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EXTENSIVE CLINICAL EXPERIENCE

Cushing's Syndrome during Pregnancy: Personal Experience and Review of the Literature

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Cushing's syndrome (CS) occurs rarely during pregnancy. We investigated and treated four patients with pituitary-dependent Cushing's syndrome during pregnancy over a 15-yr period at the National Institutes of Health. Except for preservation of menses before conception, our patients presented with typical clinical features, increased urinary free cortisol, and loss of diurnal variation of cortisol. The diagnosis was facilitated, without complications, by the use of CRH testing and inferior petrosal sinus sampling in three women. Transsphenoidal pituitary surgery achieved remission in three women, but there were two fetal/neonatal deaths. This experience and review of 136 previous reports suggest that: 1) urinary free cortisol in CS patients overlaps the normal pregnant range; 2) ACTH levels are not suppressed in adrenal causes of CS, which may be identified by the 8-mg dexamethasone test; 3) inferior petrosal sinus sampling and transsphenoidal pituitary surgery, the optimal diagnostic test and treatment for nonpregnant patients with pituitary-dependent Cushing's syndrome, can safely facilitate the management of pregnant patients; and 4) surgery may achieve remission during pregnancy, but the prognosis for the fetus remains guarded. It is likely that earlier recognition and treatment would improve outcome. There is a need for development of criteria for interpretation of diagnostic tests and increased consideration of CS in pregnancy. (*J Clin Endocrinol Metab* 90: 3077–3083, 2005)

ALTHOUGH PREGNANCY RARELY occurs during the course of Cushing's syndrome (CS), it increases the rates of spontaneous abortion, perinatal death, premature birth, and intrauterine growth retardation (1, 2). Maternal morbidity includes hypertension, preeclampsia, wound breakdown, diabetes, fracture, and opportunistic infections (2, 3).

Because of the fetal and maternal morbidity, early diagnosis and treatment of CS in pregnancy are critical. Unfortunately, the physiologic changes of pregnancy complicate this goal. Plasma cortisol, cortisol-binding protein, and urinary free cortisol all increase during the second and third trimesters of normal pregnancy (4, 5). There are no data as to how the usual diagnostic criteria should be modified to allow for the pregnancy-induced hypercortisolism. Similarly, the tests for the differential diagnosis of CS [measurement of plasma ACTH, the 8-mg high-dose dexamethasone suppression test (HDST), CRH stimulation test, and bilateral inferior petrosal sinus sampling (IPSS)] have not been evaluated systematically in pregnancy (6–10).

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Abbreviations: AA, Adrenal adenoma; AIH, ACTH-independent hyperplasia; CD, Cushing's disease; CS, Cushing's syndrome; CT, computed tomography; EAS, ectopic ACTH secretion; HDST, high-dose dexamethasone suppression test; IHC, immunohistochemical; IPSS, inferior petrosal sinus sampling; IUGR, intrauterine growth retardation; MRI, magnetic resonance imaging; TSS, transsphenoidal surgery; UFC, urine free cortisol; US, ultrasound.

Treatment of CS in pregnancy has consisted of conservative management without specific treatment as well as adrenalectomy or medical therapy (11). Currently transsphenoidal surgery (TSS) is the gold standard treatment for Cushing's disease (CD). There have been only five previous reports of TSS performed during pregnancy (7–10, 12).

We here report our evaluation and treatment of four patients who presented with CD and underwent TSS during pregnancy at the National Institutes of Health (NIH). We then review the literature and discuss the diagnosis and management of CS during pregnancy.

Case Series

When obtained, the HDST, CRH stimulation tests, and IPSS were performed as previously described (13–15), except that for IPSS, lead shielding of the abdomen, chest, and back and a direct jugular approach under ultrasonic guidance were used to minimize fetal radiation exposure. No gadopentetate dimeglumine (gadolinium) contrast was given during magnetic resonance imaging (MRI).

Case 1

This 24-yr-old Hispanic female had a 3-yr history of hypertension and a prior pregnancy complicated by gestational diabetes, preeclampsia, premature delivery, and neonatal death. She also had weight gain, hirsutism, bruising, and purple abdominal striae but no menstrual irregularity. The basal urine free cortisol (UFC) was 530 μg/d (1462 nmol/d) and serum cortisol was less than 5 μg/dl (138 nmol/liter)

after HDST. Pituitary MRI was normal and IPSS failed to demonstrate a central to peripheral gradient. Subsequently she was found to be pregnant.

On admission to the NIH at 14 wk gestation, the patient had hypertension controlled by methyldopa and newly diagnosed diabetes. She had a body mass index of 33.9 kg/m^2, blood pressure of 134/87 mm Hg, multiple pigmented striae, and a gravid uterus consistent with gestational age. Biochemical testing was largely but not entirely consistent with CD (Table 1). The plasma ACTH and cortisol levels increased after CRH, but serum cortisol did not suppress completely during HDST (32% suppression from baseline serum cortisol of 31.4 μg/dl; 866 nmol/liter). Pituitary and chest MRIs were normal. IPSS showed a maximum central to peripheral ACTH gradient of 7:1. The patient was believed to have CD. During treatment with metyrapone 500 mg daily before TSS, plasma cortisol levels ranged from 24.5 to 33.2 μg/dl (676–916 nmol/liter). At 18 wk gestation a 3 × 3 mm adenoma with positive immunohistochemical (IHC) staining for ACTH was resected without complications. Subsequently biochemical remission required hydrocortisone treatment (25 mg/d) (Table 1), insulin requirements decreased, and blood pressure improved. Perioperative fetal ultrasound (US) examinations were normal.

Labor was induced at 34 wk gestation, using stress dose hydrocortisone coverage, because of severe preeclampsia and intrauterine growth retardation (IUGR). A healthy male infant weighing 1712 g was delivered vaginally and managed initially in the neonatal intensive care unit. The induction, delivery, and infant's subsequent clinical course were otherwise unremarkable. Two years later, while still in remission, the patient became pregnant again and delivered a male infant weighing 2190 g at term.

Case 2

CS was diagnosed at 5 wk gestation in this 34-yr-old Caucasian woman reported earlier (10). She had weight gain, easy bruisability, facial rounding, and an 8-yr history of hypertension; menses were regular. Examination at the NIH at 12 wk gestation revealed a blood pressure of 130/80 mm Hg on atenolol 75 mg twice a day, difficulty standing from a squat, hirsutism, facial plethora, purple abdominal striae, and a dorsocervical fat pad.

CS was confirmed biochemically (Table 1). Pituitary MRI demonstrated a macroadenoma with invasion of the left cavernous sinus and displacement of the carotid artery. Consistent with clinical practice at that time, IPSS was performed because of concerns about interpretation of a HDST in the setting of carbamazepine treatment of epilepsy; the maximal central to peripheral ACTH gradient was 20:1.

TSS at 14 wk gestation showed tumor invading the left cavernous sinus and displacing the carotid artery laterally. The 10 × 6 mm adenoma stained for ACTH by IHC. Postoperative testing suggested persistent CD (Table 1). Her course was complicated by transient syndrome of inappropriate antidiuretic hormone secretion that resolved with fluid restriction. She remained on atenolol. A postoperative US showed a single live intrauterine fetus with a normal placenta.

Plans were made to give metyrapone if UFCs exceeded 500 μg/d (1380 nmol/d), but they did not reach this level. Serial US examinations showed normal fetal growth and anatomy until 33 wk when intrauterine death was noted. At delivery, a tight nuchal cord was found.

At 3 months postpartum, the patient underwent bilateral adrenalectomy followed by external pituitary irradiation therapy and hydrocortisone and fludrocortisone replacement. Within 12 months she delivered a healthy infant after an uncomplicated term pregnancy. She remains in apparent remission 14 yr later.

Case 3

This 32-yr-old Caucasian woman had CS diagnosed at 9 wk gestation by UFC levels of 687–748 μg/d (1896–2065 nmol/d). She had a 2-yr history of weight gain and headaches; menses were regular. A pituitary MRI revealed a 7-mm adenoma. At the NIH she had increased dorsocervical and supraclavicular fat and fundal height consistent with

TABLE 1. Results of biochemical testing during screening, differential diagnosis, and postoperatively for four cases of CD in pregnancy

Patient	Cortisol (μg/dl)		UFC μg/24 h (20–90)	Pituitary MRI	Preoperative CRH stimulation			Postoperative AM cortisol (μg/dl)	Postoperative UFC (μg/24 h)	Postoperative CRH stimulation test		
	0800 h	2400 h (<7.5)[a]			Time	Cortisol (μg/dl)	ACTH (pg/ml)			Time (min)	Cortisol (μg/dl)	ACTH (pg/ml)
Case 1	29	30	239–488	Negative	−5	32	42	1.7–4.3	<6.2–11.0			
					0	33	41			0	1.7	8.8
					15	38	125					
					30	47	137			60	5.2	10.4
					45	43	101					
Case 2	37	41	912–1410	12-mm adenoma[b]		ND		21.6–43.8	348–564	0	40.4	45
										60	61	67
Case 3	17.8	17.8	333	7-mm adenoma		ND		1.5–2.8	58–1489		ND	
Case 4	47.3	37.7	192–662	Negative	−5	49.4	37.1	2.9–9.5	1.2	0	2.5	6.2
					0	42.6	37.0					
					10	54.6	230			Peak	9.9 (+30)	52.5 (+15)
					30	71.1	194.3					

Results of plasma cortisol and UFC are expressed in μg/dl and μg/24 h. To convert these to nmol/liter and nmol/24 h multiply by 27.6 and 2.76, respectively. ACTH levels are expressed in pg/ml (to calculate values in pmol/liter multiply by 0.22). ND, Not done during differential diagnosis.

[a] Cut-off of 2400 h serum cortisol of >7.5 μg/dl provides a high sensitivity for diagnosis of CS.

[b] Left cavernous sinus invasion.

gestational age. There was elevated UFC and loss of diurnal variation of cortisol (Table 1). Plasma ACTH level at midnight was 19.6 pg/ml (4.3 pmol/liter).

A diagnosis of CD was made based on the MRI and ACTH level; TSS was performed at 10 wk 5 d gestation. Histopathology revealed a 10 × 11 mm adenoma with positive IHC staining for ACTH. Subsequent biochemical tests suggested remission (Table 1), and US revealed a single live intrauterine fetus of 11.5 wk gestation. The patient was discharged on hydrocortisone 30 mg, and she delivered a healthy full-term infant via vaginal delivery without complication. She appears to be in remission at 10 yr, with mild hypertension.

Case 4

This 33-yr-old Caucasian woman presented with a cataract, facial plethora, and hirsutism that developed over 2 yr, without weight gain, hypertension, or irregular menses. UFCs were elevated at 700 μg/d. She was found to be pregnant. At 9 wk gestation, hypertension was noted; methyldopa and subsequently labetalol were prescribed. There was no proteinuria. On examination at the NIH at 16 wk gestation, blood pressure was 160/100 mm Hg. She had facial plethora, increased dorsocervical fat, mild facial hirsutism, a few nonpigmented abdominal striae, mild peripheral edema, and bruises. The fundal height was consistent with gestational age.

Biochemical testing suggested CD (Table 1). Serum cortisol suppressed by 83% from a basal value of 47.3 μg/dl (1306 nmol/liter) after overnight HDST. IPSS showed a maximum central to peripheral ACTH gradient of 31. A pituitary MRI was normal. A 15-mm ACTH-staining pituitary tumor was removed via TSS at 17 wk gestation. Postoperatively she had transient mild asymptomatic syndrome of inappropriate antidiuretic hormone secretion; biochemical evaluation suggested remission. Fetal US examinations were normal. After discharge on hydrocortisone 30 mg daily (15 mg/m^2), she had persistent hypertension and developed toxemia. Because of reversal of cord blood flow, the baby was delivered via cesarean section at 24 wk gestation. He weighed 440 g and died 5 d later. When last seen at NIH almost 9 months postoperatively, the patient was in remission and was pregnant.

Patients and Methods

The Cochrane Library (2004) and PubMed (April 2004) were searched without language restriction to identify additional cases of CS in pregnancy. The first author read each report and compiled a database that included the current cases. Studies with adequate biochemical evidence of active CS were included. The reported diagnosis was verified by examination of the imaging and pathology results and the clinical response following definitive treatment. Patients reported in major reviews are cited via the review, but their data from other reports were included in the database.

Data are expressed as mean ± SEM. Parametric data were analyzed by Student's unpaired *t* test. For nonparametric data, the Mann-Whitney *U* test, the Kruskal-Wallis test, and the Dunn's multiple comparison test were used. Significance was assumed if $P < 0.05$. Testing was performed using the statistical package for social science (SPSS version 12 for Windows, release 09.04, 2003; SPSS Inc., Chicago, IL) and GraphPad Prism (version 4.00 for Windows; GraphPad Software, San Diego, CA)

Results

We found reports of 136 pregnancies with CS in 122 women. Seven patients had more than one pregnancy. The gestational age at diagnosis was 18.4 ± 1.0 wk (n = 92). The clinical presentation of CS during pregnancy was similar to that in the nonpregnant state, apart from preservation of menses until conception.

Biochemical screening

CS during pregnancy was characterized by a mean 8-fold elevation in UFC (range 2–22, n = 34). There was a wide range of UFC values in each trimester (mean ± 95% confidence interval): first, 725 (218–1233); second, 1061 (797–1325); and third, 942 (511–1579) μg per 24 h (nanomoles per liter). Diurnal variation in serum cortisol was absent, with morning values of 37.7 ± 2.6 μg/dl (1040 ± 72 nmol/liter; n = 52) and evening values (1600–0100 h) of 36.0 ± 2.8 μg/dl (994 ± 77 nmol/liter; n = 46). The midnight serum cortisol in 16 women was 30.9 ± 2.9 μg/dl with a range of 13.1–50.0 μg/dl (853 ± 80; 361-1380 nmol/liter). We identified 17 reports [seven cases of CD and 10 cases of adrenal CS: nine adrenal adenoma (AA) and one Carney's complex] of the response to 1 mg or 2 d 2 mg dexamethasone suppression test (Fig. 1). After dexamethasone the range of serum cortisol levels was 5.5–54.3 (152–1499 nmol/liter) and 11.0–42.5 μg/dl (304–1173 nmol/liter) for CD and adrenal CS, respectively ($P = 0.6$).

Diagnostic testing and etiology

Diagnoses included CD (n = 40); AA (n = 56); adrenal carcinoma (n = 12); ectopic ACTH secretion (EAS) (n = 4) (2, 6, 16); Carney's complex (n = 1); and ACTH-independent hyperplasia (AIH) (n = 4) possibly due to aberrant receptor stimulation (17–20), who had eight pregnancies. One pheochromocytoma was associated with ACTH-independent hypercortisolism in pregnancy (21). Pheochromocytoma accounted for two cases of EAS (6, 16). In four patients insufficient data were available to determine the diagnosis. One woman had remission during pregnancy (22).

Figure 2 illustrates the plasma ACTH levels (measured by an assay with a detection limit < 10 pg/ml) of 35 patients with CS: 13 AA [32.5 ± 17.6 pg/ml (7.2 ± 3.9 pmol/liter)]; 18 CD [69.4 ± 25.9 pg/ml (15.3 ± 5.7 pmol/liter)], three AIH

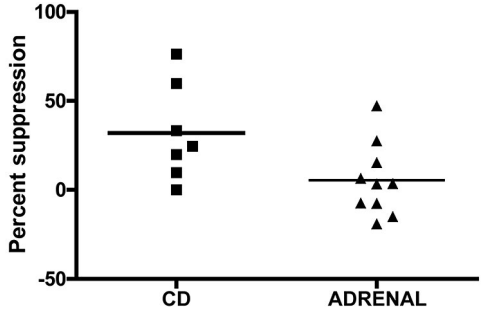

FIG. 1. Low-dose dexamethasone suppression test in CS in pregnancy. Values represent percent suppression from basal serum cortisol after either 1 mg overnight or 2-d 2-mg test in seven subjects with CD and 10 with adrenal CS (nine AA, 1 Carney's complex). The *solid line* represents the median value for each group.

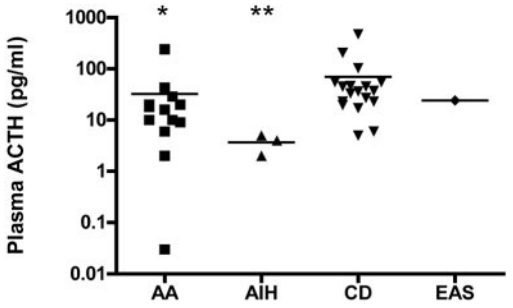

FIG. 2. ACTH levels in 39 subjects with CS in pregnancy. The *solid line* represents the median value for each group. *, $P < 0.05$ AA *vs.* CD; **, $P < 0.01$ AIH *vs.* CD. Values on the y-axis are presented in log scale. To convert values in picograms per milliliter to picomoles per liter, multiply by 0.22.

[3.7 ± 0.9 pg/ml (0.8 ± 0.2 pmol/liter)], and one EAS [24 pg/ml (5.3 pmol/liter) ($P < 0.05$ for AA and $P < 0.01$ for AIH, compared with CD]. Eight of 16 patients with AA or AIH had values less than 10 pg/ml. Conversely, two of 18 patients with CD had a value less than 10 pg/ml.

Fourteen women had sufficient data to assess the overnight or 2-d HDST. Using a criterion of 80% suppression, all patients with ACTH-independent CS were identified. However three of seven patients with CD did not suppress.

Only 13 of 40 patients with CD had adequate imaging information; six of these had a macroadenoma. Pituitary MRI correctly identified an adenoma in five of eight patients (including cases 2 and 3) (7–9) but not in two macroadenomas (case 4) or one microadenoma (case 1). Of interest, pituitary macroadenomas, reported in about half of the current series, were overrepresented, compared with nonpregnant series of CD (8–10, 12, 23–26).

Only 53 of 69 patients with adrenal CS had adequate adrenal imaging information. Thirty had imaging during pregnancy: 15 had US, three had computed tomography (CT), six had MRI, three had x-ray tomography, and three had iv pyelography. There were 23 patients in whom imaging was not conducted during gestation; 12 of these had imaging postpartum: CT alone (n = 8) or followed by iodocholesterol scan (n = 1), arteriography (n = 1), pneumography (n = 1), and urography (n = 1). Urography was not helpful. Ultrasound was correct in 11 of 15 cases leading to successful surgical localization. Three of the four cases with negative US imaging proceeded to CT (antenatal, n = 1; postpartum, n = 1) or MRI (antenatal, n = 1) with tumor localization confirmed at surgery. Apart from the negative results from urography (n = 1) and US (n = 4), the other imaging modalities successfully localized the tumor.

Treatment and outcome

Table 2 illustrates maternal and fetal complications. Two maternal deaths were associated with pheochromocytoma complicated by cerebrovascular disease and disseminated intravascular coagulation or complications after adrenalectomy and cesarean section (16, 27).

Of 107 live births, 43% were premature and 50% were male. There were eight stillbirths, six intrauterine deaths/spontaneous abortions, one ectopic pregnancy, six therapeutic abortions, and three cases with an uncertain outcome. One infant died within 24 h of delivery due to fetal respiratory distress and hyaline membrane disease (26). Another died after intraventricular hemorrhage in a pregnancy complicated by preeclampsia (28).

TABLE 2. Frequency of maternal and fetal complications arising in CS during pregnancy

Maternal morbidity	Fetal morbidity
Hypertension (68%)	Prematurity (43%)
Diabetes or IGT (25%)	Stillbirths (6%)
Preeclampsia (14%)	Spontaneous abortion/IUD (5%)
Osteoporosis and fracture (5%)	Infant death in two cases (acute hepatitis; sepsis and gastroenteritis)
Cardiac failure (3%)	IUGR (21%)
Psychiatric disorders (4%)	Hypoadrenalism (2%)
Wound infection (2%)	Single reports of cleft lip, patent ductus and coarctation
Maternal death (2%)	Intraventricular hemorrhage in two cases postpartum

IUD, Intrauterine death.

There were 59 live births in 74 women receiving conservative therapy (76%), compared with 50 live births (89%) in women treated at a mean gestational age of 20 ± 1 wk ($P = 0.07$). Of those with CD, eight women, including our own patients, underwent TSS, one (with unrecognized pregnancy) had external pituitary irradiation, seven received medical therapy, seven underwent adrenalectomy, and 17 were untreated. Twenty-four cases had unilateral adrenalectomy during pregnancy (19 AA, four adrenal carcinoma, one EAS).

Twenty women received primary or adjuvant medical therapy, generally beginning during the second and third trimesters, including metyrapone (n = 11), ketoconazole (n = 3), cyproheptadine (n = 3), aminoglutethimide (n = 1), and mitotane (n = 2); 18 had live births, but two infants subsequently died (26, 28). There were individual reports of IUGR, fetal hypoadrenalism, coarctation of the aorta, transient neonatal jaundice, and hypoglycemia (18, 29, 30). Mitotane treatment of one pregnancy ended in therapeutic abortion at 6 wk with evidence of teratogenicity (24).

Discussion

Screening

Normal physiologic changes of pregnancy, including increases in serum cortisol, UFC, and plasma ACTH levels, complicate the screening process for CS (4, 31, 32). Whereas UFC excretion is normal in the first trimester, it increases up to 3-fold by term to overlap values seen in pregnant women with CS (4). Thus, only UFC values in the second and third trimester greater than 3 times the upper limit of normal can be taken to indicate CS. (This assumption is based on normative data derived from relatively few women; it would be helpful to have delineation of normal pregnancy UFC by methodologies such as mass spectroscopy.)

The morning plasma cortisol level in this series was similar to that reported in normal pregnancy (33). Thus, as in the nonpregnant individual, morning plasma cortisol concentrations generally cannot diagnose CS. However, the plasma cortisol diurnal variation is preserved in pregnancy, albeit

with a higher nighttime nadir (4, 33) but not in CS (7, 9, 12). Unfortunately, the appropriate diagnostic threshold for evening plasma or salivary cortisol in pregnant patients is not known, although a single report highlights the potential utility of the latter measure (34).

Suppression of serum and urinary cortisol by dexamethasone is blunted in pregnancy (35, 36). In one series the mean reduction in serum cortisol after 1 mg dexamethasone at midnight was 82.9, 43.5, and 37.3% in the first to third trimesters, compared with 87.1% in the nonpregnant controls (32). Thus, this screening test has an increased potential for false-positive results in pregnancy. Because the bioavailability of dexamethasone is unchanged in normal pregnancy, these data may reflect an altered hypothalamic-pituitary-adrenal set point or increases in total serum cortisol and cortisol-binding protein in normal gestation.

Thus, screening for hypercortisolism is more difficult in pregnancy, particularly in the second and third trimesters. False-positive diagnoses will be likely until pregnancy-specific criteria are developed.

Differential diagnosis

The etiology of CS differs between the pregnant and nonpregnant state. AAs cause approximately 40–50% of CS in pregnancy, contrasting with about 15% in nonpregnant women (1, 37). Conversely, CD appears to be less common in pregnancy, with rates of 58–70% in the general population, compared with 33% in this review (1, 12, 37). EAS is quite rare in CS, perhaps because the degree of hypercortisolism causes anovulation (2, 6, 16). The increased incidence of adrenal CS suggests that anovulation may be less prevalent (1) or that unrecognized illicit LH/human chorionic gonadotropin receptor expression was considered to be adrenal adenoma (38, 39).

In nonpregnant subjects, plasma ACTH suppression (<5 pg/ml; 1.1 pmol/liter) usually identifies ACTH-independent primary adrenal causes of CS. In the present series, mean ACTH levels were nonsuppressed in half of those with primary adrenal disorders, perhaps because of continued stimulation of the maternal hypothalamic-pituitary-adrenal axis by placental CRH (40). As a result, the recommended diagnostic ACTH thresholds in the general population may lead to missed diagnoses (41).

The HDST in nonpregnant individuals distinguishes CD from EAS with a sensitivity ranging from 60 to 80% and a specificity of above 80% using a criterion of plasma cortisol suppression greater than 80% (41, 42). Its efficacy for the differential diagnosis of EAS in pregnancy is unknown due to the limited number of reported cases (7, 8, 12, 26, 28, 43). Case 1 illustrates the inability of this test to identify all cases of CD. However, the present series suggests that the HDST may help discriminate adrenal forms of CS from CD, which may be useful, given the difficulties in interpretation of plasma ACTH and the increased prevalence of adrenal disorders in pregnancy.

We recommend adrenal imaging with US, HDST, and plasma ACTH levels as an initial step in the differential diagnosis of pregnant patients with CS. Patients with borderline or low plasma ACTH or without suppression on HDST are likely to have an adrenal etiology. Whereas US imaging identified adrenal lesions in 73% of these cases, second-line imaging with MRI may be needed in the event of a negative US scan. The appropriate precautions for use of MRI are outlined below.

In nonpregnant individuals with CD, the tumor corticotrophs retain responsiveness to CRH, whereas adrenal tumors and most ectopic ACTH-producing tumors do not (44). Ovine CRH (the analog available in the United States) is a Food and Drug Administration (FDA) category C drug, recommended for use in pregnancy only when absolutely clinically indicated. Animal studies showed no teratogenic or adverse behavioral effects after 100 μg human CRH was given during organogenesis (45). Plasma ACTH responses to human CRH, 1 μg/kg, were reduced in third-trimester normal pregnancies (46). Whereas the CRH test has not been systematically studied in CS in pregnancy, in the five patients tested, there was a substantial rise in serum cortisol (44–130%), consistent with surgically confirmed CD (7, 9, 10), and no adverse effects were observed. We advocate use of the CRH test when adrenal disorders are unlikely after initial testing.

Pituitary MRI should be obtained in all nonpregnant patients with ACTH-dependent CS and provides a definitive diagnosis without further invasive testing in the setting of a 6-mm or larger pituitary adenoma with responses to CRH and dexamethasone consistent with CD (41). Pregnancy presents several challenges for using MRI because of its associated pituitary hyperplasia and safety issues. Gadolinium contrast is FDA category C. At the NIH it is not given to pregnant women. In nonpregnant individuals, noncontrast MRI had reduced sensitivity for CD (52 *vs.* 38%) (47). MRI alone is contraindicated in the first trimester because of unknown potential teratogenic effects but is considered safe after 32 wk. In the middle trimester, its risk to benefit ratio must be weighed with the knowledge that up to 10% of healthy individuals have an incidental tumor up to 6 mm in diameter. A pragmatic approach may be possible for patients with lesions larger than 6 mm, as in case 3. However, others may require further testing.

In the nonpregnant population, IPSS with CRH stimulation has the highest diagnostic accuracy for ACTH-dependent CS (15). Concerns about radiation probably have limited its use in pregnancy, reflected by the single case report using IPSS at the NIH (10). The present series adds two reports illustrating that IPSS can be used safely and effectively in a center with clinical expertise. Specific precautions are necessary during pregnancy including a direct jugular approach and use of additional lead barrier protection. We advocate that IPSS be considered during pregnancy only after completion of the noninvasive assessment above and only in experienced centers. Whereas case 2 illustrates the diagnostic utility of IPSS and reflected clinical practice in 1989, today we would not perform IPSS in that patient. In our view, patients with a definite pituitary tumor on imaging and CRH results consistent with CD, or those with HDST and CRH results consistent with CD, have a near 100% probability of having CD and do not need IPSS. Also, because it is not known whether pregnant patients with adrenal disease have com-

plete pituitary suppression, the usual criteria for interpretation may not exclude them.

Treatment

Although there are several cases of live births after conservative management during the last trimester, untreated CS is associated with significant maternal morbidity including diabetes, hypertension, heart failure, and preeclampsia (48–51). Whereas placental degradation of cortisol appears to protects the fetus from glucocorticoid excess (26), the high incidence of adverse fetal outcomes probably reflects placental and maternal abnormalities. We found a trend toward an increased live birth rate in treated, compared with nontreated, pregnancies, although this was not statistically significant. Treatment did not affect the incidence of premature births, but only one stillbirth and one intrauterine death occurred in treated pregnancies (10, 26). Rates of IUGR were similar, but the number of cases was small.

Primary medical therapy was reported in 20 women (17, 25, 26). There is most experience with metyrapone, which seems generally well tolerated (18, 43, 52). Because hypertension and progression to preeclampsia have been reported with metyrapone, its use might be best reserved as an interim treatment as in case 1, pending definitive treatment (28, 52). Ketoconazole has been used successfully in three pregnancies without adverse event (25, 29, 30). One woman who had discontinued contraception while using ketoconazole 600-1000 mg/d for CD (25) delivered a normal male infant at 37 wk, despite known antiandrogenic effects of ketoconazole (25). In the rat, ketoconazole crosses the placenta and is teratogenic and abortifacient so that the drug is FDA category C. Whereas its use has been advocated in pregnant patients requiring medical therapy, in the authors' opinion, ketoconazole should be reserved for individuals who need emergent medical therapy but cannot tolerate metyrapone (25). Cyproheptadine is not recommended due to lack of efficacy (53). Fetal masculinization precludes the use of aminoglutethimide (54). Similarly, although it is FDA category C, we consider mitotane to be contraindicated because it crosses the placenta and is teratogenic (24).

In contrast to medical therapy, surgery is more uniformly successful (7–9, 12). The live birth rate in cases with unilateral or bilateral adrenalectomy was 87%; whereas the patient group was heterogeneous, adrenalectomy appears beneficial (1, 2). The current series illustrates the consequences of failing to achieve remission in CD due to pituitary macroadenomas, consistent with results in the general population.

We recommend surgical treatment of CS in pregnancy, except perhaps late in the third trimester, with medical treatment being a second choice. There does not appear to be a rationale for supportive treatment alone. It is likely that the mixed experience with treatment of CS indicates that this disease is not recognized early enough to influence outcome. The prognosis for the fetus remains guarded when hypercortisolism persists. An increased suspicion for diagnosis of this rare disorder would likely facilitate early treatment and result in improved outcome for both mother and fetus.

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