Chapter 2. -PITUITARY AND ADRENAL DISORDERS OF PREGNANCY

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PITUITARY DISORDERS IN PREGNANCY

Anterior Pituitary Gland

The pituitary enlarges throughout pregnancy, approximately 136% overall (1) and may become hyperintense on scan.(2) This enlargement is due primarily to estrogen-stimulated hypertrophy and hyperplasia of the lactotrophs.(3) Gonadotrophs decline in number, and corticotrophs and thyrotrophs remain constant.(4) Somatotrophs are generally suppressed, and may function as lactotrophs.(5) The peak pituitary size is seen in the first 3 days postpartum, when the gland height may reach 12 mm on MRI.(1,6,7) The gland involutes rapidly following delivery regardless of breast feeding status, and is of normal size by 6 months postpartum.(6,7)

Prolactin (PRL) is secreted by the pituitary, hypothalamus, lymphocytes, uterus, placenta, and lactating mammary gland.(8) In combination with other hormones, PRL mediates mammogenesis, lactogenesis, galactopoiesis (maintenance of milk secretion), and plays a role in the regulation of humoral and cellular immune responses. Placental estrogens stimulate lactotrophic PRL synthesis in the first trimester, (9,10) while progesterone also stimulates prolactin secretion. (11,12) Prolactin levels progressively increase approximately 10-fold throughout gestation,(13) then decline postpartum in non-lactating women. Despite increased PRL levels, the normal lactotroph continues to respond to TRH and anti-dopaminergic stimulation. Postpartum, the circadian rhythm of PRL release is enhanced by the effects of suckling.

TAKE HOME POINTS

1-Cabergoline and bromocriptine are both safe for facilitating pregnancy with no increased risk of fetal malformations

2-Macroprolactinomas carry a 23% risk of significant size increase during pregnancy but this can usually be managed by reinstitution of a dopamine agonist

3-For patients with acromegaly somatostatin analogs should be stopped when pregnancy is sought because of uncertain safety for the fetus

4-Cushing's syndrome should be treated during pregnancy because of adverse outcomes to mother and fetus when left untreated

5-Pituitary adenomas other than prolactinomas very rarely increase in size during pregnancy

6-Placental vasopressinase increases the degradation of vasopressin and may unmask subclinical diabetes diabetes insipidus

7-New onset diabetes insipidus during pregnancy may be associated with acute fatty liver of pregnancy and the HELLP syndrome

8-In hypopituitary patients, thyroxine doses should be empirically increased during pregnancy because the TSH cannot be used for dose titration but hydrocortisone doses do not need to be increased except for stress and labor and delivery

9- In women with 21-hydroxylase deficiency, the spouse should have genetic testing and the couple should have genetic counseling

10-The use of dexamethasone in women with 21-hydroxylase deficiency during pregnancy to suppress the fetal adrenals is controversial

11-Women found to have pheochromocytomas during pregnancy should have laparascopic surgery after alpha blockade during pregnancy because of adverse consequences to mother and fetus if left

The placental growth hormone (GH) variant differs from pituitary GH by 13 amino acids and is synthesized by the syncytiotrophoblastic epithelium of the placenta. The regulation of placental GH secretion remains unknown, but this variant increases throughout gestation to levels of 10-20 ng/ml.(14,15) This variant has similar carbohydrate, lipid,(16) and somatogenic properties as pituitary GH, with less lactogenic activity.(17) With this increase in overall GH activity, insulin-like growth factor 1 (IGF-1) levels increase in the second half of pregnancy, (18) contributing to the acromegaloid features of some pregnant women. Through negative feedback, pituitary GH levels consequently decline in the second half of gestation and the first week postpartum, (14,15) with blunted response to hypoglycemic stimulation testing (not recommended in pregnancy), but

normal response to GHRH.(19) Patients with acromegaly have autonomous pituitary GH secretion, and both forms of GH persist in the blood throughout pregnancy.(20)

There is a transient fall in TSH in the first trimester during the 2nd and 3rd months. This is postulated to be secondary to human chorionic gonadotropin (hCG) stimulation of the thyroid due to the structural homology between the TSH and hCG molecules and their receptors.(21) The role of hCG in increasing thyroid stimulating activity was first postulated with the thyrotoxicosis noted in molar pregnancies and trophoblastic disease,(22) with cure after surgical excision of the mole or neoplasm. A negative correlation was later demonstrated between hCG and TSH in women undergoing elective abortion.(23) Sequential TSH determinations between 8 and 14 weeks gestation revealed that the nadir in TSH coincides with the peak in hCG,(24) with an inverse correlation found in individual samples such that TSH levels fall in a proportional and mirror response to the rise in hCG.(Figure 1)(25) There is also a linear relationship between hCG and free T4 concentrations early in gestation.(24) In the majority of patients, this effect is transient and not clinically significant, as the peak of hCG is brief. However, sequential evaluations of TSH in a large cohort of pregnant women revealed that 18% demonstrated transient subnormal TSH in the 1st trimester, with 5% still subnormal in the 2nd trimester, with significantly higher levels of hCG found in these women than in those who maintained a normal TSH.(26) Furthermore, in hyperplacentosis (27) and in twin pregnancies where the hCG peak is generally higher and of longer duration, there is more frequent and greater lowering of TSH than in singleton pregnancies.(28) In the second half of gestation, TSH levels return to normal prepregnant levels. In iodine deficient regions, TSH increases near term but remains within the normal range.(24) The increase in estrogens produced by the fetal-placental unit stimulates hepatic production of thyroxine-binding globulin and increases the sialylation of the TBG, thereby prolonging its half-life.(29,30) This increase in TBG results in higher levels of total T4 and T3, starting at 4-6 weeks gestation.(30) Free T4 levels may increase transiently in the 1st trimester as a result of the hCG peak. However, both free T4 and free T3 generally remain within the normal range throughout gestation,(24,29,30) though they may be 10-15% lower at term in iodine-sufficient women. Many of the Free T_4 immunoassays used commercially are not accurate during pregnancy (31) and their routine use is not recommended.(32) In fact, it has been recommended that the total T4 assay be used, adjusting by multiplying x 1.5 during the 2nd and 3rd trimesters.(32) Placental deiodination increases maternal T4 turnover.

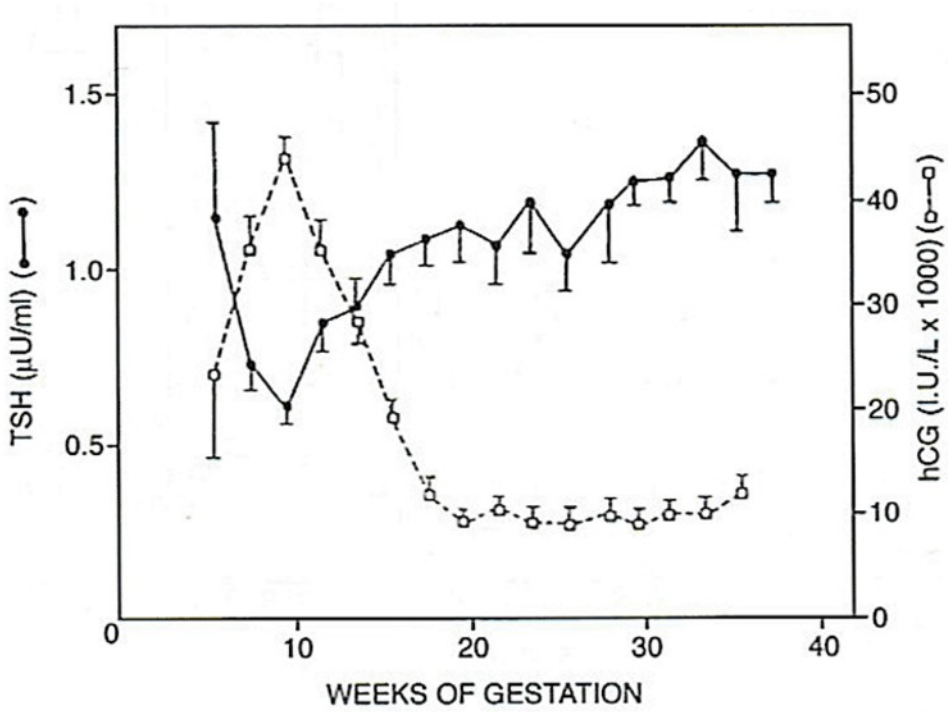

Figure 1. Maternal concentrations of serum TSH and hCG as a function of gestational age. The decrease in serum TSH at approximately 10 week's gestation may be due to

thyrotropic effects of hCG. (From Glinoer D, de Nayer P, Bourdoux P, et al. Regulation of maternal thyroid during pregnancy. J Clin Endocrinol Metab 1990; 71:276.)

Synthesis of hCG by syncytiotrophoblasts is itself partially stimulated by placental cytotrophoblast produced gonadotropin releasing hormone (GnRH). In response to placental sex steroid production, both hypothalamic GnRH and pituitary gonadotropin (FSH/LH) levels decline in the first trimester of pregnancy, with a blunted gonadotropin response to GnRH.(33) FSH levels are initially suppressed postpartum, and return to normal by 3 weeks postpartum. LH levels tend to normalize more gradually.

Corticotropin-releasing hormone (CRH) levels, synthesized primarily by the placental cytotrophoblasts and the decidua, rise several hundred fold by term.(34,35) It stimulates both syncytotrophoblastic placental and pituitary adrenocorticotropic hormone (ACTH) production,(36) although the latter has not been absolutely proven. ACTH levels consequently increase throughout gestation, with a further increase in labor.(37) The proportion of ACTH of pituitary vs. placental origin is unknown; however, placental ACTH is not suppressible by dexamethasone administration. Cortisol levels progressively increase throughout gestation with a surge during labor.(37) Cortisol binding globulin levels rise secondary to estrogen-stimulated production, leading to an increase in total cortisol of 2-3 fold by term.(37) The “free” cortisol also rises 3-fold, with a 2-3 fold elevation in urinary free cortisol.(37,38)

Pituitary adenomas constitute 15.8% of primary intracranial (malignant and nonmalignant) neoplasms in women, with an age-adjusted incidence rate of 3.13 cases/100,000 persons.(39) The stimulatory effect of pregnancy on pituitary lactotrophs will impact a patient with a prolactinoma who becomes pregnant.

Prolactinomas

Hyperprolactinemia causes one third of all female infertility.(40,41) Elevated prolactin (PRL) levels inhibit pulsatile gonadotropin secretion and the positive feedback of estrogen on gonadotropin secretion.(41) Hyperprolactinemia has multiple potential etiologies. In patients with prolactinomas, treatment choices are defined by the clinical presentation and the therapeutic goal.

Surgical therapy is initially curative in approximately 70-80% of patients with microadenomas and rarely causes hypopituitarism. The curative rate is much lower (30%) in patients with macroadenomas, and the risk of hypopituitarism and subsequent infertility increases dramatically.(41) For both microadenomas and macroadenomas there is a recurrence rate of about 20%, thereby lowering these long-term cure rates.(41)

Dopamine agonists are the primary therapy for the majority of patients with prolactinoma. Bromocriptine and quinagolide (not approved in the United States) restore ovulatory menses in 70-80% of patients. Approximately 50-75% of patients with macroadenomas experience a > 50% reduction in size.(41,42) Cabergoline is dosed once to twice weekly and is more effective and better tolerated than bromocriptine therapy with restoration of ovulatory menses in >90% of women and >90% reduction in tumor size.(41,42) To establish the intermenstrual interval prior to a pregnancy, mechanical contraception should be used for 2-3 cycles. This allows early recognition of a pregnancy so that the drugs are given for only 3-4 weeks of gestation. The long half-life of cabergoline causes fetal exposure for a further 1 or more weeks after cessation of therapy. Bromocriptine and cabergoline are approved for use in pregnancy.

The hormonal milieu of pregnancy may cause significant tumor enlargement in women with prolactin-secreting macroadenomas.(Figure 2) Published reports of pregnant patients with microadenomas previously treated with bromocriptine or cabergoline show that only 18 of 658 (2.7%) pregnancies in women with microadenomas were complicated by symptoms of tumor enlargement (headaches and/or visual disturbances) (Table 1).(43,44). For patients with macroadenomas, 49 of 214 pregnancies (22.9%) were complicated by symptoms of tumor enlargement. In addition, 148 women with macroadenomas were identified who had undergone surgery or radiation prior to pregnancy and their risk of tumor enlargement was 4.8%.(43,44) Reinstitution of bromocriptine or cabergoline therapy generally is successful in reducing tumor size when it occurs, though transsphenoidal surgery may be required.(43)

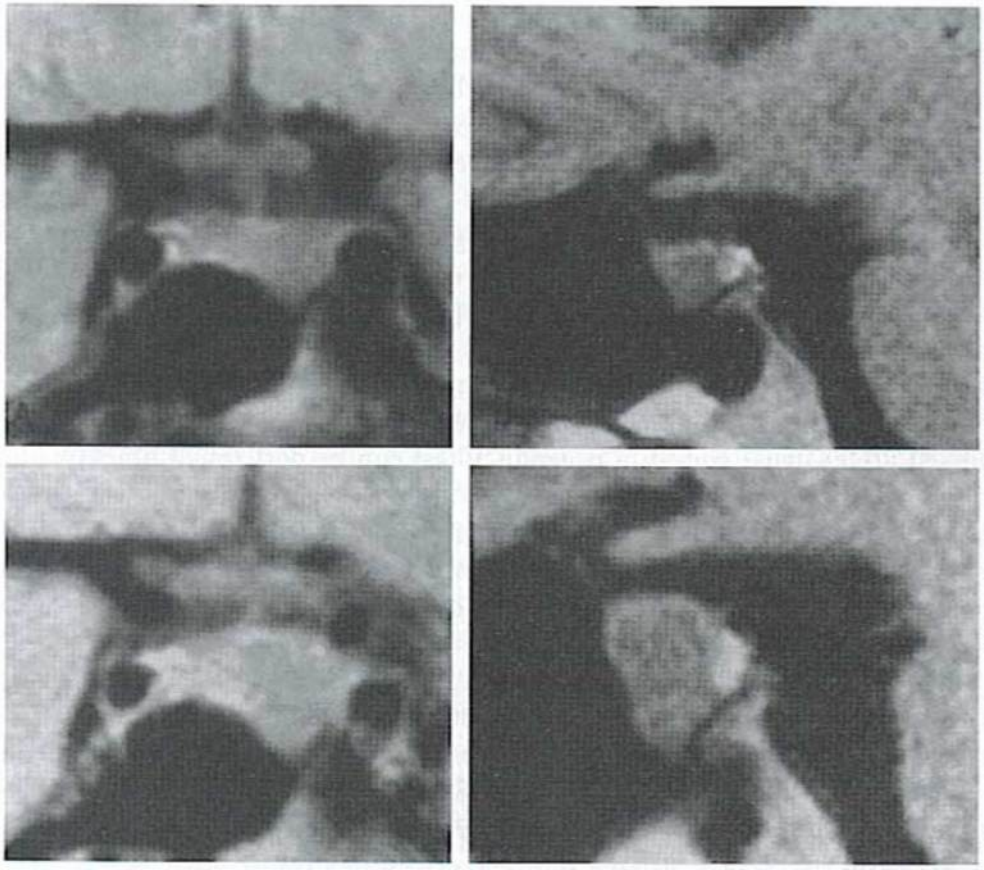

Figure 2. MRI scans with coronal (A,C) and sagittal (B,D) views demonstrating a prolactin-secreting macroadenoma before pregnancy (A,B) that progressively enlarged during pregnancy. The third trimester is shown here (C,D). The patient had been complaining of increasing headaches.

Table 1. Effect of Pregnancy on Prolactinomas*

Tumor Type	Prior Therapy	Number of Patients	Symptomatic Enlargement*
Microadenomas	none	658	18 (2.7%)
Macroadenomas	none	214	49 (22.9%)
Macroadenomas	yes	148	7 (4.8%)

*Data abstracted from Ref. 43,44

Bromocriptine crosses the placenta,(45) and continuous administration throughout gestation is not recommended. Experience with its use during the first few weeks of gestation has not been associated with increased risk for adverse events such as spontaneous abortion, ectopic pregnancies, multiple gestation, or congenital anomalies.(Table 2)(43) Long-term studies of children exposed during the early first trimester have been limited to 64 children ranging in age from 6 months to 9 years, with no ill effects

seen.(46) In more than 100 pregnancies in which bromocriptine was used throughout gestation, the only neonatal abnormalities noted were a case of undescended testicle and one case of talipes deformity, which is in the expected range.(43)

Quinagolide should not be used when pregnancy is desired. A review of 176 pregnancies in which quinagolide was maintained for a median of 37 days, reported 13.6% spontaneous abortions, 0.6% ectopic pregnancies, 0.6% stillbirths at 31 weeks, and 5.1% malformations: spina bifida, trisomy 13, Down syndrome, talipes, cleft lip, arrhinencephaly, and Zellweger syndrome.(47)

Cabergoline has been shown to cross the placenta in animal studies, but such data are lacking in humans. Data on exposure of the fetus during the first several weeks of pregnancy have been reported in over 900 cases and such use has not shown an increased percentage of spontaneous abortion, premature delivery, multiple pregnancy, or congenital abnormalities.(43,44) Follow-up studies of up to 12 years following exposure to cabergoline during gestation showed no physical or developmental abnormalities in the 83 children followed by Ono et al,(48) a slight retardation in verbal fluency in two and difficulty in achieving complete continence in 1 by age 4 among the 88 children followed by Lebbe et al , (49) and seizures in two and "pervasive developmental disorder", an autism spectrum disorder, in two of the 61 children followed by Stalldecker et al.(50)

Table 2. Pregnancy outcomes summarized for women who became pregnant while taking bromocriptine or cabergoline, compared to what is expected in the normal population

	Bromocriptine (N)	**Bromocriptine (%)**	**Cabergoline (N)**	**Cabergoline (%)**	**Normal (%)**
Pregnancies	6.239	100	932	100	100
-Spontaneous abortions	620	9.9	73	7.8	10-15
- terminations	75	1.2	63[1]	6.8	20
- Ectopic	31	0.5	3	0.3	1.0-1.5
- Hydatidiform moles	11	0.2	1	0.1	0.1-0.15
Deliveries (known duration)	4139	100	668	100	100
- at term (> 37 weeks)	3620	87.5	602[2]	90.0	87.3
- preterm (< 37 weeks)	519	12.5	67	10.0	12.7
Deliveries (known outcome)	5120	100	597	100	100
- single births	5031	98.3	585	98.0	96.8
- multiple births	89	1.7	12	2.0	3.2
Babies (known details)	5,213	100	790	100	100
- normal	5,030	98.2	769	97.3	97
- with malformations	93	1.8	21	2.7	3.0

[1]11 of these terminations were for malformations; [2] 5 of these births were stillbirths. From Refs. 43,44.

There is little specific information regarding the use of transsphenoidal surgery during pregnancy. It is presumed that the risks would be similar to other forms of surgery,(51,52) except for the increased risk of hypopituitarism.

For patients with intrasellar tumors, bromocriptine or cabergoline are preferred as they are safe for the fetus if discontinued early in gestation. These tumors demonstrate a small risk for tumor enlargement. Patients should be followed on a trimester basis for symptomatic enlargement, such as headaches or visual problems. Visual field testing should be performed if clinically indicated.

Therapeutic options for tumors extending outside the sella include prepregnancy surgical debulking, intensive monitoring without dopamine agonist therapy, or continuous dopamine agonist therapy throughout gestation. The latter is not likely to harm the fetus but the number of cases followed in this way is small. Patients require monthly assessments and visual field examinations every trimester. Prolactin levels provide little benefit in the clinical assessment, as they may not rise with tumor enlargement.(53) With evidence of tumoral enlargement, bromocriptine or cabergoline should be immediately reinstituted and the dose rapidly titrated as tolerated. Transsphenoidal surgery or delivery if gestation length is adequate, should be considered if the response to bromocriptine therapy is inadequate.(43)

Breastfeeding stimulates prolactin secretion in normal women in the first few weeks or months postpartum. However, there is no evidence that suckling stimulates prolactinoma growth.(43) Therefore, we do not discourage breastfeeding in women with prolactinomas. However, dopamine agonists must be withheld until the period of breastfeeding is over.

Acromegaly

The diagnosis of acromegaly during pregnancy may be difficult.(54,55) Conventional assays for GH cannot usually distinguish between normal pituitary GH and the placental GH variant and may consequently give misleading results with respect to assessment of pituitary GH secretion during the latter half of pregnancy.(20) Basal levels of the variant are considerably higher than normal nonpregnant GH levels and may therefore erroneously indicate excessive pituitary GH secretion. Special assays that recognize specific epitopes on the two hormones are necessary to distinguish normal from placental GH.(20) When such specific assays are not available, it may be necessary to wait until delivery to assess pituitary GH secretion accurately, because placental GH variant is undetectable within 24 hours.14 However, two differences between placental GH variant secretion and pituitary GH secretion in acromegaly may allow a distinction to be made during pregnancy: (1) pituitary GH secretion in acromegaly is highly pulsatile, with 13 to 19 pulses per 24 hours,(57) whereas secretion of the GH variant in pregnancy is nonpulsatile (15); and (2) in acromegaly, about 70% of patients have a GH response to thyrotropin-releasing hormone (TRH),(58) whereas the placental GH variant does not respond to TRH.(20) However, at present, TRH is no longer available for testing in the United States.

Acromegaly is associated with infertility in about two-thirds of cases due to a variety of causes. In a series of 55 women with acromegaly ages 17 – 45 years, 31% were eugonadal with regular menses, 20% were hyperprolactinemic and anovulatory, 11% hypopituitary due to tumor mass effects, 13% were thought to be anovulatory due to increased GH/IGF-1 levels (menses restored with lowering of GH/IGF-1 levels), and 26% had 2 or more causes.(59)

Only one patients with a tumor secreting GH has been reported to have enlargement of her tumor without any hemorrhage into the tumor with a resultant visual field defect during pregnancy.(60) Three other patients have had demonstrated tumor enlargement without hemorrhage but did not develop visual field defects (56,61,62) and in one of these cases tumor enlargement likely was more due to octreotide withdrawal than the pregnancy itself.(62) Hemorrhage into the tumor causing headache and visual symptoms during pregnancy, however, has been reported several times.(54,55) Therefore, patients with acromegaly with macroadenomas should be monitored clinically for headaches and visual symptoms (63).

Because of the GH-induced insulin resistance, the risk of gestational diabetes is increased in acromegalic patients.(54,55) The risk of gestational hypertension is also increased.(54-56) Cardiac disease has not proved to be an issue in pregnant women with acromegaly.(54,55)

The considerations regarding the safety of use of cabergoline in women with prolactinomas discussed above also apply to those with acromegaly being treated in this fashion. Fewer than 50 pregnant patients treated with somatostatin analogs have been reported; no malformations have been found in their children.(54-56,64) However, a decrease in uterine artery blood flow has been reported with short-acting octreotide64 and one fetus appeared to have intrauterine growth retardation that responded to a lowering of the dose of octreotide LAR.(56) Octreotide binds to somatostatin receptors in the placenta (64) and crosses the placenta (64) and therefore can affect developing fetal tissues where somatostatin receptors are widespread, especially in the brain. Because of the limited data documenting safety, I recommend that octreotide and other somatostatin analogs be discontinued if pregnancy is considered and that contraception be used when these drugs are administered and most (54-56) but not all (64) others concur. Considering the prolonged nature of the course of most patients with acromegaly, interruption of medical therapy for 9 – 12 months should not have a particularly adverse effect on the long-term outcome. On the other hand, these drugs can control tumor growth and for enlarging tumors, their reintroduction during pregnancy may be warranted vs. operating. Pegvisomant, a GH receptor antagonist, has been given to two patients with acromegaly during pregnancy without harm (55,65) but the safety of this is certainly not established.

TSH- and Gonadotropin-Secreting Adenomas

There are few data regarding TSH-secreting pituitary adenomas in pregnancy. Treatment of three cases of TSH-secreting adenomas has been reported.(66-68) Octreotide was used in two cases. In one octreotide was continued to control tumor size, and the second it was reinstituted to control tumor size. The hyperthyroidism may be controlled with standard antithyroid drug therapy.(68) However, with growing macroadenomas, octreotide may be necessary for tumor size control (66,67) and it is possible that it may be necessary to control the hyperthyroidism if thionamides are ineffective.

Clinically non-functioning adenomas are primarily gonadotroph adenomas.(69) Although unlikely to enlarge under the influence of estrogen stimulation in pregnancy, the lactotroph hyperplasia which occurs can cause chiasmal compression or headaches in a patient with a preexisting clinically non-functioning adenoma. Two cases have been reported of tumor enlargement in pregnancy with resulting visual field defect.(61,70) In one case, the patient responded to bromocriptine therapy which reduced the lactotroph hyperplasia and had little or no direct effect on the neoplasm.(70) Two patients with gonadotroph adenomas secreting intact follicle-stimulating hormone developed ovarian hyperstimulation syndrome.(71,72) Pregnancy occurred in both, after bromocriptine therapy in one (71) and surgery in the second.(72)

Hypopituitarism

Hypopituitarism, secondary to neoplastic, vascular, traumatic, or infiltrative disorders, is commonly associated with gonadotropin deficiency and infertility. Fertility is possible with the assistance of the reproductive endocrinologist, using human chorionic gonadotropin and follicle-stimulating hormone, pulsatile GnRH, and in vitro fertilization. Although the malformation rate is normal in such pregnancies, there seems to be an increased frequency of Cesarean sections, miscarriages and small for gestational age babies.(73-76)

Because of increased thyroxine turnover and volume of distribution in pregnancy, thyroxine (T_4) levels usually fall and TSH levels rise with a fixed *thyroxine* dose over the course of gestation.(77) The average increase in thyroxine need in these patients is about 0.05 mg/day . Because patients with hypothalamic/pituitary dysfunction may not elevate their TSH levels normally in the face of increased need for thyroxine, it is reasonable to increase the thyroxine supplementation by 0.025 mg after the first month or so and by additional 0.025 mg after the second trimester, also following total T4 levels.

In most patients, the dose of chronic glucocorticoid replacement does not usually need to be increased during pregnancy .(78) *Hydrocortisone* is metabolized by the placental enzyme 11β-hydroxysteroid dehydrogenase 2, so the fetus is generally protected from any overdose of hydrocortisone; the usual dose of hydrocortisone is in the range of 12 – 15 mg/m^2 given in two or three divided doses, e.g. 10 mg in the morning and 5 mg in the afternoon.(78) Additional glucocorticoids are for the stress of labor and delivery, such as 75 mg of hydrocortisone IV every 8 hours with rapid tapering postpartum.(78) Prednisolone does not cross the placenta and prednisone crosses only minimally.(79) Suppression of neonatal adrenal function in offspring of women taking prednisone during pregnancy is very uncommon (80) and the amounts passed in breast milk are negligible.(81)

There are few data on the use of GH during pregnancy in hypopituitary individuals and in most series GH therapy has been stopped at conception.(82,83) Whether GH replacement in GH deficient women facilitates fertility is controversial.(83) As the GH variant, which is biologically active, is produced by the placenta in substantial amounts beginning in the second half of pregnancy and can access the maternal circulation (see above), then at most the mother would be GH deficient only in the first half of pregnancy. When Curran et al analyzed 25 pregnancies that occurred in 16 patients with GH deficiency during which GH therapy was not continued, they found that there was no adverse outcome of omitting GH therapy on either the fetus or mother and concluded that GH replacement therapy during pregnancy is not essential for GH-deficient women.(82)

Hypopituitarism may also present during pregnancy or postpartum, secondary to adenoma expansion, lymphocytic hypophysitis, and pituitary infarction. Recognition may be difficult because fatigue, nausea, and vomiting are frequent accompaniments of normal pregnancies. Dynamic testing during pregnancy is also difficult to interpret in light of the physiologic changes during normal pregnancy.

Sheehan's Syndrome

Sheehan's syndrome consists of pituitary necrosis secondary to ischemia occurring within hours of delivery.(84,85) It is usually secondary to hypotension and shock from an obstetric hemorrhage. Pituitary enlargement during pregnancy apparently predisposes to the risk for ischemia with occlusive spasm of the arteries to the anterior pituitary and stalk.(84,85) The degree of ischemia and necrosis dictates the subsequent patient course. It rarely occurs with current obstetric practice.(86)

Acute necrosis is suspected in the setting of an obstetric hemorrhage where hypotension and tachycardia persist following adequate replacement of blood products In addition, the woman fails to lactate and may have hypoglycemia.(84,85,87) Investigation should include levels of ACTH, cortisol, prolactin, and free thyroxine. The ACTH stimulation test would be normal, as the adrenal cortex would not be atrophied. Thyroxine levels may prove normal initially, as the hormone has a half-life of seven days. Prolactin levels are usually low, although they are generally 5-10 fold elevated in the puerperium. Treatment with saline and stress doses of corticosteroids should be instituted immediately after drawing the blood tests. Additional pituitary testing with subsequent therapy should be delayed until recovery. Diabetes insipidus may also occur secondary to vascular occlusion with atrophy and scarring of the neurohypophysis.(88)

When milder forms of infarction occur, the diagnosis of Sheehan's syndrome may be delayed for months or years.(85,87) These women generally have a history of amenorrhea, decreased libido, failure to lactate, breast atrophy, loss of pubic and axillary hair, fatigue, and symptoms of secondary adrenal insufficiency with nausea, vomiting, diarrhea, and abdominal pain.(Table 3)(85,87) Some women experience only partial hypopituitarism, and may have normal menses and fertility.(85,87) Although the women may have episodes of transient polydipsia and polyuria, many demonstrate impaired urinary concentrating ability and deficient vasopressin secretion.(88,89) or MRI scans generally reveal partial or completely empty sellae.(90)

Table 3. Symptoms and Signs of Sheehan Syndrome

Acute Form	Chronic Form
Hypotension	Light-headedness
Tachycardia	Fatigue
Failure to lactate	Failure to lactate
Hypoglycemia	Persistent amenorrhea
Failure to regrow shaved pubic hair	Decreased body hair
Extreme fatigue	Dry skin
Nausea and vomiting	Loss of libido
	Nausea and vomiting
	Cold intolerance
(From Molitch ME. Pituitary, thyroid, adrenal and parathyroid disorders. In: Barron WM, Lindheimer MD, eds. Medical disorders during pregnancy. Chicago: Mosby-Year Book, 1991.)	

Lymphocytic Hypophysitis

Pituitary enlargement during pregnancy may also be due to lymphocytic hypophysitis.(91-93) Lymphocytic hypophysitis is characterized by massive infiltration of the pituitary by lymphocytes and plasma cells, with destruction of the normal parenchyma.(91) The disorder is thought to have an autoimmune basis.(91) Most cases occur in association with pregnancy, and women are seen during pregnancy or postpartum, either with symptoms of varying degrees of hypopituitarism or with symptoms related to the mass lesion, such as headaches or visual-field defects. Mild hyperprolactinemia and DI may also be found. By virtue of the hypopituitarism that it produces, lymphocytic hypophysitis can be clinically confused with Sheehan's syndrome postpartum, except that these women have no history of obstetric hemorrhage. On MRI scans, there is usually diffuse, symmetric, enhancement rather than a focal lesion that might indicate a tumor.(91-93) The clinical picture often allows a clinical diagnosis to be made without invasive procedures.

Treatment is generally conservative and involves identification and correction of any pituitary deficits, especially of ACTH secretion which is particularly common in this condition.(92,93) Data regarding the benefits of high dose corticosteroid treatment in reducing the size of the lesion are inconclusive.(93)

Surgery to debulk but not remove the gland is indicated in the presence of uncontrolled headaches, visual field defects, and progressive enlargement on scan.(92,93) Spontaneous regression and resumption of partial or normal pituitary function may occur, although most patients progress to chronic panhypopituitarism.(92,93) In some cases, a late finding of an "empty" sella on MRI may be found.(92,93)

Posterior Pituitary

The osmostat, the setpoint for plasma osmolality at which arginine vasopressin (AVP) is secreted, is reduced approximately 5-10 mOsm/kg in pregnancy, dropping from 285 to 275 mOsm/kg. As a result, pregnant women experience thirst and release AVP at lower levels of plasma osmolality than do nonpregnant women.106 This reset osmostat and altered thirst threshold is possibly due to high levels of human chorionic gonadotropin (hCG).(94) The placenta produces an amino-terminal peptidase, vasopressinase, an enzyme that rapidly inactivates AVP and oxytocin. Vasopressinase levels increase 1000-fold between the 4th and 38th weeks of gestation.(95) AVP consequently has a four- to sixfold increased metabolic clearance rate during gestation.(95)

Serum sodium levels may also be lower than those normally expected in patients with diabetes insipidus.(96,97) Standard water deprivation tests which require 5% weight loss should be avoided during pregnancy as they may cause uterine irritability and alter placental perfusion. Instead, dDAVP is used to assess urinary concentrating ability over 11 hours, with a value greater than 700 mosm/kg considered normal.(98) Urinary concentrating ability in the pregnant patient should be determined in the seated position, as the lateral recumbent position inhibits maximal urinary concentration.(94) Delivery of the placenta generally results in a return to normal AVP metabolism in 2 to 3 weeks.

Plasma oxytocin levels increase progressively during pregnancy, with a dramatic increase at term.(99) Oxytocin levels rise further during labor and peak in the second stage. Uterine sensitivity to oxytocin increases with a rise in oxytocin receptors in the myometrium. Hypophysectomy does not alter onset of labor, indicating that oxytocin provides only a facilitatory role.(100) Pulsatile release of oxytocin does not correlate with uterine contractions. Oxytocin levels rise rapidly during suckling.(101)

Diabetes Insipidus

Three types of diabetes insipidus may occur in pregnancy; central, nephrogenic, or transient vasopressin-resistant. Each is manifest with polydipsia, polyuria, and dehydration.(96,97)

Central diabetes insipidus may occur spontaneously in pregnancy with an enlarging pituitary adenoma, with lymphocytic hypophysitis, or with the development of other conditions such as histiocytosis X. Diabetes insipidus usually worsens during gestation, likely due to the increased clearance of AVP by the vasopressinase.(96,97) Patients with asymptomatic DI may develop symptoms during pregnancy with the lower osmostat for vasopressin release, elevation in vasopressinase levels, and increased AVP clearance.(102-104) Patients with mild disease treated with chlorpropamide should discontinue this agent, as it readily crosses the placenta and causes hypoglycemia in the fetus. The AVP analog desmopressin (dDAVP) is resistant to vasopressinase, and provides satisfactory treatment during gestation without any harm to the fetus, although a higher dose may be required.(96,97) During monitoring of the clinical response, clinicians should remember that normal basal plasma osmolality and sodium concentration are 5 mEq/L lower during pregnancy.(96,97) No adverse events have been described in the offspring of pregnancies in which dDAVP was used throughout gestation.(105,106) DDAVP transfers minimally into breast milk and is poorly absorbed from the gastrointestinal tract, so its use will not adversely affect an infant's water metabolism.(97)

Transient AVP-resistant forms of DI secondary to placental production of vasopressinase may occur spontaneously in one pregnancy, but not in a subsequent one.(107) Some of these patients may respond to dDAVP therapy. The symptoms resolve within several weeks of delivery.(107,108) Another rare cause of transient DI of pregnancy is placental abruption, in which the abruption causes a rise in vasopressinase.(109)

Acute fatty liver of pregnancy and other disturbances of hepatic function such as hepatitis may be associated with late onset transient DI of pregnancy in some patients.(110,111) Other cases have been

reported in patients with the HELLP (hemolysis, elevated liver-enzyme levels, low platelets) syndrome.(96) It is presumed the hepatic dysfunction is associated with reduced degradation of vasopressinase, further increasing vasopressinase levels and the clearance of AVP. The polyuria may develop either prior to delivery or postpartum. Thus, women in whom DI develops very late in gestation should also be screened for liver function abnormalities. Complete resolution of the hepatic abnormalities and DI occurs by the 4th week postpartum.

DI that develops postpartum may be a result of Sheehan's syndrome, particularly in the setting of an obstetric hemorrhage.(see above) Transient DI of unknown etiology has been described postpartum, lasting only days to weeks.(112)

In patients with idiopathic, central DI, oxytocin levels are normal and labor may begin spontaneously and proceed normally.(113) Patients with DI secondary to trauma, infiltrative disease, or a neoplasm may have adversely affected oxytocinergic pathways, resulting in poor progression of labor and uterine atony.

Syndrome of Inappropriate Antidiuretic Hormone Secretion

As mentioned earlier, the normal serum sodium is reset about 5 mEq/L lower during pregnancy. However, true hyponatremia due to the syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported in a small number of cases with preeclampsia, but the mechanism is not clear.(114)

ADRENAL DISORDERS IN PREGNANCY

Pregnancy modifies the hypothalamic-pituitary-adrenal axis, with increases in placental CRH and ACTH production (see above). Despite the increase in the placental hormones, the normal maternal circadian rhythm of ACTH secretion persists throughout pregnancy.(38)

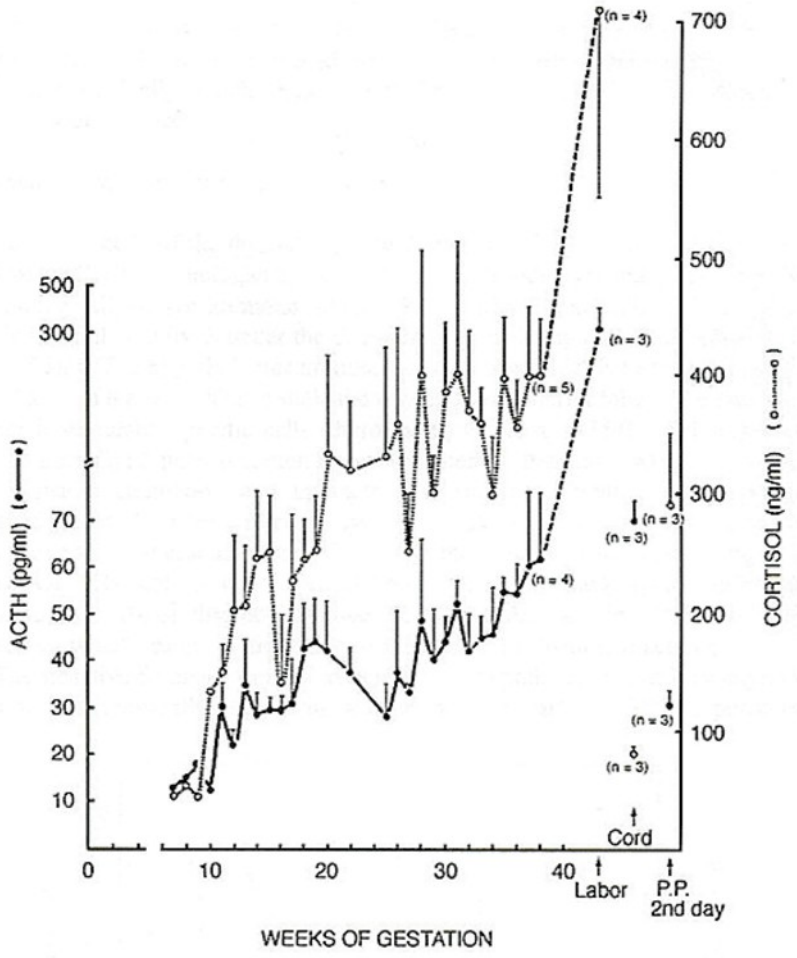

Figure 3. Plasma concentrations of adrenocorticotropic hormone (ACTH) and cortisol during normal pregnancy. Blood samples were obtained from five normal pregnant women weekly at 8:00 to 9:00 AM and from three women during labor and on the second postpartum day. In addition, umbilical cord plasma was obtained from the newborn infants of three of these subjects. The mean plasma concentrations for ACTH are denoted by the solid circles, whereas plasma cortisol levels are denoted by open circles. The vertical bars correspond to the magnitude of the standard error of the mean. (From Carr BR, Parker Jr CT, Madden JD, et al. Maternal plasma adrenocorticotropin and cortisol relationships throughout human pregnancy. Am J Obstet Gynecol 1981;139:416.)

Numerous changes occur in the renin-angiotensin-aldosterone system as well. Plasma renin activity increases fourfold by 8 weeks and then increases only minimally over the subsequent 32 weeks of gestation.(115,116) The renin is produced by the ovaries and decidua as well as from the estrogen-stimulated kidney.(116) Plasma angiotensinogen levels increase fourfold over the course of the first 20 weeks of gestation and then increase only minimally over the subsequent 20 weeks of gestation due to the increased estrogen levels as well.(115,116) These changes lead to a doubling of angiotensin II levels early in pregnancy and with a further increase to 3-4 fold by term.(115,116) Similar increases occur in plasma aldosterone levels, a 5-fold increase occurring by 16 weeks and ultimately a 7- to 10-fold elevation occurring by term.(38,115,116) This increase in plasma aldosterone levels is reflected in a 7-fold elevation in urinary aldosterone levels by 12 weeks and ultimately a 20- to 25-fold elevation by term.(115) Aldosterone secretion continues to respond normally to physiologic stimuli such as posture and varies inversely to changes in volume or dietary salt.(117) The increase in aldosterone correlates with the pregnancy increase in GFR and in progesterone,(118) which

competitively inhibits sodium retention by aldosterone at the distal renal tubules. Progesterone also demonstrates an anti-kaliuretic effect,(117) with a report of amelioration of hypokalemia during pregnancy in a woman with primary aldosteronism.(119)

The relative hypercortisolism and hyperaldosteronism of normal pregnancy are not generally clinically apparent.

Adrenal disorders occurring in pregnancy cause significant maternal and fetal morbidity.

Cushing's Syndrome During Pregnancy

The diagnosis of Cushing's syndrome should be made during pregnancy, because untreated, the condition is associated with high fetal mortality and increased prematurity, as well as maternal hypertension, preeclampsia, and myopathy.(78,120,121) Fertility is generally reduced by the altered gonadotropin secretion in pituitary disease and amenorrhea is a common symptom. Although fewer than 150 cases of Cushing's syndrome during pregnancy have been reported, (78,120-125) it is apparent that the distribution of causes of Cushing's syndrome is different in pregnancy. Less than 50% are due to pituitary adenomas, a like number are due to adrenal adenomas, and 10% are due to adrenal carcinomas. Ectopic ACTH secretion causing Cushing's syndrome during pregnancy has been reported only rarely.(123) Interestingly, in many cases Cushing's syndrome first became manifest or exacerbated during the pregnancy, with improvement after parturition. It has been speculated that in some cases of Cushings disease, the unregulated placental CRH was instrumental in causing this pregnancy-induced exacerbation.(120,121)

It may be difficult to diagnose Cushing's syndrome during pregnancy because the typical symptoms of central weight gain, fatigue, emotional lability, glucose intolerance, hypertension, and edema are also common accompaniments of pregnancy. Pigmentation of striae and development of hirsutism or acne may suggest the hyperandrogenemia of Cushing's syndrome, and proximal myopathy may also help to distinguish Cushing's syndrome from normal pregnancy symptoms. Pathologic fractures may occur.(126)

The laboratory evaluation is confounded by the normal pregnancy rise in ACTH and cortisol levels. Urinary free cortisol levels greater than 3 times the upper limit of normal may be interpreted as indicating Cushing's syndrome in the second and third trimester.(120) Furthermore, at least in the latter part of the third trimester, these elevated levels are nonsuppressible by low-dose dexamethasone. In pregnant patients reported with Cushing's disease, plasma cortisol levels are minimally suppressed with 2 days of low-dose dexamethasone but suppressed quite well with the high dose.(122,123) In pregnant patients with adrenal adenomas, plasma cortisol is also not suppressed with high-dose dexamethasone,(125) as expected. Basal ACTH levels have been reported to be normal to elevated in pregnant patients with all forms of Cushings syndrome.(122,123,125,128) These "normal" rather than suppressed levels of ACTH in patients with adrenal adenomas may be due to production of ACTH by the placenta or nonsuppressible stimulation of pituitary ACTH by placental CRH (see previous discussion). Thus, the presence of "normal" levels of ACTH may be quite misleading in the differential diagnosis of Cushing's syndrome during pregnancy.

The finding of a persistent diurnal variation in elevated levels of total and free serum cortisol may be helpful in establishing that hypercortisolism is this normal pregnancy increase, (38,127,129) since diurnal variation is characteristically absent in all forms of Cushing's syndrome. Salivary cortisol measurements may turn out to be useful in this regard, but normal limits for midnight levels of salivary cortisol during pregnancy have not yet been standardized.

Little experience has been reported with newer techniques such as CRH stimulation testing or petrosal venous sinus sampling in diagnosing Cushing) disease during pregnancy. CRH testing during late gestation has the potential hazard of inducing premature labor, because CRH has been shown to potentiate the contractile response of pregnant myometrium to oxytocin and has been implicated in participating in the process of parturition.(130) CRH stimulation tests have

been shown to elicit normal ACTH responses in the early second trimester but no ACTH response in the late third trimester in normal pregnancies.(36,131) Thus, the finding of a blunted ACTH response to CRH would be more in favor of simple pregnancy than Cushings disease, in which hyperresponsiveness to CRH is generally seen. Indeed, Ross and colleagues found the typical exaggerated ACTH response to CRH in a woman with Cushings disease, and this patient had no ill effects from such testing.(124) In two patients studied by Lindsay et al., ACTH levels increased more than threefold, but cortisol level increases were less than twofold.(123) In addition, CRH testing during petrosal sinus sampling was performed without ill effects by Pinette and co-workers in a woman at 14 weeks' gestation (132) and by Lindsay et al.(123) in four women, but catheterization was performed via the direct internal jugular vein approach rather than the femoral vein approach to minimize fetal irradiation.

When biochemical evidence points to the presence of Cushing's syndrome and to a pituitary or adrenal origin, radiologic imaging becomes necessary. The pituitary volume is often increased during pregnancy (see previous discussion), and pituitary CT or MRI may yield false-positive findings. Careful review of the MRI findings, however, may indicate a focal abnormality in a patient with a tumor as opposed to the diffusely enlarged, homogeneous gland seen with pregnancy (see earlier). On the other hand, in many patients with Cushing's disease, no pituitary adenoma is visible on MRI and the finding of a microadenoma on MRI is nonspecific, given the high rate of in finding pituitary incidentalomas.(133,134) Often an adrenal mass will be visible on ultrasound if the cause is an adrenal neoplasm.(135) Usually, however, CT or MRI of the pituitary or adrenal will be necessary, especially to detect masses with a diameter less than 3.0 cm.(135) With the techniques and equipment available at present, CT and MRI appear to be about equal in detecting adrenal masses.(135) Because MRI may be safer during pregnancy, it may be the technique of choice for localizing the mass. However, radiologists are reluctant to perform MRI's with contrast during pregnancy despite no evidence of toxicity to the fetus.(136) Most adrenal lesions are unilateral, so localization is important.

Cushing's syndrome is associated with a pregnancy loss rate of 25% due to spontaneous abortion, stillbirth, and early neonatal death because of extreme prematurity.(123,137-139) The passage of cortisol across the placenta may rarely result in suppression of the fetal adrenals.(140) Hypertension develops in most mothers with Cushing's and diabetes and myopathy are frequent.(138,139) Postoperative wound infection and dehiscence are common after cesarean section.(138,139)

In a review of 136 pregnancies collected from the literature, Lindsay et al found that the frequency of live births increased from 76% to 89% when active treatment was instituted by a gestational age of 20 weeks.(123) Therefore, treatment *during* pregnancy has been advocated.(123,137) Medical therapy for Cushing's syndrome during pregnancy with metyrapone and ketoconazole is not very effective.(123,138) Intrauterine growth retardation has been reported with ketoconoazole.(123) However, a recent case was described in whom ketoconazole was used during the 1st trimester and metyrapone in the 2nd and 3rd trimesters with a good fetal outcome.(141) Recently, the FDA has issued a black box warning for ketoconazole with respect to severe liver toxicity and so its use cannot be recommended. Aminoglutethimide and mitotane should be avoided because of potential fetal toxicity.(123,138) Two new medications have been approved for the treatment of Cushing's disease recently. Mifepristone, a cortisol receptor blocker, is highly effective but because it is also a progesterone receptor blocker and an abortifacient, it cannot be used during pregnancy.(142) Pasireotide is a new somatostatin analog with modest efficacy in patients with Cushing's disease (143); it has the adverse effect of hyperglycemia and there is no experience with its use during pregnancy. However, the same cautions discussed above for somatostatin analogs should also hold true for when pasireotide might be used in a patient with Cushing's disease.

Transsphenoidal resection of a pituitary ACTH-secreting adenoma has been carried out successfully in several patients during the second trimester.(122-124,132,138) Although any

surgery poses risks for the mother and fetus,(51,52) it appears that with Cushing's syndrome, the risks of not operating are considerably higher than those of proceeding with surgery.

Adrenal Insufficiency

The prevalence of primary adrenal insufficiency in pregnancy is unknown, with a series from Norway suggesting an incidence of 1 in 3000 births from 1976 to 1987.(144) In developed countries, the most common etiology for primary adrenal insufficiency is autoimmune adrenalitis, which may be associated with autoimmune polyglandular syndrome. Primary adrenal insufficiency from infections (tuberculosis or fungal), bilateral metastatic disease, hemorrhage or infarctions is uncommon.(120,121) Secondary adrenal insufficiency, from pituitary neoplasms or glucocorticoid suppression of the hypothalamic-pituitary-adrenal axis, is more common.

Recognition of adrenal insufficiency may be difficult in the first trimester as many of the clinical features are found in normal pregnancies, including weakness, lightheadedness, syncope, nausea, vomiting, hyponatremia, and increased pigmentation. Addisonian hyperpigmentation may be distinguished from chloasma of pregnancy by its presence on the mucous membranes, on extensor surfaces, and on non-exposed areas. Weight loss, hypoglycemia, salt craving, hyponatremia more severe than the normal 5 mmol/L decrease of pregnancy, or seizures, should prompt a clinical evaluation. If unrecognized, adrenal crisis may ensue at times of stress, such as a urinary tract infection or labor.(144) Fetal cortisol production may be protective, shielding the mother from severe adrenal insufficiency until postpartum.(145)

The fetoplacental unit largely controls its own steroid milieu, so maternal adrenal insufficiency generally causes no problems with fetal development.(78) Maternal antiadrenal autoantibodies may cross the placenta, but usually not in sufficient quantities to cause fetal or neonatal adrenal insufficiency.(146) Women with Addison's disease have a relative infertility and babies born to mothers with Addison's disease have increased risks of preterm birth, low birth weight and need for cesarean section.(147) Severe maternal hyponatremia or metabolic acidosis may cause a poor fetal outcome, including death.(148) Association with other autoimmune conditions such as anticardiolipin antibodies may lead to additional risks such as miscarriage.(149)

Adrenal insufficiency is associated with laboratory findings of hyponatremia, hyperkalemia, hypoglycemia, eosinophilia, and lymphocytosis. Hyperkalemia may be absent, because of the pregnancy increase in the renin angiotensin system.(148,150) Early morning plasma cortisol levels of < 3.0 mcg/dl (83 nmol/L) confirms adrenal insufficiency, while a cortisol >19 mcg/dl (525 nmol/L) in the first or early second trimester excludes the diagnosis in a clinically stable patient.(151) Plasma cortisol levels may fall in the normal "nonpregnant" range due to the increase in CBG concentrations in the second and third trimesters, but will not be appropriately elevated for the stage of pregnancy.(120,121,144) Recently, normal basal and ACTH-stimulated cortisol values have been established for pregnant women; for the first, second, and third trimesters, basal morning values (mean ± SD) were 9.3 ± 2.2 µg/dL, 14.5 ± 4.3 µg/dL, and 16.6 ± 4.2 µg/dL. Stimulated values were 29.5 ± 16.1 µg/dL, 37.9 ± 9.0 µg/dL, and 34.7 ± 7.5 µg/dL.(152) McKenna et al examined the 1 mcg low dose cosyntropin test for diagnosis of secondary adrenal insufficiency in women at 24-34 weeks gestational age, finding high sensitivity of diagnosis using a cutoff of 30 mcg/dl (828 nmol/L).(153) Accuracy of dosing is more difficult with this than with the standard cosyntropin test. The cosyntropin test is less sensitive in detecting early secondary or tertiary forms of adrenal insufficiency. Standard metyrapone testing (750 mg every 4 hours for 6 doses) has also been performed during pregnancy, and 75% of normal pregnant subjects showed diminished responses, whereas the other 25% had normal responses.(154) Therefore, metyrapone testing does not appear to be valid during pregnancy.

Cortisol and ACTH responses to CRH are blunted in pregnancy,(131) making the CRH stimulation test unreliable for differentiating secondary and tertiary adrenal insufficiency in pregnancy. With primary adrenal insufficiency, ACTH levels will be elevated, and a level above

100 pg/ml (22 pmol/L) is consistent with the diagnosis.(151) However, ACTH will not be low with secondary forms because of the placental production of this hormone, which is nevertheless insufficient to maintain normal maternal adrenal function. ACTH values fluctuate widely, and a single value is insufficient for diagnosis. Adrenal antibodies may assist in confirming idiopathic adrenal insufficiency, as approximately 90% of patients will have 21-hydroxylase antibodies and 30% will have antibodies to 17-hydroxylase and side-chain cleavage enzymes.(155) Aldosterone to renin ratios are low with elevated plasma renin activity in patients with mineralocorticoid deficiency from adrenal atrophy.(156()

Despite the normal increase in plasma cortisol during pregnancy, baseline maternal replacement doses of corticosteroids usually are not different from those required in the non-pregnant state.(120,121,157) Higher doses are needed at times of stress, such as during the course of “morning sickness” or during labor and delivery. Patients should be educated in the self-administration of intramuscular hydrocortisone. Hydrocortisone 50 mg IV is generally given in the second stage of labor and then continued every 6 – 8 hours through labor and delivery. (157) Mineralocorticoid replacement requirements usually do not change during gestation, though some clinicians have reduced doses of fludrocortisone in the third trimester in an attempt to treat Addisonian patients who develop edema, exacerbation of hypertension, and preeclampsia.(144,158)

Patients who have received glucocorticoids as antiinflammatory therapy are presumed to have adrenal axis suppression for at least one year.(159) These patients should be treated with stress doses of glucocorticoids during labor and delivery. They are at risk for postoperative wound infection and dehiscence as are patients with endogenous Cushing’s, and their offspring are at risk for transient adrenal insufficiency. Although prednisone readily crosses the placenta,(160) the maternal:fetal gradient is higher than with other available agents.(79,161) Corticosteroid therapy during pregnancy is generally safe and suppression of neonatal adrenal function is uncommon.(80) Glucocorticoid therapy during lactation is also safe, as less than 0.5% of the dose is passed into breast milk.(81,162)

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) occurs in a family of monogenic inherited enzymatic defects of adrenal steroid biosynthesis, with manifestations secondary to an accumulation of precursors proximal to the enzymatic deficiency. The most common form of CAH in the population is 21-hydroxylase (CYP21 gene) deficiency, seen in more than 90% of the CAH cases in pregnancy.(163-165) Classic, severe 21-hydroxylase deficiency is associated with ambiguous genitalia, an inadequate vaginal introitis, and progressive postnatal virilization including precocious adrenarche, advanced somatic development, central precocious puberty, menstrual irregularity, a reduced fertility rate, and possibly salt wasting.(163-168) Cephalopelvic disproportion from an android pelvis may occur, sometimes complicated by the previous reconstructive surgery.(163-168) Conception requires adequate glucocorticoid therapy, which then continues at stable rates during gestation, except at labor and delivery. Nonclassic (late-onset) 21-hydroxylase deficiency patients present with pubertal and postpubertal hirsutism and menstrual irregularity, and may have improved fertility and fewer miscarriages with glucocorticoid therapy.(169,170)

Fetal risk depends on the carrier status of the father; CYP21 genotyping should be performed. (165,166) Virilization is not seen in the female fetus with nonclassic 21-hydroxylase deficiency but occurs in a fetus with classic 21-hydroxylase deficiency unless fetal adrenal androgen production is adequately suppressed.(166) The risk of an offspring having classic 21-hydroxylase deficiency with a mother with nonclassic disease is 3%.(170)

When the father is appropriately genotyped and found to not be a carrier, the fetus then is not at risk for the development of CAH. Dexamethasone most readily crosses the placenta, as it is not bound to CBG, and is not metabolized by placental 11β-hydroxysteroid dehydrogenase. Hydrocortisone is metabolized by this enzyme, so that the fetus is protected from excessive

amounts. Thus, when the fetus is not expected to be affected, hydrocortisone is the preparation of choice and doses should be monitored each trimester by keeping maternal levels of androstenedione and testosterone in the normal range.(164,166)

When the father is found to be a carrier, then 25% of the fetuses are at risk of having CAH and the half of these that are female are at risk of virilization. Whether dexamethasone should be given to suppress the adrenals in such at risk pregnancies is controversial.(165,166) The suppressive regimen advocated by some is dexamethasone at doses of 20 µg/kg maternal body weight per day to a maximum of 1.5 mg daily in 3 divided doses beginning at recognition of pregnancy before the 9th week of gestation,(166) though lower doses are recommended by some.(171) Treatment by the 9th week of gestation is very effective in reducing the risk of virilization in the affected female fetus.(166) Maternal plasma and/or urinary estriol levels reflect fetal adrenal synthesis and are monitored to assess efficacy. Maternal cortisol and DHEA-S levels will represent maternal adrenal suppression. As only 25% of female fetuses are affected in a family with CAH, it is important to discontinue therapy as soon as possible in the male fetus and unaffected female fetus. Chorionic villus sampling at 9-11 weeks gestation may be used for gender determination and direct DNA analysis for the 21-hydroxylase gene CYP21. An alternative is karyotyping and DNA analysis or measuring androstenedione and 17-OH progesterone levels in amniotic fluid at 16-18 weeks of gestation after dexamethasone has been withheld for 5 days.(172) However, waiting until amniotic fluid is available for testing would cause the mothers of unaffected offspring to be treated for an extra 6 -8 weeks. Side effects of dexamethasone therapy are potentially significant, including excessive weight gain, severe striae with scarring, edema, irritability, gestational diabetes mellitus, hypertension, and gastrointestinal intolerance.(166,173) In affected pregnancies, dexamethasone may be lowered to 0.75 to 1.0 mg/day in the second half of pregnancy to decrease maternal side effects while avoiding fetal virilization.(171) Steroid doses should be increased for the stress of labor and delivery.(165)

Primary Hyperaldosteronism During Pregnancy

Primary hyperaldosteronism has been rarely reported in pregnant women.(174-179) Moderate to severe hypertension is seen in 85%, proteinuria in 52%, and hypokalemia in 55%, and symptoms may include headache, malaise, and muscle cramps.(174-179) Placental abruption and preterm delivery are risks.(175,176) Whereas the elevated aldosterone levels found in patients with these tumors are similar to those found in pregnancy, in hyperaldosteronism, plasma renin activity should be suppressed rather than elevated, as normally found in pregnancy. Reported patients in whom simultaneous renin and aldosterone levels were determined during pregnancy had markedly elevated levels of aldosterone, with low renin levels. (174,175,177,178)

In addition to measuring simultaneous plasma aldosterone and renin levels, diagnostic testing may also involve determining whether the aldosterone levels can be suppressed by salt loading or the administration of exogenous mineralocorticoid. During normal pregnancy, basal elevated aldosterone levels also fall normally with such maneuvers, (117) so these maneuvers can be of diagnostic utility. Pregnant patients with aldosteronomas who were put through such testing failed to demonstrate normal suppressibility of aldosterone levels.(175,178) If the results of baseline renin and aldosterone levels or suppression tests are equivocal, and/or CT or MRI does not suggest unilateral disease, it has been recommended that patients be treated medically until delivery, when more definitive scanning and/or selective venous sampling can be done if there is diagnostic uncertainty.(78,174) Spironolactone, the aldosterone antagonist generally used for such treatment, can cross the placenta. Because spironolactone is a potent antiandrogen, it may cause abnormal development of the genitalia180 and is thus contraindicated during pregnancy. Eplerenone, a more selective aldosterone receptor blocker without antiandrogen activity has been used successfully in one case during pregnancy without any untoward consequences on the fetus.(179) Amiloride has also been used safely in one patient.(178) Successful laparoscopic removal of the aldosteronoma during pregnancy has

also been reported when blood pressure could not be controlled by medical means.(174,177) Both hypertension and hypokalemia may exacerbate postpartum due to removal of the progesterone effect.(181,182)

A rare variant of hyperaldosteronism, referred to as *glucocorticosteroid-remediable aldosteronism,* is characterized by severe hypertension, hypokalemia, volume expansion, and suppressed plasma renin activity; it is due to a chimeric gene duplication that results from an unequal crossing over between the 11 β-hydroxylase and aldosterone synthase genes.(183) A review of 35 pregnancies in 16 women with this disorder showed relatively modest adverse consequences, consisting primarily of pregnancy-associated blood pressure aggravation in 39%, a slight decrease in infant birth weight, and an increased cesarean section rate.(183) Interestingly, an activating mutation of the mineralocorticoid receptor has also been reported to be one of the causes of pregnancy-exacerbated hypertension.(184)

Pheochromocytoma in Pregnancy

Exacerbation of hypertension is a typical presentation of pheochromocytoma in nonpregnant patients, but during pregnancy is frequently mistaken for pregnancy-induced hypertension or preeclampsia.(185-187) The prevalence is estimated at 1 in 54,000 pregnancies.(185-187) As the uterus enlarges and an actively moving fetus compresses the neoplasm, maternal complications such as severe hypertension, hemorrhage into the neoplasm, hemodynamic collapse, myocardial infarction, cardiac arrhythmias, congestive heart failure, and cerebral hemorrhage may occur. The maternal mortality rate from undiagnosed pheochromocytoma is about 50%; this rate falls to less than 10% if the diagnosis is made antepartum.(78,185-187) The fetal loss rate also of about 50% is reduced to 10 – 20% if diagnosis is made during pregnancy and treatment instituted.(185-187)

There is minimal placental transfer of catecholamines, likely due to high placental concentrations of catechol-O-methyltransferase and monoamine oxidase.(188,189) Adverse fetal effects such as hypoxia are a result of catecholamine-induced uteroplacental vasoconstriction and placental insufficiency,(185,190-192) and of maternal hypertension, hypotension, or vascular collapse.

Because of this high maternal and fetal mortality in undiagnosed and untreated patients, it is critical to make the diagnosis antepartum. Symptoms may be vague, or classic symptoms may be seen and be due to the episodic secretion of catecholamines, as in the nonpregnant state. Some patients may have episodes that are very infrequent, so the first suspicion of pheochromocytoma may occur with a blood pressure rise during the induction of anesthesia or during labor or surgery. Failure to recognize this possibility may result in death of the patient.(186,193) Some patients have sudden shock appearing spontaneously or induced by anesthesia or labor and delivery.(194)

Catechoamine-secreting paragangliomas represent about 10 - 20% of cases and may provoke paroxysmal symptoms after particular activities. A frequent site is the organ of Zuckerkandl, located at the bifurcation of the aorta, and the enlarging uterus may cause pressure on such a tumor, with hypertensive episodes occurring after changes in position, uterine contractions, fetal movement, and Valsalva maneuvers.(195) Although about 10% of pheochromocytomas are found to be malignant, this frequency appears to be considerably less when the diagnosis is made in a pregnant woman, because only four such cases have been reported.(196) Hereditary syndromes are also important, and 25-30% of patients whose pheochromocytomas were initially diagnosed during pregnancy have been reported who later were found to have multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau syndrome, neurofibromatosis or succinate dehydrogenase subunit gene mutations.(185-187)

The diagnosis should be considered in pregnant women with severe or paroxysmal hypertension, particularly in the first half of pregnancy or in association with orthostatic hypotension or episodic symptoms of pallor, anxiety, headaches, palpitations, chest pain, or diaphoresis. Symptoms may occur or worsen during pregnancy because of the increased

vascularity of the tumor and mechanical factors such as pressure from the expanding uterus or fetal movement.(191)

A key consideration in diagnosing pheochromocytoma during pregnancy is differentiation from preeclampsia and pregnancy-induced hypertension. Onset of hypertension prior to 20 weeks is not characteristic of pregnancy-induced hypertension and preeclampsia occurs in the last trimester.(186) Careful evaluation reveals the absence of proteinuria, edema, or hyperuricemia in the patient with a pheochromocytoma. Catecholamine production does not increase and urinary and plasma levels remain normal or are only slightly increased with preeclampsia 186 and even in severe preeclampsia.(197,198) Urinary and plasma catecholamines, however, are twofold to fourfold elevated for more than 24 hours after a seizure in eclampsia.(197,198) Therefore, to make a diagnosis in a woman not having eclampsia, measurement of 24-hour urinary collections for fractionated metanephrines and catecholamines or plasma metanephrines can be used as for nonpregnant patients.(186-187) Elevated urinary or plasma metanephrines or normetanephrines have a 98% to 99% sensitivity but considerably lower specificity.(186) Spurious elevations of catecholamines can be caused by many medications, including labetalol, acetaminophen, isoproterenol, methyldopa, L-dopa, norepinephrine, tricyclic antidepressants, pseudoephedrine, phenoxybenzamine, monoamine oxidase inhibitors, β-blockers, α-blockers, calcium channel blockers, and buspirone.(194) Furthermore, physical and psychological stress may cause mild elevations of catecholamines.(194) In patients with just mild elevations, repeated testing with avoidance of stress may be necessary to make the diagnosis biochemically.(194) Stimulation tests have been associated with hypotension, and their use has been discouraged.(194)

Once the diagnosis is made biochemically, efforts should be made to localize the tumor. Both CT and MRI are excellent for detecting the presence of tumors, but MRI has been preferred during pregnancy because of the lack of exposure of the fetus to ionizing radiation and the relative safety of MRI scanning during pregnancy.(136,185,199)

Initial medical management involves α-blockade with phenoxybenzamine, phentolamine, prazosin, or labetolol. All of these agents are well-tolerated by the fetus, but phenoxybenzamine is considered the preferred agent as it provides long-acting, stable, non-competitive blockade.(185-187,191,200) Phenoxybenzamine is started at a dose of 10 mg twice daily, with titration until the hypertension is controlled for at least two weeks prior to surgery.(200) Perioperative management strategies are similar for pheochromocytomas and secreting paragangliomas.(200) Placental transfer of phenoxybenzamine occurs,(201) but is generally safe.(202-204) However, two neonates of mothers treated with phenoxybenzamine have been reported with respiratory distress and hypotension requiring ventilatory and inotropic support.(205) If hypertension remains inadequately controlled, metyrosine has also been used successfully to reduce catecholamine synthesis in a pregnancy complicated by malignant pheochromocytoma,(206) but may potentially adversely affect the fetus. Beta blockade is reserved for treating maternal tachycardia or arrhythmias which persist after full α-blockade and volume repletion. Beta blockers may be associated with fetal bradycardia and with intrauterine growth retardation, when used early in pregnancy.(185-187) All of these potential fetal risks are small compared to the risk of fetal wastage from unblocked high maternal levels of catecholamines. Hypertensive emergencies should be treated with phentolamine (1-5 mg) or nitroprusside, although the latter should be limited because of fetal cyanide toxicity.

The timing of surgical excision of the neoplasm is controversial and may depend on the success of the medical management and the location of the tumor. As noted above, pressure from the uterus, motion of the fetus, and labor contractions are all stimuli that may cause an acute crisis, particularly in patients with a tumor at the organ of Zuckerkandl. In the first half of pregnancy, surgical excision may proceed once adequate α-blockade is established, although there is a higher risk of miscarriage with first trimester surgery. In the early 2nd trimester, abortion is less likely and the size of the uterus will not make excision difficult. If the pheochromocytoma is not recognized until the second half of gestation, increasing uterine size

makes surgical exploration difficult. Successful laparoscopic excision of a pheochromocytoma in the 2nd trimester of pregnancy has been described.(185,204,207)

Other options include combined cesarean delivery and tumor resection or delivery followed by tumor resection at a later date. Delivery is generally delayed until the fetus reaches sufficient maturity to reduce postpartum morbidity, providing successful medical management exists. Although successful vaginal delivery has been reported,(208) it has been associated with higher rates of maternal mortality than cesarean section. Labor may result in uncontrolled release of catecholamines secondary to pain and uterine contractions. Severe maternal hypertension may lead to placental ischemia and fetal hypoxia. However in the well-blocked patient, vaginal delivery may be possible with pain management with epidural anesthesia and employment of techniques of passive descent and instrumental delivery. There is no available information regarding the impact of maternal use of phenoxybenzamine on the nursing neonate.

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