22 Endocrine diseases and pregnancy

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INTRODUCTION

The epidemiology and natural history of endocrine diseases are such that they commonly occur in women of childbearing age. While major endocrinopathies often adversely affect fertility, and thereby in effect prevent pregnancy, the innate resilience of the human reproductive system, and the fundamental good health of most endocrine patients, assures that incidental pregnancies will frequently be encountered in patients with established endocrine disease. Pregnancy profoundly affects many of the endocrine systems and the laboratory testing upon which confirmation of disease relies; thus, physicians who treat pregnant patients are well advised to have familiarity with these alterations. Endocrine diseases may have adverse consequences for maternal, fetal, and neonatal health; likewise, the pregnancy may alter the expression of endocrine disease and as well may alter the interpretation of diagnostic laboratory testing commonly performed in non-gravid patients. Additionally, pregnancy alters choice of pharmacotherapy and diagnostic modalities and reagents.

THYROID DISORDERS

Physiologic Adaptations of Pregnancy

In the normal woman, serum thyroxine (T₄) and triiodothyronine (T₃) concentrations increase by approximately 50% because of expansion of the protein-bound pool of thyroid hormones. This in turn is due to marked increase in plasma thyroxine-binding globulin (TBG), a consequence of reduced hepatic clearance owing to estrogen-induced sialylation of TBG (1). In addition to the expansion of the total circulating pool of thyroid hormones, renal clearance of iodide increases, due to the increase in glomerular filtration rate accompanying pregnancy-related volume expansion. Finally, early in gestation, maternal thyroid hormones are passed via the placenta to the fetus, and throughout pregnancy, iodide is transferred to the fetus transplacentally (2). To meet the expanded requirement for total serum thyroxine and to offset increased loss of iodide in the urine and to the fetus, maternal thyroid synthesis and secretion of T₄ and T₃ increases throughout gestation. Accurately assessing the adequacy of circulating maternal thyroid hormones is challenging. Clinical laboratory measurement of free T₄ is increasingly available and has largely supplanted older methodology wherein total T₄ ("free" plus TBG-bound T₄) was measured. However, at this time, free T₄ normal ranges have not been benchmarked well for each trimester of pregnancy, and there are inconsistent data reporting values of free T₄ lower, the same, or higher than that in nonpregnant patients (1,3). At the present time, it is prudent to request measurement of total serum T₄ and adjust the normal reference range to 1.5 times the nonpregnant adult normal range (4).

Thyroidal iodide transport, synthesis of thyroid hormone, and release of stored thyroid hormone are all controlled by the secretion of thyroid-stimulating hormone (TSH) from the

pituitary gland. In turn, TSH is stimulated by hypothalamic thyrotropin-releasing hormone (TRH). TRH and TSH secretion is inhibited in negative feedback fashion by rise in serum T₄ and T₃ to the equilibrium set point. During the first trimester of pregnancy, TSH levels consistently fall below the non-gravid baseline. Since this change accompanies the rise in serum human chorionic gonadotropin (beta-hCG), and since hCG has considerable structural homology to TSH, it has been assumed that in the first trimester, hCG transiently supplants TSH as the primary stimulator of maternal thyroid function. As hCG concentrations wane from gestational weeks 10 to 20, serum TSH returns toward its usual baseline value (1). In the first trimester, to allow for partial replacement of TSH function by hCG, it has been suggested that the normal upper limit for maternal TSH be adjusted to no more than 2.5 mU/L (5). With this caveat, TSH is an excellent screening test for thyroid disease in pregnancy and is generally recommended as the test of first choice.

Normal Fetal and Neonatal Thyroid Physiology

The fetal thyroid begins to take up iodine and synthesize T₄ at 10 weeks of gestation. Fetal T₃ is low throughout gestation (6). Normally, only a small amount of maternal thyroid hormone traverses the placenta to reach the fetal circulation, but may be vital for fetal brain development (7), particularly in athyrotic fetuses (8). Iodides, antithyroid drugs, and thyroid-stimulating immunoglobulins (TSIs) cross the placenta maternal-to-fetus readily and affect fetal thyroid function. In the immediate postpartum period, neonatal plasma TSH peaks at approximately 30 mU/mL several hours after birth, accompanied by increased plasma T₄ and T₃. Thereafter, plasma TSH falls to the adult reference range within a few days, and plasma T₄ and T₃ fall to the adult reference range within 1 month.

Hypothyroidism

Primary hypothyroidism is defined by elevated serum TSH above the normal reference range, and this finding occurs in about 2.5% of pregnancies (3,9). Severity of the thyroid deficiency is further characterized by the magnitude of TSH elevation ("mild" disease = TSH 2.5–10 mU/L; "moderate" disease = TSH 10 to <20 mU/L; "severe" disease = TSH >20 mU/L and T₄ below the lower limit of the pregnancy-adjusted reference range). Secondary hypothyroidism due to pituitary insufficiency is far less common (unless the patient is known to have pituitary or hypothalamic disease), since anterior pituitary insufficiency commonly adversely affects pulsatile gonadotropin secretion to a profound degree, with the result that unassisted conception is unusual in such patients. Secondary hypothyroidism is defined by subnormal plasma T₄ without an appropriate degree of TSH elevation.

Unless the patient has a history of radioactive iodine treatment or thyroid surgery, primary hypothyroidism is

overwhelmingly due to chronic lymphocytic thyroiditis (Hashimoto's thyroiditis). Postablation hypothyroidism or post-thyroidectomy hypothyroidism, stemming from radioactive iodine or surgical treatment of hyperthyroidism, goiter, or thyroid nodular disease (including thyroid cancer), is the other principal cause of hypothyroidism encountered in pregnant women. In most instances, the patient will be known hypothyroid prior to pregnancy, although of course exceptions will be encountered in clinical practice.

Symptoms of hypothyroidism in pregnant women are subtle and often attributed to the pregnancy itself. Cold intolerance, mild weight gain, fatigue, somnolence, depression, dry skin, constipation, and myalgias are some of the "classic" symptoms. There may have been a history of anovulation, dysfunctional uterine bleeding, or infertility pre-dating the pregnancy. Physical signs offering clues to diagnosis include goiter (Hashimoto's thyroiditis glands are often of palpably firm consistency), pretibial myxedema (rare), and delayed return phase of deep tendon reflexes, particularly at the ankle. Untreated maternal hypothyroidism increases the risks of gestational hypertension (up to 36%) (10), caesarean section due to fetal distress (up to 56%) (11), placental abruption (threefold increased risk vs. euthyroid pregnancies) (12), and pre-term labor (approximately twofold increased risk vs. euthyroid pregnancies) (12). Neonatal consequences of maternal hypothyroidism include a two- to threefold increased risk for low birth weight and delayed mental and motor developmental milestone attainment. There is also concern that ultimate cognitive attainment of offspring of hypothyroid mothers is slightly less than offspring of euthyroid mothers (5).

Hypothyroidism in pregnancy should be treated with levothyroxine (13). Owing to the increased TBG-bound pool of circulating T4, higher levothyroxine doses are prescribed for pregnant than for nonpregnant patients. For the patient newly diagnosed and not previously treated, if the serum TSH is $>10\text{ mU/L}$, a starting levothyroxine dose of 2 mcg/kg/day is prudent (4), whereas for $\text{TSH} < 10\text{ mU/L}$, a starting levothyroxine dose of 1 mcg/kg/day may be sufficient (2). For women already receiving levothyroxine treatment at the time of conception, the dose requirement increases predictably by 25% to 50%. Functionally athyrotic patients (those with postablation hypothyroidism or post-thyroidectomy hypothyroidism) have a larger dose increase than patients with primary hypothyroidism due to Hashimoto's thyroiditis, probably because in the latter condition, the thyroid is still capable of some T4 generation albeit to a subnormal extent (14). Conservatively, a serum $\text{TSH} < 2.5\text{ mU/L}$ should be targeted as goal for therapy; dose of levothyroxine should be increased for values $> 2.5\text{ mU/L}$ and TSH retested monthly with further dose titration until stable. A suggested formula for dose increase based on TSH is to increase levothyroxine by 50 mcg/day for $\text{TSH} < 10\text{ mU/L}$; by 75 mcg/day for TSH 10 to 20 mU/L ; and by 100 mcg/day for $\text{TSH} > 20\text{ mU/L}$ (2,14).

Congenital Hypothyroidism

Approximately 1 in 5000 live births is associated with congenital hypothyroidism, most usually due to thyroid agenesis or dysgenesis (15). Other causes include genetic defects of hormone synthesis, maternal treatment with

antithyroid drugs or radioactive iodine, and placental transfer of maternal TSH receptor inhibitory antibodies. Antithyroid drugs and iodides may induce fetal goiter large enough to produce tracheal obstruction (16). Hypothyroid infants appear normal at birth, but develop mental retardation due to the syndrome of cretinism unless treated soon after birth. Neonatal screening of TSH is essential for early diagnosis and prevention of irreversible neurologic damage and has become a universal practice in the United States.

Thyrotoxicosis (Hyperthyroidism)

The term "thyrotoxicosis" distinguishes excessive serum T4 and/or T3 from all causes (including, importantly, excessive ingestion of levothyroxine, liothyronine, or desiccated thyroid hormone), from "hyperthyroidism," which specifically implies excessive active production of thyroid hormones by the native thyroid gland. In practice, the term "hyperthyroidism" is generally used interchangeably with "thyrotoxicosis." Hormonally, the syndrome is defined by suppressed serum TSH (usually $< 0.1\text{ mU/L}$); if T4 and/or T3 are not elevated beyond the normal range but the TSH is suppressed, the condition is referred to as "subclinical hyperthyroidism." Prevalence of hyperthyroidism in pregnancy is in the range of 0.1% to 0.5%, and 85% to 90% of cases are due to diffuse toxic goiter (Graves' disease). As the name suggests, Graves' disease is usually accompanied by a fleshy-consistency goiter ranging from minimally enlarged to three to four times that of the normal thyroid. Graves' disease is caused by an autoantibody, TSI, which binds to and activates the thyroidal TSH receptor, usurping the normal function of TSH in unregulated fashion (17). Other than Graves' disease, possible causes of hyperthyroidism in pregnancy include toxic adenoma (a solitary, usually large, thyroid nodule with autonomous, TSH-independent production of T4 and/or T3), toxic multinodular goiter (typically with multiple thyroidal nodules or regions autonomously producing T4 and/or T3), subacute thyroiditis (painless lymphocytic thyroiditis), and excessive ingestion of thyroid hormones either prescribed or obtained surreptitiously. Trophoblastic tumors associated with very high levels of beta-hCG (typically $> 100,000\text{ IU/L}$) can cause hyperthyroidism due to activation of the TSH receptor by hCG (18,19). In the first trimester, some patients with hyperemesis gravidarum have elevation of T4 and non-suppression of T3, in contrast to other conditions with nausea, vomiting, and poor oral intake, wherein T3 levels are invariably low (20). Sixty percent of patients with hyperemesis have serum $\text{TSH} < 0.4\text{ mU/L}$ and approximately half have a serum free T4 elevated above the normal range. TSH and T4 normalize as hCG serum levels decline beyond week 20 of gestation.

Symptoms of thyrotoxicosis include heat intolerance, weight loss, anxiety, palpitations, tachycardia, and excessive sweating, along with poor exertional tolerance and easy fatigability. Not surprisingly, in many instances, the symptoms will be erroneously attributed to those of normal pregnancy. Physical clues to the possibility of thyrotoxicosis include goiter, proptosis, lid lag, stare, a fine resting hand tremor, warm moist palmar skin, and generalized hyperreflexia.

Maternal–Fetal Risks of Hyperthyroidism

Untreated maternal hyperthyroidism is associated with several adverse outcomes of the pregnancy. Preterm labor occurs in up to 88% of untreated mothers, compared with 8% whose hyperthyroidism is optimally treated (21). Pre-eclampsia in untreated or poorly controlled hyperthyroid mothers occurs at approximately twice the frequency as in well-controlled hyperthyroid mothers (22), and stillbirth may occur in up to 50% of untreated mothers, compared with a 0% to 16% risk in optimally treated mothers (21). Small-for-gestational age and various congenital malformations may occur at increased frequency in the neonates of untreated or poorly controlled hyperthyroid mothers (17).

Treatment

Thionamide drugs are the only treatment, which can be recommended with respect to both maternal and fetal health during the course of pregnancy and can be used to treat hyperthyroidism due to Graves' disease, toxic adenoma, or toxic multinodular goiter. Due to the mechanism of action of this class of drug and the pathophysiology of subacute thyroiditis (passive leakage of pre-formed T4 and T3 from a damaged gland, rather than excess production), thionamides are ineffective in the treatment of subacute thyroiditis. Propylthiouracil (PTU) and methimazole (MMI) are the available thionamides in the United States. The mechanism of action of thionamides is interference with the key steps of thyroid hormone synthesis (thyroidal organification of iodine and coupling of iodotyrosines), by serving as a competitive substrate for the thyroid peroxidase enzyme. Accumulation of thionamide in the thyroid gland, rather than serum levels of drug, is required for optimal effect. Thus, 7 to 8 weeks of treatment is usually required before a euthyroid state can be expected clinically (23). Both drugs cross the placenta and have potential to cause fetal hypothyroidism and, for this reason, can be used to treat fetal hyperthyroidism. Historically, PTU is preferred over MMI in pregnancy because MMI is thought to be associated with a rare congenital scalp defect, aplasia cutis. The association is, however, very weak and has not been observed in several well-done case-control series. Therefore, for patients who do not tolerate PTU, MMI could be considered as alternative therapy and is probably far preferable to the alternative of no treatment of severe maternal hyperthyroidism (2). PTU is given in a dose range of 50 to 150 mg/day orally three times; doses >600 mg/day pose high risk of fetal/neonatal hypothyroidism. Even at a maternal dose of PTU <100 mg/day, about one in five neonates have above-normal serum TSH at birth (24). To minimize the risk of significant neonatal hypothyroidism, the general recommendation is to titrate treatment of maternal hyperthyroidism so as to minimize symptoms, but maintain T4 levels in the upper third of the normal range for pregnancy and not necessarily normalize serum TSH during the pregnancy (25). The lowest possible dose of PTU, which attains these goals of treatment, should be maintained if at all possible. Adequacy of treatment can be reassessed at 2- to 4-week intervals throughout gestation, with adjustment of the PTU dose at about that frequency (2). Most authorities recommend not exceeding a dose of 450 to 600 mg/day PTU. If MMI is used as an alternative to PTU, the dose should not exceed 30 to 40 mg/day.

Unlike PTU, MMI can be effectively administered as a single daily dose, which may be of value in patients who have difficulty fully adhering to a thrice-daily medication schedule. Adverse effects of thionamides include, commonly, skin rashes, most characteristically, urticaria. Serious drug-related hepatitis (due to PTU) and cholestasis (due to MMI) are possible, and periodic monitoring of hepatic transaminases (aspartate aminotransferase and alanine aminotransferase) is recommended. Approximately 1 in 200 users of PTU or 1 in 300 users of MMI develop agranulocytosis, which usually declares as neutropenic fever. Standard recommendation to patients is to seek prompt care and have a complete blood count with differential for any febrile illness, while they are taking a thionamide drug (26).

A beta blocker drug can be used during pregnancy as an adjunct to thionamide therapy and is especially useful to quickly gain control of tachycardia, extreme nervousness, and tremor in extremely symptomatic patients. The best-studied drug in pregnancy is propranolol, which can be given in a dose range of 10 – 40 mg/day orally four times. The dose is titrated to subjective symptomatic improvement and to heart rate <90 beats/min. Curtailing the dose to the minimum necessary to attenuate symptoms is prudent, as beta blockers may cause fetal growth retardation in dose-dependent fashion. If possible, delaying the initiation of propranolol until the second trimester may also be prudent, because of evidence from one study that combined use of thionamide and propranolol was associated with a 24% risk of first-trimester miscarriage, versus 5.5% miscarriage rate when thionamide alone was used (27). Beyond the first trimester, the only significant risk of propranolol has been low birth weight.

Stable low-dose iodide used for 1 to 2 weeks in conjunction with thionamide therapy appears safe, as long as the dose is limited to 6 to 40 mg/day of potassium iodide or equivalent (28). The major practical usage of iodide therapy would be in short-term preparation of a patient for thyroid surgery in pregnancy or to rapidly reduce circulating T4 and T3 in a patient with severe hyperthyroid illness. Radioactive iodine, which is a popular treatment for Graves' disease, toxic adenoma, and toxic multinodular goiter in non-gravid patients, is strictly contraindicated in pregnancy, due to concern not only for fetal thyroid ablation but also for possible induction of various congenital defects.

For very severe maternal hyperthyroidism that cannot be controlled by PTU or MMI, or for patients unable to take thionamides due to serious adverse drug reactions, or for large maternal goiter threatening airway obstruction, subtotal thyroidectomy prior to gestational week 24 in the second trimester is a reasonable consideration (29). Preparation of the patient for surgery can include PTU or MMI, if tolerated, plus a beta blocker and potassium iodide 6 to 40 mg/day beginning 10 to 14 days preoperatively. The role of iodide in this setting is to reduce the vascularity of the thyroid prior to surgery, thereby limiting operative blood loss (2).

Fetal and Neonatal Hyperthyroidism

Fetal and neonatal hyperthyroidism is caused by placental transfer of maternal TSI to the fetus (30). Fetal disease is heralded by tachycardia (>160/min), growth retardation, goiter, craniosynostosis, and increased perinatal mortality (31). Fetal hyperthyroidism can be treated in utero by prescribing

PTU 50 to 150mg/day orally three times to the mother, anticipating that the drug will cross the placenta and be incorporated into fetal thyroid, thereby inhibiting synthesis of T4 and T3. Active previously untreated Graves' disease obligates PTU treatment in the mother as well as in the fetus. However, a common dilemma involves a mother previously treated with radioactive iodine (less commonly, with subtotal thyroidectomy) prior to gestation for Graves' disease who now has postablation hypothyroidism, is euthyroid on replacement levothyroxine, but who continues to have high-titer TSI. In such pregnancies, there is still a finite risk of fetal and neonatal hyperthyroidism due to placental transmission of TSI to the fetus. A strategy for the detection and treatment of fetal disease, and prevention of neonatal disease, is to measure maternal TSI titer during the second trimester in mothers who have a history of Graves' disease. A highly positive TSI test leads to careful surveillance of fetal growth and heart rate (2). For poor growth or excessive tachycardia, the mother continues to receive her usual levothyroxine dose but is concurrently treated with PTU 50 to 150mg/day three times, titrating the dose to fetal heart rate and goiter size as assessed by ultrasound at 2-week intervals (31). Neonatal hyperthyroidism complicates 1% to 2% of pregnancies in women with Graves' disease (32) and manifests as irritability, tachycardia, poor weight gain, goiter, and, potentially, heart failure and death. T4 and TSH should be measured in cord blood if the mother has a history of Graves' disease. Neonatal hyperthyroidism is treated with PTU, iodine, and propranolol and usually resolves within 1–3 months, as TSIs are cleared from plasma.

POSTPARTUM THYROID DISORDERS

Graves' disease commonly spontaneously improves during the third trimester and flares in the postpartum period, and may first become evident then. The differential diagnosis of postpartum thyrotoxicosis is principally between Graves' disease and postpartum subacute thyroiditis (also known as painless lymphocytic thyroiditis), which affects about 5% of postpartum women (33). It occurs within the first 3 postpartum months and produces mild or moderate thyrotoxicosis that lasts up to 3 months, and then either resolves or is followed by transient hypothyroidism, which lasts for several months and then spontaneously resolves. In up to one-third of affected patients, permanent hypothyroidism ensues; such cases are difficult to distinguish from Hashimoto's thyroiditis and are usually accompanied by high levels of thyroid peroxidase autoantibody. Distinguishing postpartum Graves' disease from postpartum thyroiditis can be difficult. Graves' disease is very likely to be associated with a significant goiter, which may be accompanied by a bruit over the thyroid or supraclavicular fossa, while postpartum thyroiditis is associated with normal thyroid or minimal goiter, and no bruit. Proptosis is not seen in postpartum thyroiditis, so if present implies Graves' disease. Measurement of radioactive iodine uptake (RAIU) can be performed if the patient is not nursing; uptake is always nearly undetectable (<5% 24-hour RAIU) in thyroiditis and is elevated (>30% 24-hour RAIU) in Graves' disease. TSI would only be positive in Graves' disease, but is an expensive and usually unnecessary test. The pathophysiology of postpartum thyroiditis involves leakage of T4 and T3 from a

damaged gland; thus, thyroid hormones are not being actively synthesized, and antithyroid drug therapy with thionamides has no rational role. Treatment of postpartum thyroiditis is limited to beta blocker for control of symptoms, including heart rate, nervousness, and tremor. Close follow-up with measurement of TSH and T4 every 1 to 2 months is desirable. If hypothyroidism occurs and is bothersome to the patient, treatment with levothyroxine can be entertained for up to 6 months. Hypothyroidism persisting beyond 6 months postpartum is likely to be permanent, and levothyroxine titrated to normalization of TSH is desirable at that time. Women who experience postpartum thyroiditis during one pregnancy are likely to experience recurrences with subsequent pregnancy and can be counseled and monitored accordingly (33).

Thyroid Nodules

Solitary thyroid nodules occur in up to 15% of women in the first trimester and in up to 24% of women in the first 3 months postpartum (34). Upward of 90% of such nodules represent benign disease (follicular or colloid adenomas), but deserve cytologic diagnosis to exclude the possibility of thyroid carcinoma. As in non-gravid patients, women in the first two trimesters of pregnancy can be evaluated by ultrasound-guided fine needle biopsy (35). If cytology confirms papillary thyroid carcinoma, the patient could undergo thyroidectomy during the second trimester. Alternatively, the size of the lesion may be followed by repeat ultrasound at midtrimester. A known cancer, which has enlarged significantly, can be referred for surgery; if it has remained stable in size, surgery is deferred until the patient is postpartum (2). Conversely, if cytology is read as "consistent with follicular neoplasm" (which conveys an approximately 20% risk of malignancy), it is a reasonable practice to delay thyroidectomy until the postpartum period. Conclusively benign cytologic findings in euthyroid patients provide excellent reassurance, and simple long-term clinical follow-up is sufficient.

ANTERIOR PITUITARY DISORDERS

Normal Physiology

Thyrotropin (TSH), corticotropin (ACTH), the gonadotropins [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)], prolactin, and growth hormone (GH) comprise the hormonal products of the anterior pituitary gland. With one key exception, the secretion of anterior pituitary hormones is governed by secretion of stimulatory hypothalamic releasing hormones, which traverse the pituitary stalk via the portal veins. The known hypothalamic releasing hormones specific for each of the anterior pituitary are TRH, corticotrophin-releasing hormone (CRH), gonadotropin-releasing hormone (GnRH, for both LH and FSH), and growth hormone–releasing hormone (GHRH) for GH. Control of prolactin secretion, in contrast to the other trophic hormones, is primarily inhibitory, with the inhibitory signal hormone being dopamine of hypothalamic origin, circulated to the anterior pituitary via the hypothalamic–hypophyseal portal veins in the pituitary stalk. Knowledge of the normal hypothalamic stimulatory and inhibitory control of anterior pituitary hormone secretion explains common patterns of disease. Hypothalamic lesions are frequently heralded by deficiency of GH, ACTH, TSH, LH, and FSH and concurrently

by hyperprolactinemia. Anatomically large secretory tumors of one discrete cell type of anterior pituitary origin usually overexpress one hormonal product (ACTH, TSH, or GH) producing a clinically recognizable syndrome; compression of the pituitary stalk by the tumor may impede communication of releasing hormones and dopamine, and therefore such large tumors commonly are accompanied by partial hypopituitarism and modest hyperprolactinemia.

Pituitary Adaptations in Normal Pregnancy

Beginning soon after conception, under the influence of rising estrogen concentration, hypertrophy and hyperplasia of lactotroph cells result in an approximately 40% increase in pituitary volume by term (36,37). In accord with the gain in lactotroph cell numbers, serum prolactin increases, usually peaking at approximately 200 ng/mL during the third trimester of pregnancy. Pituitary LH and FSH secretion are inhibited by prolactin, due to feedback inhibition of GnRH secretion by hyperprolactinemia (38).

Placental production of a variant GH stimulates elevated serum levels of somatomedin-C during the third trimester, which in turn inhibits GHRH and native GH of pituitary origin secretion in the third trimester (39,40).

Throughout gestation, serum cortisol levels progressively increase, reaching two to three times the non-gravid baseline value by term. Some of the increase is accounted for by the expansion of the serum pool of protein-bound, biologically inactive cortisol due to estrogen-stimulated hepatic synthesis of cortisol-binding globulin. However, plasma free cortisol is also approximately three times elevated versus the non-gravid baseline value and is reflected by 24-hour urinary free cortisol values of the same magnitude.

Because rising concentrations of human chorionic gonadotropin early in gestation transiently usurp control of thyroid hormone secretion from TSH, TSH levels normally decline in the first trimester, gradually returning to baseline values by the third trimester (3,40).

Pituitary Tumors

Pituitary tumors, which are most frequently benign adenomas of a single cell type, are classified as microadenomas if <1 cm in diameter, and as macroadenomas if >1 cm in diameter. They may be either clinically nonfunctional (in which case, immunostaining is commonly positive for FSH), or secretory, with prolactin, GH, or ACTH excess. Microadenomas produce clinical effects only through hormone excess or hormone deficiency caused by feedback signaling, whereas macroadenomas can cause hypopituitarism by either stalk compression or displacement of normal anterior pituitary cells and can produce symptoms due to mass effect, with headaches due to dural stretch, and/or visual field defects due to encroachment of optic chiasm (40,41).

Clinically important pituitary hormone deficiencies during pregnancy are secondary hypothyroidism and secondary adrenal insufficiency, caused respectively by TSH and ACTH deficiency. Prolactin deficiency poses no significant hazard to the viability of the pregnancy or to maternal-fetal health; however, prolactin deficiency would declare in the postpartum period as failure to lactate. Evaluation of suspected hypopituitarism or pituitary tumor during pregnancy should include

measurement of serum free T4 measurement, assessment of cortisol response to injected cosyntropin (synthetic ACTH), and magnetic resonance imaging (MRI) (without gadolinium contrast) of the sellar region. If there is suspicion of visual field compromise based on clinical exam, or if the MRI shows encroachment of the optic chiasm, formal visual field assessment (Goldman fields) by an ophthalmologist is recommended (40). If adenoma resection is required, the vast majority can be removed by a transsphenoidal approach (31).

Hyperprolactinemia

Hyperprolactinemia is a common endocrine disorder in young women and may be responsible for up to one-third of cases of infertility. Because hyperprolactinemia suppresses GnRH, which in turn results in diminished gonadotropin pulsatility, disruption of ovulation and consequent anovulatory bleeding, amenorrhea, or luteal phase defects can all occur, and the hyperprolactinemia may also produce galactorrhea. Significant and persistent hyperprolactinemia may be due to either micro- or macro-sized prolactinomas. Modest hyperprolactinemia (serum prolactin, 20–50 ng/mL) may be due to microprolactinoma, pituitary stalk compression by a non-prolactinoma pituitary tumor, hypothalamic lesions, or a variety of dopamine antagonist medications (40).

Prolactin levels >200 ng/mL are virtually certainly due to prolactinoma; however, since physiologic hyperprolactinemia of pregnancy approaches 200 ng/mL, and since lactotroph hyperplasia and hypertrophy of normal pregnancy may mimic pituitary adenoma, it is rare that prolactinoma would be suspected or confirmed during pregnancy (40).

Because medical therapy or surgical therapy of prolactinoma can be highly effective in restoring ovulatory function to formerly infertile hyperprolactinemic women, intended or unintended pregnancy in such patients is an entirely likely outcome. Drugs used to treat prolactinoma are bromocriptine, pergolide, quinagolide (not approved for use in the United States), and cabergoline; commonly, when pregnancy is recognized, the patient with prolactinoma will be receiving one of these agents. What is known about this class of drugs during pregnancy is largely reassuring. Bromocriptine and cabergoline are classified by the U.S. Food and Drug Administration as class B (no definite evidence of harm; available information and reported experience indicates probably safe for use) in pregnancy. Once pregnancy is recognized, a decision about how to manage dopamine agonist drug therapy for the duration of pregnancy should be based on the tumor size, symptoms, and the natural history of prolactinomas during pregnancy. Pooled reported experience with 376 patients suggests that only 1.3% of microprolactinomas enlarge sufficiently during pregnancy so as to produce clinical symptoms of mass effect (visual compromise or intractable headache) (40,42). Given the favorable prognosis, recommendation is that drug therapy for microprolactinoma be discontinued as soon as pregnancy is confirmed. Neuroimaging during the pregnancy would be recommended only if symptoms of visual field defect or intractable headache were to occur. Monitoring of serum prolactin during pregnancy is not helpful and not advised. Of the previously untreated patients with macroprolactinoma, 20% to 25% may develop symptomatic tumor enlargement during pregnancy, but if

the macroprolactinoma has been previously treated with surgery, the risk of symptomatic enlargement is only 2% to 3%. For the patient who has previously undergone transsphenoidal resection of macroprolactinoma, and who is not receiving medication therapy at the time of conception, careful follow-up during the pregnancy, with monthly visits emphasizing symptoms of headache or visual compromise, is a prudent recommendation. Women with macroprolactinoma treated with primary medication treatment (no surgery) often respond with considerable size reduction of the tumor, are able to conceive, and constitute the most problematic group of hyperprolactinemic patients in pregnancy for whom generic recommendations are made. Consideration is given to simply continuing bromocriptine or cabergoline throughout the pregnancy, as rapid enlargement of macroadenomas is a risk when medication therapy is discontinued. At a minimum, careful surveillance and monthly office visits to elicit symptoms, and reinstitution of medical therapy or transsphenoidal tumor debulking should be pursued if symptomatic tumor enlargement occurs. Formal testing of visual fields in each trimester of pregnancy is commonly advised (40,42).

Acromegaly

Maternal Effects

Infertility or hypogonadotropic hypogonadism frequently accompany acromegaly, and pregnancy is an unusual enough occurrence that there have been fewer than 100 cases of pregnant acromegals reported in the literature. Acromegaly is caused by GH excess and is most commonly due to a pituitary adenoma. Approximately 80% of recognized acromegalic pituitary tumors are >1 cm in size (macroadenomas), with the remainder being microadenomas. Characteristic clinical findings include enlargement of hands (particularly broadening of the digits) and feet, with increased glove, ring, and shoe size often reported by patients. Characteristic facial features include wide spacing between teeth and prognathism, consequent to enlargement of the mandible, frontal bossing consequent to the enlargement of frontal sinuses, thick lips and broad fleshy nose consequent to soft-tissue expansion, and prominent nasolabial folds. Carpal tunnel syndrome, hypertension, and diabetes mellitus occur with increased frequency in actively acromegalic patients (40).

Confirmation of acromegaly suspected for the first time during pregnancy is complicated by the normal increase in serum IGF-1 in late pregnancy, and by the GH variant of placental origin, which cannot be easily distinguished from GH of pituitary origin. Early in pregnancy, a very high serum IGF-1 would be suggestive of acromegaly, and the diagnosis can be confirmed by documenting failure of GH suppressibility (<2 ng/mL) during a 75-g oral glucose suppression test. MRI of the sella and suprasellar region should be performed to identify and assess the size of the responsible pituitary adenoma. By the third trimester, definitive diagnosis of acromegaly may reasonably be deferred until after delivery (40).

Fetal Effects

The limited reported clinical experience with acromegalic pregnancies suggests no ill effect on fetal development directly attributable to maternal GH and IGF-1 excess. Rather, the major fetal risks are likely related to acromegaly-linked

complications of diabetes mellitus (which can occur in up to 20% of acromegalic pregnancies) and hypertension (up to 35% of acromegalic pregnancies) (43). If observed, these complications are managed in usual fashion for the duration of the pregnancy.

Management of the Pregnant Acromegalic Woman

The most likely clinical scenario involving acromegaly and pregnancy is pregnancy in a woman previously diagnosed and treated for the disease. She may in fact have been cured by transsphenoidal resection of an adenoma; confirmation of cure rests with sustained suppressibility of GH to oral glucose challenge and normalization of serum IGF-1. If so, pregnancy should be managed as a normal pregnancy. For patients not surgically cured, the most conventional and effective long-term management involves use of a long-acting somatostatin analog, either octreotide or lanreotide. Frequently, treatment with a somatostatin analog normalizes IGF-1 and restores fertility; consequently, pregnancy can occur. The available information about pregnancies occurring in treated women identifies no adverse fetal consequences (44–46). However, because octreotide and lanreotide do cross the placenta (47) and because experience with continuation of these drugs throughout pregnancy is extremely limited, a conservative and mainstream recommendation is to discontinue the somatostatin analog once pregnancy is recognized (40). Symptomatic enlargement of acromegalic pituitary adenomas during pregnancy is an uncommon complication (one reported case) (48); should this be encountered in the first two trimesters, consideration could be given to transsphenoidal resection or to reinstitution of somatostatin analog therapy.

Lymphocytic Hypophysitis

Late in the third trimester or early in the postpartum period, lymphocytic hypophysitis represents a rare cause of hypopituitarism or visual field defects. Anatomically, the disorder may be suspected by thickening of the pituitary stalk or by sellar mass, which cannot be distinguished from a pituitary tumor. The diagnosis is definitively established by surgical resection or biopsy demonstrating absence of tumor cells and diffuse lymphocytic infiltration (40). Clinically, lymphocytic hypophysitis is distinguished from Sheehan's syndrome by the absence of obstetric hemorrhage in the former and its presence in the latter (49). If surgical biopsy is not undertaken, spontaneous resolution may occur (50,51), and attention should be given to treatment of hypopituitarism. The limited available experience suggests that ACTH deficiency is especially common (49), so assessment of the hypothalamic–pituitary–cortisol axis is especially important; identified deficiency should be treated with a cortisol agonist in standard physiologic replacement dose (e.g., hydrocortisone 20 mg orally in the morning and 10 mg in the late afternoon or equivalent).

Sheehan's Syndrome

Postpartum pituitary necrosis (Sheehan's syndrome) results from an ischemic insult to the pituitary as a complication of peripartum hemorrhage (52) and is distinctly rare in modern obstetric practice (53). Physiologic enlargement of the pituitary in late gestation, consequent to the physiologic

expansion of lactotrophs, seems to render the gland especially sensitive to hemodynamic insult. In the setting of known obstetric hemorrhage or maternal hypotension during the labor and delivery process, Sheehan's syndrome is suspected if postpartum lactation fails to occur. Lactation failure heralds possible loss of other critical pituitary hormonal function, including ACTH and TSH, which should be assessed through appropriate testing. Diagnosis is confirmed by MRI, typically demonstrating the absence of a pituitary tumor and possibly demonstrating an edematous or hemorrhagic gland. Frequently, deficiencies of ACTH and TSH are not evident for years, so long-term follow-up of affected women is essential (40).

POSTERIOR PITUITARY DISORDERS

In normal pregnancy, the osmotic thresholds for vasopressin [arginine vasopressin (AVP), also known as antidiuretic hormone (ADH)] release and thirst are lowered, resulting in plasma osmolality about 10 mOsm/kg lower than that in nonpregnant women (54). The metabolic clearance of AVP is markedly accelerated by mid-pregnancy, probably owing to circulating placental vasopressinase, which degrades AVP.

Diabetes Insipidus

Diabetes insipidus (DI) is the inability to concentrate urine, owing to AVP deficiency [central or neurogenic diabetes insipidus (CDI)] or renal tubular resistance to AVP (nephrogenic diabetes insipidus) (55). Causes of CDI include head trauma and hypothalamic tumors and other anatomic lesions; many cases are idiopathic. Transient forms of CDI may occur in pregnancy, owing to unmasking of subclinical disease by circulating vasopressinase (56) or to excessive circulating vasopressinase in the setting of hepatic dysfunction (57). Other causes of polyuria should be excluded by appropriate and pragmatic patient assessment. Diabetes mellitus causes polyuria, but if so, it is always accompanied by glycosuria. Urine dipstick consistently negative for glucose excludes this possibility. So long as thirst sensation is intact, plasma osmolality remains normal if patients are able to drink and have access to water. In the presence of CDI or nephrogenic DI, nonavailability of water or inability of the patient to drink because of nausea, vomiting, or impaired cognition will quickly result in dehydration and hyperosmolar hyponatremia. Various forms of dipsogenic DI also occur, but since AVP secretion and response are typically normal, a strong clinical clue suggestive of dipsogenic DI is significant hypoosmolar hyponatremia (as opposed to slight hyponatremia or normal serum sodium concentration, which is expected in either CDI or nephrogenic DI). Dipsogenic DI is commonly due to a primary psychiatric disorder—notably, schizophrenia—or may be due to hypothalamic disorders (e.g., neurosarcoidosis), which reset the “osmostat” for thirst.

Cardinal symptoms of DI are polyuria and polydipsia. Polyuria must not be confused with increased frequency of voiding, which is a common symptom of normal pregnancy. Actual polyuria is defined by increased urine volume (more than 2.5 liters/24 hours), in the absence of glycosuria. A water deprivation test (55), which includes hourly measurement of urine volume and osmolality, body weight, and vital signs, and measurement of plasma sodium every 3–4 hours, is the “gold

standard” traditional method of establishing the diagnosis of DI, but may be unnecessary if matched serum and urinary sodium, osmolality, and urine volumes reconcile with the clinical history. If a water deprivation test is performed, the patient should be seated or standing throughout the test, since urinary concentrating capacity is compromised during pregnancy by the lateral recumbent position. Water deprivation is achieved by enforced withholding of beverages and food, until a clinical endpoint is reached during the test. Endpoints justifying termination of water deprivation include (i) 3% decrease in baseline (time 0) body weight, (ii) urine osmolality rise <30 mOsm/kg/hr for 3 consecutive hours, or (iii) plasma sodium > upper limit of normal reference range. Upon attainment of an endpoint, the AVP analog desmopressin (DDAVP) 0.1 mL is administered intranasally, and urine osmolality is measured again after 1 to 2 hours. In severe CDI, maximal urine osmolality increases more than 50% after administration of DDAVP. In nephrogenic DI, maximal urine osmolality increases significantly less than 50%, and often not at all following administration of DDAVP.

Pregnant women with severe CDI may be treated with maintenance dosing of DDAVP, which is not degraded by placental vasopressinase. The usual dose is 0.1 to 0.2 mL (10–20 mg) intranasally once daily at bedtime or else twice daily. The major clinical risk of DDAVP treatment is excessive dosing, with the potential for seizures due to water intoxication (severe plasma hypoosmolar hyponatremia). In the authors' experience, this risk is minimized by limiting therapy to once-daily dosing, administered at bedtime, deliberately allowing a late-day period of breakthrough polyuria. Some patients with preexisting CDI may require an increase in the dose of DDAVP during pregnancy; therapy can be titrated by clinical response of symptoms and further guided by matched urine and serum sodium and osmolality.

ADRENAL DISORDERS

Normal Glucocorticoid Physiology

The adrenal cortex produces two hormones of biologic importance, cortisol and aldosterone. If cortisol or aldosterone production is biologically inefficient due to defective steroidogenic enzymes, androgenic precursor steroids may accumulate to a physiologically significant degree. Important roles of cortisol include sustainment of blood glucose under physiologically stressful or fasting conditions via facilitation of gluconeogenesis, modulation of the systemic inflammatory response, sustainment of blood pressure, and facilitation of renal free water excretion and promotion of renal sodium conservation and potassium excretion. Cortisol circulates in plasmas in both free and protein-bound forms; the free form is biologically active and the protein-bound form represents a slow-release reservoir pool. Cortisol-binding globulin (CBG) is the predominant binding protein for cortisol, and CBG production can be reduced or increased in disease states and under a variety of physiologic conditions. Cortisol secretion is controlled by circadian pulses of ACTH (in synergy with ADH). Normal circadian ACTH fluctuation results in peak secretion during the nocturnal hours after midnight, resulting in peak serum cortisol between 0600 and 0800 hours. Throughout the day, ACTH secretion wanes toward nadir between 2200 hours and midnight, at which time serum

cortisol normally does not exceed 5 mcg/dL. Signals for ACTH release include hypothalamic CRH as well as ADH. CRH and ADH secretion is stimulated by physiologic stress and hypoglycemia, and CRH and ACTH secretion is inhibited by rising concentrations of serum cortisol (negative feedback inhibition).

The other major adrenal cortical steroid hormone, aldosterone, is a mineralocorticoid promoting renal sodium reabsorption and potassium excretion, and maintenance of extracellular fluid volume and blood pressure. Although ACTH stimulates aldosterone secretion, the primary regulation of aldosterone secretion is via the renin-angiotensin signal pathway. Decreased delivery of sodium to glomeruli via afferent arterioles in the nephron stimulates renin secretion by juxtaglomerular cells. Renin in turn activates the angiotensin-converting enzyme, resulting to conversion of inactive angiotensin-1 to active angiotensin-2 in the lung; angiotensin-2 is the major stimulant of aldosterone synthesis and secretion by the adrenal. Aldosterone in turn promotes renal sodium conservation and extracellular fluid volume expansion, resulting in rising arterial pressure and increasing delivery of water and sodium to the proximal nephron. Renin secretion is inhibited by increased sodium delivery to the afferent renal arteriole, thereby completing the feedback loop of the renin-angiotensin-aldosterone axis.

In pregnancy, total plasma cortisol is increased, not only because of estrogen-stimulated increased CBG but also because of increased free cortisol. These changes occur early and progressively during gestation, increase further during labor, and persist for several days postpartum. Suppression of CRH and ACTH by exogenous glucocorticoids such as dexamethasone is impaired during pregnancy (58). It is possible that tissue responsiveness to cortisol is reduced, as normal pregnant women do not show physiologic consequences of cortisol excess. Maternal plasma renin and aldosterone are increased throughout pregnancy. The fetal adrenal gland (with a large fetal zone) contributes substantial dehydroepiandrosterone sulfate, which is converted by the placenta to estrogens (59).

Adrenal Insufficiency

Adrenal insufficiency in pregnancy has an estimated frequency of 1 per 300 births (60). Recognition and treatment of adrenal insufficiency has virtually eliminated maternal mortality, and the miscarriage rate may be as low as 15% (61). However, primary adrenal insufficiency due to autoimmune adrenalitis (Addison's disease) is frequently associated with other autoimmune disorders, including antiphospholipid antibody syndrome and systemic lupus erythematosus, which independently confer hazard to the pregnancy (62).

Adrenal failure can result in either disease of the adrenocortical tissue itself (primary adrenal insufficiency), due to autoimmune-mediated destruction of adrenocortical tissue (Addison's disease), or replacement of normal adrenocortical elements by metastatic tumor or granulomatous tissue, or from loss of trophic stimulation of the adrenal cortex by ACTH (secondary adrenal insufficiency). Secondary adrenal failure may be caused by any anatomic hypothalamic or pituitary lesion, including lymphocytic hypophysitis (49). In most cases, adrenal insufficiency will have been diagnosed

prior to pregnancy, which will then usually be uneventful provided maternal therapy is not interrupted. New-onset adrenal insufficiency in a pregnant woman may be heralded by symptoms such as malaise, salt-craving, orthostatic faintness, persistent vomiting, and weight loss (63). Significant hyponatremia is present in over 90% of cases, but may be difficult to distinguish from the "physiologic" hyponatremia of normal pregnancy. Hyperkalemia, present in about two-thirds of non-gravid patients with untreated primary adrenal insufficiency, is usually absent in the pregnant patient (64). Definitive diagnosis of adrenal insufficiency rests with measurement of plasma ACTH and cortisol, and performance of a cosyntropin (synthetic ACTH; Cortrosyn) stimulation test. A very low early morning (0600–0800hr) plasma cortisol (≤ 3.0 mcg/dL) accompanied by a plasma ACTH > 100 pg/mL is adequate to establish the diagnosis of primary adrenal insufficiency at any stage of gestation (65,66). After drawing basal blood samples for ACTH and cortisol, the cosyntropin stimulation test is performed by administering cosyntropin 250 mcg intramuscularly or intravenously, and drawing blood samples for cortisol 30 and 60 minutes post-cosyntropin. While cutoff points for "normal" and "abnormal" have not been formally established for pregnant patients, there is general agreement that maximum stimulated cortisol > 30 mcg/dL, even in the late third trimester, is adequate to exclude the diagnosis of adrenal insufficiency (66). Likewise, a maximum stimulated cortisol < 18 mcg/dL is adequate to establish the diagnosis of adrenal insufficiency with confidence (63). Additional testing of patients found to have adrenal insufficiency may include measurement of serum 21-hydroxylase autoantibodies (positive in 90% of patients with Addison's disease), and plasma renin-to-aldosterone ratio, which will be markedly elevated in primary adrenal insufficiency (63). Patients with "normal" or "suppressed" ACTH can be evaluated with pituitary imaging via non-gadolinium-enhanced MRI, whereas those with primary adrenal insufficiency who test negative for 21-hydroxylase antibodies can be assessed with MRI of the adrenals. Adrenal insufficiency caused by neoplastic or granulomatous disease is most usually associated with adrenal enlargement, whereas autoimmune disease causes adrenal atrophy.

Treatment of adrenal insufficiency is straightforward and largely empiric. Primary adrenal insufficiency obligates hormone replacement for both cortisol and aldosterone, whereas secondary adrenal insufficiency obligates replacement only for cortisol (since the renin-angiotensin-aldosterone axis is preserved). For cortisol replacement, a physiologically sound surrogate regimen is hydrocortisone 20 mg orally in the morning and 10 mg orally in the late afternoon; a pharmacologically equivalent alternative glucocorticoid such as cortisone acetate or prednisone may be substituted. As aldosterone surrogate, the synthetic mineralocorticoid fludrocortisone (Florinef) is used in a dose averaging 0.1 mg (range 0.05–0.2 mg) orally each morning (67). The dose of fludrocortisone can be adjusted to maintain blood pressure and plasma potassium within the normal range. During labor and delivery, surgery, or severe intercurrent illness, supplemental glucocorticoid in doses intended to mimic natural stress-stimulated hypercortisolemia is prescribed. A traditional "stress" regimen is hydrocortisone 50 mg intravenously every 8 hours (63). At

this dosage, hydrocortisone exhibits sufficient mineralocorticoid agonism that fludrocortisone is unnecessary.

Cushing's Syndrome

Cushing's syndrome is the consequence of hypercortisolism (68). When diagnosed in pregnancy, the predominant cause (60% of total) is an adrenal tumor (benign or malignant) (69). Other causes include ACTH-dependent Cushing's syndrome from a pituitary adenoma or from an ectopic source, or hypercortisolism of an iatrogenic or surreptitious source from exogenous glucocorticoids.

Clinical manifestations of Cushing's syndrome include central obesity, moon-like plethoric face, dorsal cervical and supraclavicular fat pads, thin skin with easy bruising and wide, deeply recessed, reddish or violaceous striae, proximal muscle wasting and weakness, osteoporosis, and hirsutism. Hypokalemia, hypertension, and diabetes mellitus commonly complicate Cushing's syndrome, but are not invariably present. Anovulatory oligomenorrhea and infertility frequently prevent pregnancy, so Cushing's syndrome during pregnancy is an unusual occurrence. However, the presence of gonadotropin receptors in pigmented nodular adrenal hyperplasia and in some adrenal adenomas may account for first expression of Cushing's syndrome manifestations during pregnancy (69). When pregnancy does accompany Cushing's syndrome, pre-eclampsia, hypertension, miscarriage, premature labor, intrauterine growth retardation, and stillbirth are distinct risks (58,70). However, neonatal ACTH suppression and adrenal insufficiency are rare, and fetal virilization does not occur. Thus, most therapeutic attention and diagnostic efforts are directed toward maternal health during the pregnancy.

Accurate diagnosis of Cushing's syndrome during pregnancy is difficult based on physiologic changes in cortisol secretion in normal pregnancy. Ascertaining whether or not the hypercortisolism is ACTH-dependent is an important first step, and plasma ACTH <10 pg/mL establishes ACTH independence (63). In the first trimester, daily cortisol production is comparable with the non-gravid state, and 24-hour urine free cortisol reflects this. Thus, in the first trimester, 24-hour urine free cortisol values distinctly above the normal range establish the diagnosis with some confidence. As pregnancy progresses into the second and third trimesters, cortisol production normally increases, peaking at about three times the non-gravid normal range in the third trimester; thus, to confirm hypercortisolism in the third trimester, one would need to observe 24-hour urine free cortisol well in excess of three times the normal upper limit to diagnose Cushing's syndrome with confidence. Salivary cortisol can be collected at home by patients and reflects production of cortisol on an hour-to-hour basis. Cushing's syndrome eliminates the normal diurnal fluctuation of cortisol production, such that the secretory trough normally observed at 2200 to 2400 hours is lost. Hence, salivary cortisol at midnight significantly above the upper limit of the normal range confirms loss of diurnal fluctuation and is consistent with Cushing's syndrome. The combination of 24-hour urine free cortisol > three times the upper limit of the normal range and elevated midnight salivary cortisol possibly represents the optimal means of confirming Cushing's syndrome in patients in the second and third trimesters (63,71).

If Cushing's syndrome is confirmed by 24-hour urine free cortisol and midnight salivary cortisol, appropriate adrenal or pituitary imaging is performed, based on whether plasma ACTH is suppressed or non-suppressed. If the ACTH is <10 pg/mL, the adrenals should be imaged by non-gadolinium-enhanced MRI. For non-suppressed ACTH, the pituitary should be assessed by MRI (63).

Because of the hazards posed by hypercortisolism to the pregnancy and to maternal health, treatment during the pregnancy is recommended. Adrenal tumors can be resected by flank incision, since up to 20% may be malignant. For patients with ACTH-producing pituitary adenoma (Cushing's disease), transsphenoidal adenoma resection has been successfully performed in pregnancy (72). If imaging does not localize the site of disease with confidence, medical therapy can be entertained, although experience with effective drugs in pregnancy is very limited. Metyrapone and ketoconazole are categorized as FDA class C agents and represent the best available alternative treatments for patients whose Cushing's syndrome cannot be treated surgically (63,73).

Fetal Virilizing Disorders

Fetal virilization from maternal androgen excess is uncommon in pregnancy, since hyperandrogenemia suppresses GnRH and gonadotropins and thus is far more likely to cause oligomenorrheic infertility or amenorrhea. Rarely, virilizing adrenal (74) or ovarian tumors (75) can occur and are generally heralded by signs of maternal virilization, including hirsutism, male-pattern balding, increasing skin seborrhea, and deepening of the voice.

A more commonly encountered scenario in pregnancy is in couples with a prior history of a virilized newborn with 21-hydroxylase deficiency, the most common form of virilizing congenital adrenal hyperplasia. For couples with a personal or family history of 21-hydroxylase deficiency, genetic screening is available through GYP21 genotyping. The couple genetically at risk may elect prenatal treatment of the mother with dexamethasone, at a dose of 20 mcg/kg/day of non-gravid baseline maternal weight. Chorionic villous sampling performed at 9 to 11 weeks of gestation is performed to establish fetal sex and presence of fetal CYP21 gene (76). Maternal treatment is unnecessary for a male fetus or if fetal CYP21 is negative. Dexamethasone treatment of the pregnant woman is not without risk, as excessive weight gain, edema, impaired glucose tolerance or frank diabetes mellitus, or hypertension occurs in up to 50% of treated patients (63).

Primary Hyperaldosteronism

Just over 30 cases of primary aldosteronism in pregnancy have been reported in the past 40 years (77). Aldosteronism is characterized by suppressed plasma renin accompanied by autonomous adrenal secretion of aldosterone, with clinical consequences of hypertension, metabolic alkalosis, and frequently (but not invariably) hypokalemia. Plasma renin activity increases in the first trimester, and steadily throughout gestation, reaching levels three to seven times non-gravid baseline values by the late third trimester. Likewise, plasma aldosterone increases 5- to 20-fold during pregnancy (63). Normally, despite high levels of these hormones, maneuvers such as plasma volume expansion with saline or administra-

tion of synthetic mineralocorticoid result in appropriate suppression of the renin–angiotensin–aldosterone axis. Rising plasma progesterone throughout gestation is an important physiologic antagonist of mineralocorticoids and offers protection against maternal hypertension, despite markedly elevated levels of renin, angiotensin, and aldosterone. Very low levels of plasma renin (approaching undetectable), accompanied by elevated plasma aldosterone in a pregnant woman with hypertension or hypokalemia, would establish the diagnosis of primary aldosteronism with some accuracy. Adrenal imaging with non-gadolinium-enhanced MRI would then represent the next step in evaluation; identification of a unilateral adrenal nodule would be consistent with aldosterone-producing adenoma. In nonpregnant patients, catheterization of adrenal veins for measurement of aldosterone and cortisol is frequently performed. Such invasive testing would be difficult and largely contraindicated in a pregnant patient, so consideration may be given to medical management until after delivery (78). Amiloride is an FDA class C antagonist of aldosterone and may be the drug of choice for treatment of a pregnant patient with hyperaldosteronism (79).

Pheochromocytoma

Pheochromocytoma is a tumor of the adrenal medulla or extra-adrenal chromaffin tissue that hypersecretes catecholamines (80). Prevalence in pregnancy is estimated to be approximately 1 in 54,000, and over 200 cases have been reported in the literature (81). Typical clinical manifestations include sustained or paroxysmal hypertension, pallor, headache, palpitations, and diaphoresis. Hypertensive crisis can occur and is a feared complication. Serious sequelae include chest or abdominal pain, which can mimic acute myocardial infarction or acute surgical abdomen, seizures, hemodynamic shock (due to volume contraction induced by the excessive vasoconstricted state, when catecholamine secretory troughs occur), and death. Approximately 10% of pheochromocytomas are familial, including the multiple endocrine neoplasia (MEN) 2a and 2b syndromes (with pheochromocytoma about half as prevalent as medullary thyroid carcinoma), von Hippel–Lindau, and neurofibromatosis syndromes. Timely evaluation and definitive treatment of pheochromocytoma in pregnancy is essential, as untreated maternal mortality may exceed 15%, and if treated, mortality may be as low as 1% (82). Abdominal palpation and labor are known provocateurs of catecholamine secretion by pheochromocytoma tumors, and hypertensive crisis may accompany a secretory surge of adrenomedullary hormones.

Pheochromocytoma is generally suspected based on the presence of maternal symptoms, hypertension, or identification of a family history of MEN, von Hippel–Lindau, or neurofibromatosis. Elevated plasma catecholamines and metanephrines are strikingly elevated and are reflected in 24-hour urinary samples for catecholamines (epinephrine and norepinephrine) and metanephrines (metanephrine and normetanephrine). Most surgically confirmed pheochromocytomas have been associated with 24-hour urinary secretion three or more times the upper limit of normal for one or more of these hormones (83). When clinical suspicion is heightened by the finding of one or more extremely elevated urinary

catecholamines or metanephrines (epinephrine, norepinephrine, metanephrine, or normetanephrine), adrenal imaging with non-gadolinium-enhanced MRI is accomplished, to investigate whether there is a unilateral adrenal tumor. Characteristically, pheochromocytomas image very bright on T2-weighted MRI and may be very helpful in the pregnant patient, for whom imaging modality options are limited (84).

Confirmation of a pheochromocytoma prior to the third trimester should lead to expedited surgical evaluation, to optimally perform adrenalectomy during the second trimester. In the third trimester, surgery is usually deferred until postpartum, but the patient is treated medically for the pheochromocytoma, and caesarian section is usually planned so that the hypertensive crises associated with vaginal delivery can be avoided (63). Prior to surgery, or otherwise if the patient cannot be treated surgically, drug treatment emphasizes alpha blocker and later beta blockers. The traditional alpha blocker drug is phenoxybenzamine 10 to 20 mg/day orally twice; the drug may be titrated to a maximum dose of 1 mg/kg/day until symptoms and hypotension are controlled (82). After several days of phenoxybenzamine therapy, a beta blocker is added, titrating to heart rate control, with two caveats. First, because pheochromocytoma hypertension is a profoundly vasoconstricted state, successful vasodilation may unmask clinical hypovolemia with orthostatic hypotension. Orthostatic blood pressure and symptoms should be routinely checked in the drug-treated patient. Second, alpha blocker drugs are always used first, for several days, to avoid theoretically catastrophic unopposed beta blockade, exacerbating vasoconstriction and potentially provoking a hypertensive crisis (63). After successful surgical resection of a pheochromocytoma, 24-hour urinary metanephrines and catecholamines should normalize, and medication therapy can be gradually tapered to complete withdrawal.

CALCIUM DISORDERS

Physiologic Adaptations of Maternal Calcium Metabolism in Pregnancy

Approximately 50% of circulating plasma calcium is ionized (free), and the remainder is complexed with plasma protein, most significantly albumin. Parathyroid hormone (PTH) is the most important determinant of plasma calcium, directly or indirectly controlling all routes of calcium intake and egress. Direct effects of PTH are on bone, the body's largest endogenous reservoir of calcium, and on kidney, which can up- or downregulate calcium egress. In bone, PTH induces osteoblasts to release cytokines stimulating osteoclastic resorption of calcium and phosphorus from bone, into the circulation. In the proximal nephron, PTH induces active reclamation of calcium from glomerular filtrate to interstitial fluid and from thence to the circulation. Indirectly, PTH also promotes absorption of calcium and phosphorus from the gut, by inducing the 1-alpha-hydroxylase enzyme in renal epithelium to convert comparatively inactive calcidiol (25-hydroxy-vitamin D3) to calcitriol (1,25 dihydroxy-vitamin D3), which directly activates gut absorption of calcium and phosphorus. PTH is exquisitely sensitive to serum-ionized calcium; slight decrement in ionized plasma calcium rapidly results in increased PTH secretion; conversely, slight increment in ionized plasma calcium inhibits PTH synthesis and secretion.

Mineralization of the fetal skeleton requires approximately 30g of calcium by term, about 80% of which accrues during the third trimester of pregnancy. This need is met by increased maternal absorption of calcium from the gut, mediated by calcitriol (1,25 dihydroxy-vitamin D3), as opposed to hyperresorption of calcium salts from the maternal skeleton. Compared with the non-gravid state, maternal adaptations of calcium homeostasis to pregnancy include decreased serum PTH, increased PTH-related peptide (PTHrP), and increased calcitriol. It is presumed that PTHrP is largely responsible for increased calcitriol production. Maternal serum calcitonin also increases, but its physiologic significance is unknown (85).

Hypercalcemia

Primary hyperparathyroidism (PHP) is the most common cause of hypercalcemia and is rare in pregnancy, with about 150 reported cases (86,87). The only entirely satisfactory treatment for this disease is surgical resection of a solitary parathyroid adenoma (the most common culprit) or debulking of diffuse parathyroid hyperplastic glands; about 0.8% of large surgical series of parathyroidectomies were performed in pregnant patients (88). While PHP in pregnancy is rare, recognition and treatment are important, as maternal complications occur in about 67% and fetal or neonatal complications in 80% (89). Approximately 80% of pregnant women with PHP will have at least one symptom; these include nausea, vomiting, abdominal pain, renal colic, muscle weakness, mental sluggishness, depression, and bone pain (90). Additionally, hyperemesis gravidarum, weight loss, seizures, and pancreatitis may occur more frequently in women with PHP than in unaffected women (87,88). Fetal complications of maternal PHP include stillbirth (approximately 2%), neonatal death (approximately 2%), and neonatal tetany (approximately 15%) (91). Neonatal tetany results from profound suppression of the neonatal parathyroid function by maternal hypercalcemia, which is unmasked at the time of delivery, when the previous continuous milieu of hypercalcemia is rapidly lost. The condition commonly persists for 3 to 5 months, but permanent neonatal hypoparathyroidism can rarely be permanent (91).

Optimal management of PHP recognized during pregnancy is parathyroidectomy performed during the second trimester (89). Risk of all neonatal complications was reduced by 53% as compared with surgically untreated patients, in one large reported series (87). Premature labor is a distinct risk when parathyroidectomy is delayed until the third trimester, occurring in four of seven treated cases in one reported series (92). Influencing the decision of whether or not to perform surgery should be the awareness that there are no evidence-based medical therapies to offer patients as a surgical alternative; treatments would be limited to saline hydration and high-dose magnesium infusions (93). Neonates suffering from hypocalcemic tetany are treated with oral or parenteral calcium, and calcitriol, as needed until the condition resolves.

Hypercalcemic disorders other than PHP are very rarely encountered in pregnancy. Familial hypocalciuric hypercalcemia, also known as familial benign hypercalcemia, was first characterized in the early 1970s as an autosomal dominant

genetic disorder notable for mild to moderate hypercalcemia accompanied by extremely low fractional excretion of calcium (ratio of calcium to creatinine clearance <0.01). It is now known to result from a mutation of the calcium-sensing receptor in both parathyroid and renal tubular tissues. There are no maternal consequences of this disorder, but neonatal hypocalcemic tetany can occur, with management similar as in maternal hyperparathyroidism (85). It is important to recognize the disorder for what it is so that maternal parathyroidectomy is not attempted. Malignancy-related hypercalcemia has only been reported in two pregnant patients, with maternal demise occurring within 4 months postpartum in both cases (94,95).

Hypocalcemic Disorders

Apparent hypocalcemia in pregnant patients may simply represent physiologic dilutional hypoalbuminemia. If necessary, measurement of serum ionized calcium can confirm this possibility, which is otherwise usually inferred by the concurrent findings of slight hypocalcemia and hypoalbuminemia. The traditional estimate of total serum calcium for hypoalbuminemia is to add 0.8mg/dL to measured serum calcium for every decrement of serum albumin of 1.0mg/dL below the lower limit of the normal laboratory range. True hypocalcemia (low serum ionized calcium) is most often consequent to hypoparathyroidism (which can be idiopathic, but is more often secondary to a complication of thyroid or parathyroid surgery) or pseudohypoparathyroidism (hereditary resistance to PTH). Most often, a pregnant woman with these disorders will have come to clinical attention prior to becoming pregnant and is likely to already be receiving chronic therapeutic intervention. Maternal consequences of severe hypocalcemia include oral and acral paresthesias, carpopedal spasms, and potentially fatal laryngospasm; fetal consequences include skeletal demineralization and possibly hypercalcemia due to neonatal hyperparathyroidism. Because maternal PTH normally declines during pregnancy, and calcitriol increases under the influence of PTHrP, maternal hypocalcemia is sometimes ameliorated by pregnancy, and need for oral calcium supplements and exogenous calcitriol is reduced (85,96). However, this is by no means universal, and careful monitoring of maternal serum calcium is important throughout the pregnancy.

Emergent therapy of symptomatic hypocalcemia (seizures or carpopedal or laryngospasm) should be treated with intravenous infusion of 10% calcium gluconate, 20mL intravenously over 10 minutes, followed by continuous intravenous drip infusion of calcium 0.5 to 2mg/kg/hr, adjusted to keep the plasma calcium level at 8 to 9mg/dL (97). Oral maintenance therapy of chronic hypocalcemic disorders is usually accomplished with synthetic calcitriol (Rocaltrol), 0.25 to 0.5mg orally daily to three times daily, and calcium carbonate 1 to 2g orally three times a day with meals. The dose of calcitriol is titrated as needed at 2- to 4-week intervals to maintain plasma serum calcium of 8 to 9mg/dL. As noted, pregnancy may either decrease or increase the non-gravid maintenance dose, and frequent (every 2–4 weeks) measurement of serum calcium throughout the gestational period is recommended.

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