamethasone suppression test is a common initial workup for Cushing syndrome in non-pregnant patients. However, its utility in pregnancy is limited as ~40% of pregnant patients have abnormal dexamethasone suppression.⁶ This leads to increased Type I Error, with literature endorsing false positive dexamethasone suppression tests in >80% of normal pregnant women.^{6,8} To account for this, urine free cortisol may be used, as it

is elevated at most to three times the upper limit of normal in pregnancy after the first trimester.⁸ Therefore, it can be helpful if levels are >3 times the upper limit of normal.

Robotic adrenalectomy is considered equivalent to laparoscopic adrenalectomy, which is arguably the standard of care. Initially it was believed that laparoscopy was contraindicated in pregnancy, as the implications of the pneumoperitoneum on the mother and developing fetus were of concern.^{9,10} Specifically, the carbon dioxide exposure to the fetus and the increased intraabdominal pressure on the mother's already altered physiology were thought to pose more risk than benefits. However, it has since been shown that the laparoscopic approach did not have additional risk and was superior to the open approach in terms of length of stay, diet advancement and duration of narcotic use.¹¹ The first successful laparoscopic adrenalectomy in pregnancy was reported in 1999 and quickly became the preferred method of intervention.¹² The use of the robot builds on the advantages of laparoscopy in pregnant patients by allowing for three-dimensional visualization, precise dissection and resection, and fine-tuned articulations. The ergonomics of the technology, in the hands of a skilled robotic surgeon, make this ideal for manipulation around the gravid uterus. A recent meta-analysis in non-pregnant patients compared robotic adrenalectomy to laparoscopic and demonstrated lower blood loss, shorter hospital stays, and no difference in conversion rates.¹³ Furthermore, Brunaud et al. demonstrated that, when controlling for learning curve of robotic usage, there was no significant difference in operation duration between the two approaches.¹⁴ In regard to the timing of surgery, second trimester intervention reduces risk of spontaneous abortion. Organogenesis is mostly complete by this time and the uterine size does not limit surgical access, making this the ideal period for

intervention.⁶ Potential disadvantages of the robotic approach include upfront costs of a robotic system, although with each subsequent use the cost of an individual procedure decreases. Additionally, set up and footprint in the operating room can limit its practical use.

A literature review showed two robotic adrenal surgeries in pregnancy in addition to this case.^{5,15} Podolsky et al. employed similar pregnancy-related robotic modifications while performing their right adrenalectomy indicated for pheochromocytoma. These included second trimester timing of surgery and maximum pneumoperitoneum of 12 mmHg. This latter modification limits deleterious effects on the fetus and mother, while still providing adequate visualization. Their case had an operative duration of 270 minutes, estimated blood loss of 350 cc and the patient was discharged on POD 4. Key to proper management in Podolsky's case, as well as ours, was the prompt determination of the functional status of the tumor along with perioperative care appropriate to the specific nature of the functional mass. Additionally, they suggest continuous monitoring for acidosis and placing the patient in left lateral cubitus positioning to maximize maternal cardiac output and uterus and placental blood flow.¹⁵ Nassi et al. also described a cortisol producing mass in their report, but their patient demonstrated physical symptoms of Cushing with moon facies, acne, hirsutism, and proximal muscle weakness. They also elaborated on the challenges of Cushing diagnosis in pregnancy, and ultimately decided to intervene in the second trimester due to fetal risks of adrenal pathology. Critical to the patient safety was the additional endocrine medical management of the patient with steroid replacement therapy intraoperatively, post-operatively and post-partum. Similar to our patient, Nassi et al.

described a healthy neonate that did not need glucocorticoid replacement during the neonatal period.⁵ These reported cases demonstrate the utility of robotic adrenalectomy in pregnancy, especially due to the maternal-fetal complications associated with untreated adrenal disease.

Despite description of partial adrenalectomy in the literature,^{16,17} given that the patient was pregnant, it seemed prudent to perform a more definitive procedure to prevent extended operative time or reentry. Additionally, the adenoma's anatomy, which was central with involvement of a medial limb, made total adrenalectomy a more attractive approach. However, since the procedure was successful, there is no clear contraindication to a partial adrenalectomy in this situation for future cases and amenable lesions.

Conclusion:

This case demonstrates the complexity of diagnosing adrenal adenomas in pregnancy, as physiologic hormonal changes can interfere with standard diagnostic testing. Robotic adrenalectomy should be considered as a feasible surgical treatment alternative in second trimester pregnant patients in the hands of a competent robotic surgeon. A multidisciplinary team approach is pivotal for delivery of best patient care.

Table 1 – Biochemical evaluation from initial hospital admission prior to pregnancy and preoperative testing during the second trimester. Values are plasma unless specified otherwise.

<i>Pre-pregnancy hospital admission testing^a</i>				
	First Hospital Admission	Normal Range (non-pregnant)		
Aldosterone, ng/dL	3	<28		
PRA, ng/mL/h	0.08	0.9-28.9		
Aldosterone:PRA ratio	37.5	0.9-28.9		
Metanephrine, pg/ml	<35	<57		
Normetanephrine, pg/mL	<57	<148		
24 hr urine metanephrine, catecholamine, mcg/24 hr	44	36-190		
	155	35-482		
Testosterone, ng/dL	17	2-45		
Androstenedione, ng/dL	108	follicular phase: 35-250; luteal phase: 30-235		
DHEA, mcg/dL	43	45-430		
Potassium, mmol/L	2.9	3.3-4.8		
<i>Preoperative 2nd trimester testing</i>				
	Preoperative Testing	Normal Range (1 st Trimester)	Normal Range (2 nd Trimester)	Normal Range (3 rd Trimester)
Aldosterone, ng/dL	13	6-104	9-104	15-101
PRA, ng/mL/h	1.42		7.5-54.0	5.9-58.8
ACTH, pg/mL	<9 <9 ^b	6 – 50 ^c	6 - 50	6 - 50
Potassium, mmol/L	3.4	3.6-5.0	3.3-5.0	3.3-5.1

PRA, plasma renin activity

^a Pregnancy test done prior to CT scan was negative

^b Repeat ACTH done at 2-week interval after initial measurement

^c ACTH values unchanged in pregnancy²



Figure 1 - CT scan identifying 4.2 cm right adrenal incidentaloma with heterogeneously attenuating lesions and punctate calcifications

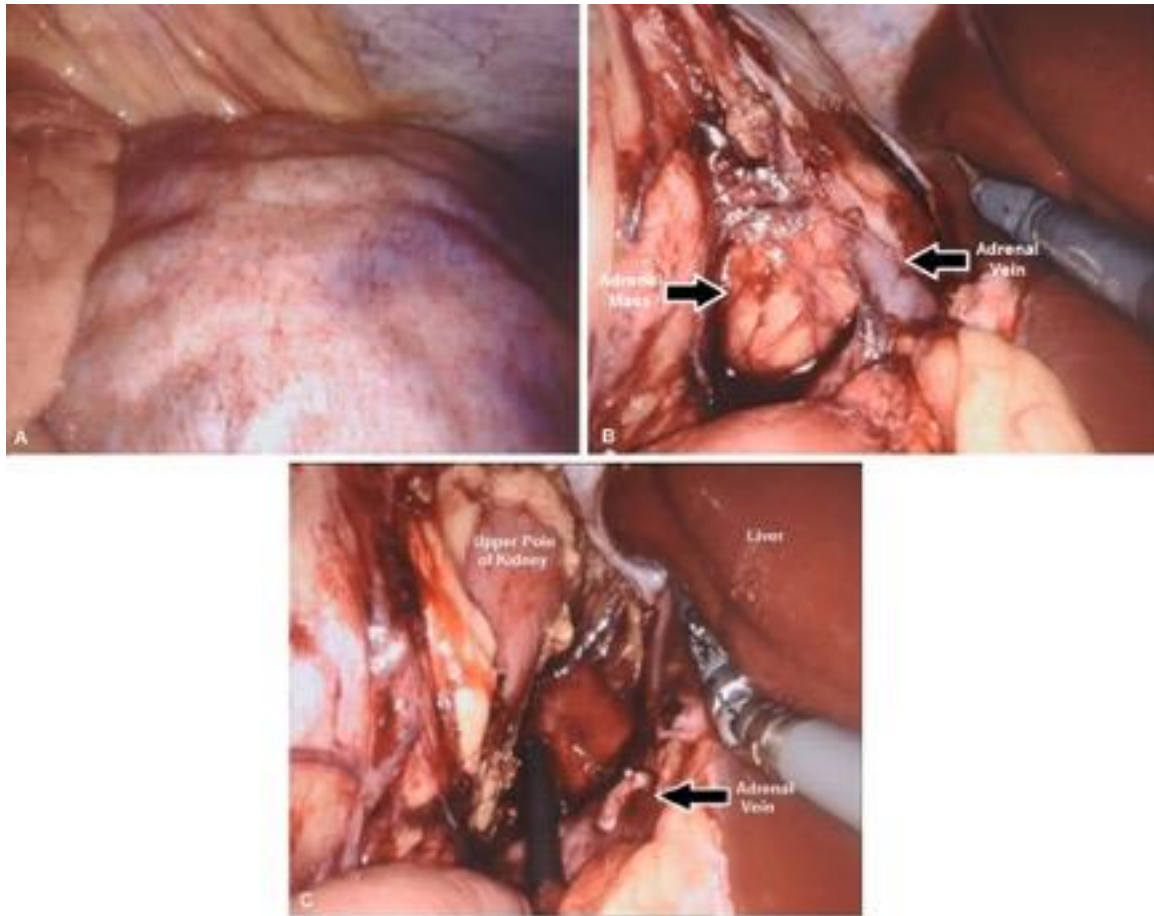


Figure 2 - **A.** Gravid uterus identified during port placement **B.** Adrenal Mass identified with isolation of the adrenal vein **C.** Adrenal fossa after resection showing clipped adrenal vein (arrow), upper pole of kidney, liver, inferior vena cava and duodenum.

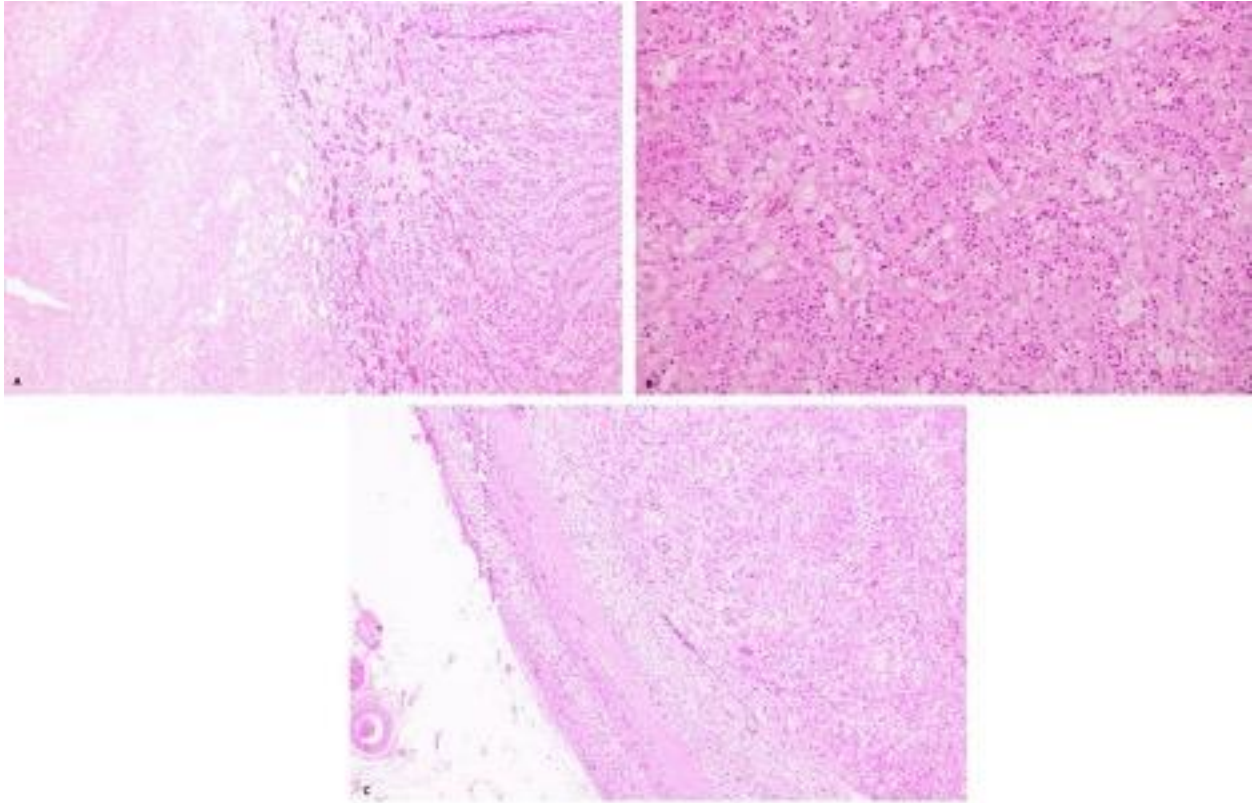


Figure 3 - **A.** Tumor surrounded by thin capsule, with a rim of residual normal adrenal tissue, 40x magnification. **B.** Tumor cells, 100x magnification. **C.** Focus of infarct necrosis, 40x magnification.

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