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ENDOCRINE DISORDERS OF PREGNANCY

Mark E. Molitch

Professor of Medicine, Division of Endocrinology, Metabolism, and Molecular Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

Lisa P. Purdy, MD, CM

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Endocrine disorders in pregnancy provide a unique challenge to the practitioner. The introduction of the fetal-placental unit alters the maternal endocrine metabolism and hormonal feedback mechanisms. Disease manifestations may be altered by the pregnancy environment and may be difficult to distinguish from the normal hypermetabolic state of pregnancy. Therapeutic needs for the mother and the fetus may differ, requiring a fine balance.

PITUITARY DISORDERS IN PREGNANCY

Anterior Pituitary Gland

The pituitary enlarges during pregnancy (1) and may become hyperintense on scan (2). This enlargement is primarily due to estrogen-stimulated hypertrophy and hyperplasia of the lactotrophs (3), while gonadotrophs decline in number, and corticotrophs and thyrotrophs remain constant (4). Somatotrophs are generally suppressed and may function as lactotrophs (5). Placental estrogens stimulate prolactin synthesis (6,7), while progesterone also stimulates prolactin secretion (8). Prolactin levels progressively increase approximately 10-fold throughout gestation,(9) then decline postpartum in non-lactating women. Despite this increase, the normal lactotroph continues to respond to TRH and anti-dopaminergic stimulation.

Growth hormone variant, which differs from pituitary growth hormone by 13 amino acids and is synthesized by the syncytiotrophoblastic epithelium of the placenta, increases to levels of 10-20 ng/ml during pregnancy (10,11). This variant has similar carbohydrate, lipid (12), and somatogenic properties as pituitary GH, with less lactogenic activity (13). With this increase in GH activity, insulin-like growth factor 1 (IGF-1) levels dramatically increase in the second half of pregnancy (14), contributing to the acromegaloid features of some pregnant women. Through negative feedback, pituitary growth hormone levels consequently decline in the second half of gestation (10,11), with blunted response to stimulation testing.

TSH levels fall in the first trimester, in response to the rise of bhCG (15), but increase within the

normal range in the third trimester (16). CRH and ACTH levels rise, despite an increase in cortisol (see below). 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 (17).

Prolactinomas

Hyperprolactinemia causes one third of all female infertility (18,19). It inhibits pulsatile gonadotropin secretion and the positive feedback of estrogen on gonadotropin secretion (19). 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% of patients with microadenomas and rarely causes hypopituitarism. The curative rate is much lower (31.8%) in patients with macroadenomas, and the risks of hypopituitarism and subsequent infertility increase dramatically (19). For both microadenomas and macroadenomas there are recurrence rates of about 20%, therby lowering these long-term cure rates (19). Bromocriptine therapy results in ovulatory menses in 80-90% of patients. Approximately 40% of patients with macroadenomas experience a > 50% reduction in size (19). Pergolide demonstrates similar benefits. Cabergoline is another dopamine agonist which is administered only once or twice weekly. It is more effective and better tolerated than bromocriptine therapy (20) and has a similar efficacy in reducing tumor size (21,22).

The hormonal milieu of pregnancy may cause significant tumor enlargement in women with prolactin-secreting macroadenomas (Figure 1). In pregnant patients with microadenomas previously treated with bromocriptine, 5 of 376 women (1.3%) experienced symptomatic enlargement manifested by headaches and visual field disturbances (23). Symptomatic enlargement was noted in 20 of 86 patients (23.2%) patients with macroadenomas previously treated with bromocriptine, while 2 of 71 (2.8%) individuals previously treated with transsphenoidal surgery or irradiation had symptoms (Table 1). Bromocriptine therapy or transsphenoidal surgery was required to treat 25-50% of those with symptomatic enlargement (23).

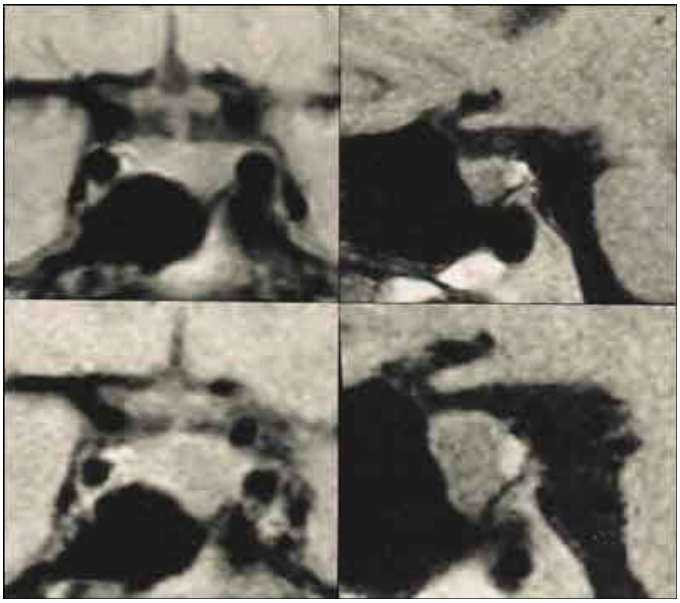

Figure 1.MRI scans with coronal (A,C) and sagittal (B,D) views demonstrating a prolactin-secreting macroadenoma before pregnancy (A,B) that progressively enlarged during pregnancy. The third trimester is shown here (C,D). The patient had been complaining of increasing headaches.

TABLE 1. Effect of Pregnancy on Prolactinomas

Tumor Type	Prior Therapy‡	Number	Symptomatic Enlargement*
MICROADENOMAS	None	376	5 (1.3%)
MACROADENOMAS	None	86	20 (23.3%)
MACROADENOMAS	Yes	71	2 (2.8%)

*Requiring intervention_surgery or dopamine agonist.‡Surgery of irradiation.

Bromocriptine crosses the placenta (24) and is therefore not recommended throughout gestation. Used during the first few weeks of gestation, it has not been associated with increased risk for adverse events such as spontaneous abortion, ectopic pregnancies, multiple gestation, or congenital anomalies (23,25). In more than 100 pregnancies where 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 (23,25). There are few data on pergolide safety in pregnancy. Cabergoline has been utilized in more than 200 pregnancies. During this limited experience, it has appeared to be safe (26). However, because of the broader range of experience, bromocriptine therapy is preferred in women who are undergoing therapy for the purpose of fertility.

There are few specific data regarding the use of transsphenoidal surgery during pregnancy. It is presumed that the risks would be similar to other forms of surgery, except for the increased risk of hypopituitarism.

For intrasellar tumors, bromocriptine therapy is preferred as it is safe for the fetus if it is discontinued early in gestation. These tumors demonstrate a small risk for tumor enlargement. Patients should be followed on a trimester basis for symptomatic enlargement. Visual field testing should be performed if clinically indicated.

Therapeutic options for tumors extending outside the sella include prepregnancy surgical debulking, intensive monitoring without bromocriptine therapy, and continuous bromocriptine therapy throughout gestation. The latter is not likely to harm the fetus, based on the small number of cases available to date. 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 (27). With evidence of tumoral enlargement, immediately reinstitute bromocriptine therapy and rapidly titrate the dose as tolerated. Transsphenoidal surgery or, if gestation length is adequate, delivery should be considered if the response to bromocriptine therapy is inadequate (23).

Breastfeeding stimulates prolactin secretion in normal women in the first few weeks or months postpartum (19). However, there is no evidence that suckling stimulates prolactinoma growth. Therefore, we do not discourage breastfeeding in women with prolactinomas.

Anovulation secondary to hyperprolactinemia in untreated women is associated with hypoestrogenemia and a potential for osteoporosis (19). Although the estrogen in oral contraceptives stimulates lactotrophs and mild increases in prolactin levels in normal women, it does not usually cause growth of microadenomas or precipitate neoplastic development in women with idiopathic hyperprolactinemia (28). Prolactin levels should be evaluated periodically to find the rare estrogen-sensitive tumor. If prolactin levels are found to increase substantially, the estrogen should be stopped to forestall tumor growth. For patients with macroadenomas, dopamine agonists are preferred to estrogens because of their efficacy in reducing tumor size.

Acromegaly

Infertilily is common in women with acromegaly, as approximately 75% of acromegalic women of

child-bearing years have menstrual irregularities (29). The ovarian dysfunction is often the result of the hyperprolactinemia found in 30-40% of cases(30) and to possible mass effects of the tumor. An additional factor is the coexisting polycystic ovary syndrome seen in a number of patients (31). Many patients require bromocriptine to ovulate and conceive, as normalization of the hyperprolactinemia frequently restores menstruation. GH and IGF-1 also regulate ovarian function, as GH increases ovarian responsiveness to gonadotropins (32) either directly or through IGF-1 production in the ovarian follicle (33).

Pituitary growth hormone secretion is autonomous in acromegaly, so both pituitary and placental GH variants persist throughout pregnancy (34). Diagnosing acromegaly during gestation may be difficult as conventional radioimmunoassays are unable to distinguish between the 2 forms of GH; such distinction requires special radioimmunoassays with antibodies which recognize specific epitopes on the pituitary and placental GH variants (10). However, pituitary growth hormone secretion in acromegaly demonstrates a pulsatility of 13-19 pulses per 24 hours (35) vs. the tonic secretion seen with the placental variant (11). In addition, paradoxical GH release after TRH occurs with pituitary GH excess (30) and is not seen with the placental variant (34). Postpartum, the placental variant, disappears from the circulation within 24 hours (10). IGF-1 levels are not useful in the diagnosis of acromegaly in pregnancy, as they elevate in the second half of both normal and acromegalic pregnancies (36).

To date, pregnancy has exacerbated the underlying condition in 4 of the 24 (17%) pregnant patients with acromegaly who have been described in the literature (37). Tumor enlargement during pregnancy has been described in 2 patients with acromegaly (38,39). Glucose tolerance, hypertension, and cardiac derangements also require monitoring (30). Glucose intolerance occurs in 50% of patients with acromegaly, with overt diabetes mellitus in 10-20% (30). The risk for gestational diabetes mellitus is consequently increased by the insulin resistance of acromegaly. Sodium retention leads to hypertension in 25-35% of patients, with potential for exacerbation in pregnancy. Because of their underlying cardiomyopathy and increased risk for coronary artery disease, these complications may also be exacerbated during pregnancy (30,40).

GH does not cross the placenta, and maternal acromegaly has little direct impact on the fetus. Fetal somatic growth is largely GH-independent, and macrosomia in such pregnancies is likely secondary to maternal glucose intolerance.

Bromocriptine therapy may provide limited benefit in treating individuals with acromegaly, with no reduction in tumor size and rare normalization of GH levels. Its use in pregnancy has been described above. Somatostatin analogs can cross the placenta. Ten cases of women with acromegaly treated with octreotide during pregnancy have been described (40-42), two cases with acromegaly treated with lanreotide (43,44), one with a TSH-secreting tumor treated with octreotide during pregnancy (45), and one with nesidioblastosis treated with octreotide during pregnancy (46). In most cases the somatostatin analog was stopped before the end of the first trimester, but in two cases octreotide was given throughout the pregnancy (40,46). No malformations were noted in any case, but because of such limited data, the use of somatostatin analogs cannot be recommended for use during pregnancy except under extraordinary circumstances.

Other Pituitary Adenomas

The ACTH-secreting neoplasm will be described in the adrenal disorders section. There are little data regarding nonsecreting, gonadotropin-secreting, or TSH-secreting pituitary adenomas in pregnancy. Although unlikely to enlarge under the influence of estrogen stimulation in pregnancy, there are case reports of enlargement of 1 nonsecreting (38) and 1 TSH-secreting adenoma during pregnancy (45).

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. 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. During gestation, adrenal and thyroid hormones should be replaced as needed (see below). Inadequately treated hypopituitarism may lead to poor pregnancy outcome, including spontaneous abortion, intrauterine fetal demise, maternal hypotension, hypoglycemia, and even maternal death.

Sheehan's Syndrome

Sheehan's syndrome consists of pituitary necrosis secondary to ischemia occurring within hours of delivery (47). 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 (47). The degree of ischemia and necrosis dictates the subsequent patient course.

Acute necrosis is suspected in the setting of an obstetric hemorrhage where hypotension and tachycardia persist following adequate replacement of blood products (Table 2). In addition, the woman fails to lactate and may have hypoglycemia (47,48). Investigation should include levels of ACTH, cortisol, prolactin, and free T4. The ACTH stimulation test would be normal, as the adrenal cortex would not be atrophied. T4 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. DI may also occur secondary to vascular occlusion with atrophy and scarring of the neurohypophysis (49).

TABLE 2. 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
	Loss of libidoNausea and vomiting
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.)

When milder forms of infarction occur, the diagnosis of Sheehan's may be delayed for months or years. 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 2). Some women experience only partial hypopituitarism and may have normal menses and fertility (48). Although the women may have episodes of transient polydipsia and polyuria, many demonstrate impaired urinary concentrating ability and deficient vasopressin secretion (50). CT or MRI scans generally reveal partial or completely empty sellas (51).

Lymphocytic Hypophysitis

Lymphocytic hypophysitis is thought to be autoimmune in nature and is manifested by massive infiltration and destruction of the parenchyma of the pituitary and infundibulum by lymphocytes and plasma cells. It generally occurs during pregnancy or the postpartum period. It is associated with symptoms of hypopituitarism or an enlarging mass lesion and is suspected based on its timing and lack of association with an obstetric hemorrhage or prior history of menstrual difficulties or infertility. It is generally associated with mild hyperprolactinemia (<150 ng/ml) and diabetes insipidus. Differentiation from a pituitary neoplasm cannot be made based on CT or MRI scans, but only on biopsy results (52,53). Treatment is generally conservative and involves identification and correction of any pituitary deficits, particularly of ACTH secretion (54). There are no data to indicate that high dose corticosteroids may be of benefit in treating the destructive process. Surgery to debulk but not remove the gland is indicated in the presence of uncontrolled headaches, visual field defects, and progressive enlargement on scan. Spontaneous regression and resumption of partial or normal pituitary function may occur, although most patients progress to chronic panhypopituitarism. Other autoimmune disorders may also be associated.

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. As a result, pregnant women experience thirst and release AVP at lower levels of plasma osmolality than do nonpregnant women (55). This reset osmostat is possibly due to high levels of human chorionic gonadotropin (hCG) (55). 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.(56) AVP consequently has a four- to sixfold increased metabolic clearance rate during gestation (57,58).

The lower osmostat and increased clearance of AVP by vasopressinase in pregnancy alter the nomograms of plasma osmolality and AVP used in the nonpregnant patient. Serum sodium levels may also be lower than those normally expected in patients with diabetes insipidus (58). Urinary concentrating ability in the pregnant patient should be determined in the seated position, as the lateral recumbent position inhibits maximal urinary concentration (55,58). 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 (59). Hypophysectomy does not alter onset of labor, indicating that oxytocin provides only a facilitatory role (60). Oxytocin levels rise rapidly during suckling (61).

Diabetes Insipidus

Diabetes insipidus usually worsens during gestation (58), likely due to the increased clearance of AVP by the vasopressinase. Patients with asymptomatic DI may develop symptoms during pregnancy

(62,63). Patients with mild disease usually 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, although a higher dose may be required (58). During monitoring of the clinical response, clinicians should remember that normal basal plasma osmolality and sodium concentration are 5 mEq/L lower during pregnancy (64). No adverse events have been described in the offspring of pregnancies where dDAVP was used throughout gestation (65,66). DDAVP transfers minimally into breast milk(58) and is poorly absorbed from the gastrointestinal tract, so its use will not adversely affect an infant's water metabolism.

Transient AVP-resistant forms of DI may occur spontaneously in one pregnancy, but not in a subsequent one (64). Some of these patients may respond to dDAVP therapy. The symptoms resolve within several weeks of delivery (58,64).

Acute fatty liver of pregnancy may be associated with late onset transient DI of pregnancy in some patients (67,68). 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. 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 (69).

Congenital nephrogenic DI is a rare disorder which predominantly affects males. Female carriers of this disease may have significant polyuria during pregnancy. Treatment is with thiazide diuretics (58), which should be used with caution in pregnant women.

In patients with idiopathic DI, oxytocin levels are normal and labor may begin spontaneously and proceed normally (70). 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.

THYROID DISORDERS IN PREGNANCY

Thyroid disorders are commonly encountered during pregnancy. Three major factors alter maternal thyroid physiology in pregnancy. These include significant alterations in iodide physiology, the stimulation of the thyroid by the increase in hCG, and an increase in thyroxine-binding globulin (TBG).

Iodine Metabolism

Renal iodide clearance dramatically increases early in gestation secondary to the increased glomerular filtration rate (GFR), resulting in a fall in plasma iodine concentrations. The thyroid compensates by increasing thyroidal iodine clearance, elevating iodide entry into the gland (71). This supports the increase in thyroidal activity which occurs early in gestation. Later in gestation, maternal iodine losses increase with transplacental passage of iodine to the fetus to support fetal thyroid function. To sustain these roles, adequate iodine intake for pregnant and lactating women is estimated at 150-200 mg/day (71), which is provided in the U.S. in the form of prenatal vitamins and iodized salt. Nevertheless, the recent NHANES III report indicates that iodine intake has declined 50% in the U.S. since the completion of NHANES I (72). Iodine deficiency has increased 4-fold and is found in 6.7% of pregnant women and 14.9% of women of child-bearing age (72). Iodine deficiency is the leading cause of

intellectual deficiency in the world (73) as iodine is critical for the myelination and maturation of the CNS. Furthermore, iodine deficiency increases miscarriage rates, stillbirths, and neonatal mortality and reduces birth weights (73). Iodine supplementation is critical to reduce these risks. Small amounts of iodine supplementation may cause a transient, mild fall in fetal free T4 levels, but both the fetus and mother soon escape this inhibition (74). In areas with mild to moderate iodine deficiency, maternal supplementation of iodine throughout pregnancy apparently improves fetal thyroid function, with normal thyroid volumes seen in the neonates (75,76). If iodine supplementation is gven at term (77), or iodine disinfectants are used at delivery (78,79), higher cord levels of TSH are found, suggesting an inhibitory effect of iodine supplementation on the fetal thyroid. This fetal thyroid inhibition does not occur when iodine is given to iodine-replete mothers (80). Excessive iodine intake should be avoided because of a risk for fetal goiter.

In areas of marginal iodine intake and inadequate supplementation, the demands of pregnancy can result in overt iodine deficiency and thyroid enlargement in an attempt to produce sufficient thyroid hormone (71). Goiter ensues if the plasma iodine concentration falls below 0.08 mg/dl (81). Thyroid enlargement varies proportional to iodine intake (82), with an inverse relationship between iodine intake and thyroid blood flow. Goiter is not found with increased frequency in iodine-replete pregnant women (83,84). In a study of 309 pregnant adolescents, 19 had goiters, 2 with Graves' disease, 3 with Hashimoto's thyroiditis, 4 with subacute thyroiditis, and 9 with simple nontoxic goiters (84). Therefore, the occurrence of a palpable goiter in iodine-replete areas indicates clinical disease in approximately 50% and warrants investigation. In patients with goiters from a variety of thyroid conditions, an increase in size of 17-55% may occur during gestation (85).

Hypothalamic-Pituitary-Thyroid Axis

There is a transient fall in TSH in the first trimester during the 2nd and 3rd months. This is postulated to be secondary to hCG stimulation of the thyroid due to the structural homology between the TSH and hCG molecules and their receptors (86). The role of hCG in increasing thyroid stimulating activity was first postulated with the thyrotoxicosis noted in molar pregnancies and trophoblastic disease (87), 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 (88). Sequential TSH determinations between 8 and 14 weeks' gestation revealed that the nadir in TSH coincides with the peak in hCG (71) with an inverse correlation found in individual samples. There is also a linear relationship between hCG and free T4 concentrations early in gestation (71). 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 (89). Furthermore, in hyperplacentosis(90) 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 (91). 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 (71).

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 (92,93). This increase in TBG results in higher levels of total T4 and T3, starting at 4-6 weeks gestation (93)(Figure 2). 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 (71,92,93), though they may be 10-15% lower at term in iodine-sufficient women. Placental deiodination increases maternal T4 turnover.

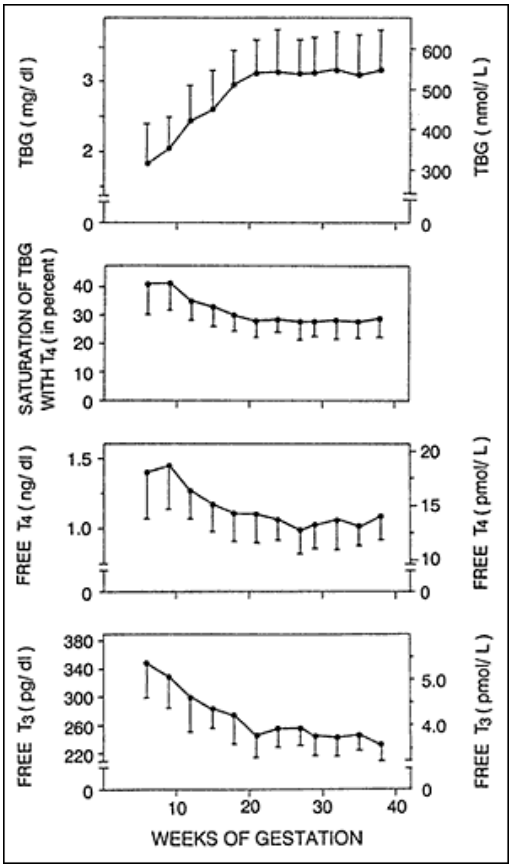

Figure 2.Serum thyroid hormone binding globulin (TBG), percent saturation of TBG, Free T4, and Free T3 levels from 606 normal pregnancies in Brussels, showing the progressive rise in serum TBG during the first part of gestation , accompanied by a a progressive decrease in the free T4 index (saturation level of TBG by T4), and free T4 and T3 concentrations. (From Glioner D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocrine Revs 1997;18:404.)

Initial studies indicated that minimal maternal TSH, T4 and T3 crossed the placenta (94). However, early in gestation the fetus is totally dependent on maternal thyroid function. Maternal T4 is present in the coelomic fluid by 6 weeks of gestation (95). Precolloid stage thyroid follicular cells are detected between the 7 and 10 weeks' gestation. The fetal brain contains T3 receptors by 10 weeks' gestation (96), and these receptors increase dramatically in number through 18 weeks. The fetal thyroid begins to concentrate iodine by 11 to 15 weeks, and TSH, thyroglobulin, and T4 are detected in the circulation. The fetal thyroid is fully functional by week 26 (94). Fetal serum TSH, TBG, T4, and T3 rise throughout gestation (97). Maternal thyroid hormone continues to cross the placenta in small amounts and is even present in cord blood (94). T4 crosses the placenta in larger amounts than T3, and its administration to the mother can provide an amelioration of the effects of congenital hypothyroidism in the fetus (98).

Hyperthyroidism

Hyperthyroidism occurs in 0.2% of pregnancies (99). Approximately 95% of these cases are secondary to Graves' disease. Autoimmune hyperthyroidism often ameliorates during pregnancy, likely due to the immune modification of pregnancy which allows the successful allograft of the fetus, a foreign tissue (99,100). This decline in immune surveillance includes a decrease in thyroid stimulating

immunoglobulins (100), a decrease in the CD4+/CD8+ ratio (101), and a depression of both humoral and cell-mediated immunity. Soluble factors produced by activated fetal suppressor T cells may also cross the placenta and cause a transient decrease in the intensity of maternal Graves' disease during pregnancy. The postpartum exacerbation of Graves' disease may in part be due to the loss of these fetal suppressor T cells at delivery (102). Other factors which may assist in amelioration of hyperthyroidism in pregnancy include the increased clearance of iodine stores and the increase in TBG, which decreases the fraction of free hormones in the circulation.

Untreated hyperthyroidism has adverse consequences on maternal morbidity and fetal outcome. It increases the risk of maternal congestive heart failure, preeclampsia (RR 4.7), premature labor (RR 16.5), low birthweight infants (RR 9.2), and perinatal mortality (103,104). There may also be a mild increase in congenital anomalies in offspring of untreated or incompletely treated women with hyperthyroidism. These complications are not increased in women whose hyperthyroidism was controlled throughout the pregnancy (103).

Hyperthyroidism may be difficult to distinguish from the hypermetabolic state of pregnancy. Heat intolerance, warm skin, tachycardia and systolic flow murmurs are common to both. Goiter may occur in iodine-deficient pregnant women. Weight loss, hyperdefecation, thyroid eye signs, thyroid bruit and significant tachycardia suggest thyrotoxicosis (99,100). The diagnosis is confirmed by finding a suppressed TSH and elevated free T4 and T3 levels in the blood. Radioactive tracers such as 131I or technecium-99 should not be used in the diagnostic process to avoid fetal exposure.

Medical therapy with one of the thionamide derivatives, PTU or methimazole, is generally the treatment of choice. An early in vivo study showed that methimazole crosses the placenta at a rate 4-times greater than PTU, attributed to differences in protein binding (105). More recent data suggest that there is little difference in the placental transfer of the drugs (106), confirmed by equal concentrations of PTU in simultaneously obtained maternal and cord blood (107). However, there are multiple anecdotal case reports of the localized congenital scalp anomaly aplasia cutis with methimazole use (108). Furthermore, there is a 3-fold increase in this anomaly in regions of Spain where methimazole is used as a fattening agent in animal feed (109). More recently, there are descriptions of a methimazole embryopathy including choanal atresia, tracheo-esophageal fistula, facial anomalies, and psychomotor delay (110,111). PTU is therefore the preferred modality in pregnancy, though methimazole may be used as a second-line agent in the case of patient intolerance or an adverse reaction to PTU. Except in mild cases, initial doses of PTU of 100-150 mg every 8 hours are used, with dose titration based on serial measurements of free T4 and TSH. Doses up to 800 mg/day may be required, though most patients require lower doses as pregnancy progresses and may even be able to discontinue the agent. Maintenance of maternal free T4 concentration in the upper normal range with a mildly suppressed TSH may be optimal to avoid fetal hypothyroidism or goiter (99,112,113). Pregnant women tolerate mild degrees of hyperthyroidism without much difficulty. Children exposed to PTU in utero have demonstrated no intellectual or physical defects in long-term studies (114).

As a clinical response to thionamides is delayed until the thyroid hormone stored in colloid is used, b-blockers may be useful to control symptoms, including significant tachycardia (> 120 beats/min) or tachyarrhythmias, in severely hyperthyroid women. These agents also cross the placenta. However, earlier reports of neonatal bradycardia and hypoglycemia have not been confirmed (115). These drugs should not be used in isolation, as they do not reduce the basal metabolic rate or protein catabolism of hyperthyroidism, nor protect from thyroid storm at delivery (116).

As noted above, iodides cross the placenta readily and may cause fetal hypothyroidism and large goiters (117). This complication has not been seen in the offspring of pregnant women with milder forms of Graves' disease who were treated with iodine alone during their pregnancies (74). In general, iodides should only be used in a short course to prepare patients for surgery or for rare cases of thyroid

storm. Ultrasound should be used to evaluate for fetal goiter, which may complicate delivery (118).

Lithium carbonate should not be used in pregnancy as it is teratogenic in the first trimester, and may cause neonatal lithium intoxication and goiter if given near term (119). Surgery is reserved for patients who develop adverse effects to the medications (rash, hepatitis, vasculitis, or agranulocytosis), or demonstrate an inadequate response. Surgery may pose an increased risk to the fetus (99,100,120). Surgery is delayed until after the first trimester, as the spontaneous abortion rate is highest during that time. The risks of thyroid surgery are lowest in the second trimester, though fetal loss may still occur. After 24 weeks' gestation, surgery may increase the risk of premature labor. Patients are prepared medically with thionamides and ß-blockers to prevent thyroid storm. Surgeons believe that iodine administration will reduce the vascularity of the gland, minimizing intraoperative blood loss (121). Studies have not demonstrated any benefit of adding iodine to hyperthyroid patients prepared with propranolol (122), or to patients rendered euthyroid with thionamides (123).

Radioactive iodine is contraindicated in pregnancy as it can cross the placenta and ablate the fetal thyroid. A pregnancy test is performed prior to the administration of radioactive iodine to women of child-bearing years. If a pregnant woman is mistakenly given a therapeutic dose of radioactive iodine, she may immediately be treated with PTU 300 mg/day for 7 days to attempt to block the organification and the recycling of the radioactive iodine in the fetal gland (148,149). There are no case reports to determine the efficacy of this therapy, but PTU is known to decrease thyroidal uptake and organification of iodide, and several studies have demonstrated diminished effectiveness of 131I therapy in Graves' patients previously treated with PTU (150-152).

Thyroid Storm

Thyroid storm is a medical emergency associated with 25% mortality for mother and fetus. It generally occurs in previously undiagnosed hyperthyroid patients who are subject to a stress, such as an infection, labor, or surgery. The presentation includes fever, marked tachycardia, severe dehydration, and prostration. Treatment involves alleviating the precipitating factor, replacing fluid losses, and using high dose PTU, b-blockers, corticosteroids, and sodium iodide. In this setting, the theoretic risks to the fetus of iodine administration are outweighed by the benefits of acute reduction in maternal thyroid hormone release and control of the hyperthyroidism. Subsequent ultrasound monitoring for fetal goiter is recommended.

Hyperemesis Gravidarum

Hyperemesis gravidarum is defined as severe nausea and vomiting that develops in the first trimester, and can result in nutritional deficiencies, ketosis, dehydration, and electrolyte imbalance. It starts at 6-9 weeks' gestation and usually resolves by 18-20 weeks' gestation. It is generally idiopathic but on occasion may be associated with an underlying pathology such as hyperthyroidism.

Elevated free T4 levels with a suppressed TSH may be found transiently in up to 30-60% of patients with hyperemesis gravidarum (124-127). These elevated thyroid hormone levels require no pharmacologic intervention and are caused by the high rate of hCG secretion (128). The elevation in hCG contributes to an elevation in estradiol levels that may contribute to the nausea and emesis. The degree of biochemical hyperthyroidism and severity of vomiting generally correlate with the level of hCG, although deglycosylated and desialylated modifications of its oligosaccharide side chain have the greatest thyrotropic effect and are more often isolated from women with hydatidiform moles and women with hyperemesis gravidarum (129,130).

Clinical evaluation of the patient is critical to distinguish between autoimmune thyrotoxicosis and transient hyperthyroidism of hyperemesis gravidarum (THHG). Patients with THHG have few manifestations of thyrotoxicosis, have no goiter, and their hyperthyroxinemia is generally transient and resolves by 18 weeks' gestation without antithyroid drug therapy (131)(Figure 3). Symptomatic patients can be treated with beta blockers. Thionamide therapy should be considered for women with a prepregnancy history suggestive of hyperthyroidism, overt manifestations of Graves' disease, or with persistent hyperemesis and hyperthyroxinemia past 20 weeks' gestation.

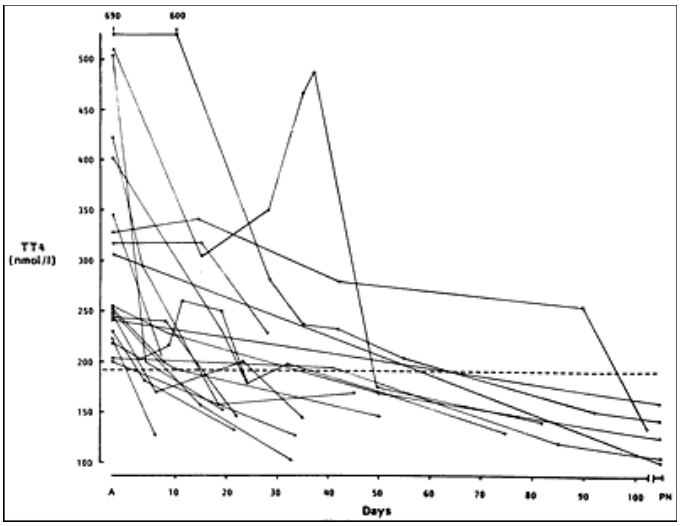

Figure 3.Changes in plasma total thyroxine (TT4) concentration in 20 subjects with hyperemesis on admission to the hospital (A) and during the course of their pregnancy. The interrupted line represents the mean + SD value seen in normal pregnancy.PN, postnatal.(From Swaminathan R, Chin RK, Lao TH, et al. Thyroid function in hyperemesis gravidarum. Acta Endocrinol (Copenh), 1989;120:155.)

A rare cause of gestational hyperthyroidism has been found in families with a missense mutation in the extracellular domain of the TSH receptor. This receptor was found to be more sensitive to hCG and created gestational hyperthyroidism at normal levels of hCG (132).

Graves' Disease and Neonatal Thyroid Function

As noted above, all of the potential medical therapies for Graves' disease cross the placenta and may affect fetal thyroid function. Fetal hypothyroidism and goiter may result. A goiter may cause hyperextension of the fetal neck, resulting in malpresentation and trauma at vaginal delivery. In addition, the goiter may compress the non-calcified tracheal rings of the neonate, causing airway obstruction and asphyxia. Fetal hypothyroidism may impair intellectual development. Cord blood should be obtained for TSH and T4 levels, with repeat levels drawn at 3 days as transient hypothyroidism may resolve by that time (113).

Thyroid stimulating immunoglobulins and thyrotropin-binding inhibitor immunoglobulins may also cross the placenta and cause fetal hyperthyroidism in less than 1% of infants born to mothers with Graves' disease (99). Higher titers of these immunoglobulins in the maternal serum in the third trimester increases the risk of hyperthyroidism in the fetus. This may still occur in women who were previously treated for Graves' disease with radioactive iodine, who are currently on thyroid hormone replacement. The hyperthyroidism may manifest as fetal tachycardia, intrauterine fetal growth restriction, and fetal goiter. Cordocentesis may help with the diagnosis. Fetal hyperthyroidism may be treated by increasing the maternal thionamide dosage and titrating it to the fetal heart rate (133). Postpartum, the hyperthyroidism may persist for up to 3 months in the neonate, resulting in irritability,

failure to thrive, and poor feeding. It is associated with a mortality rate of 16%. Long-term complications include craniosynostosis. The neonate may be transiently treated with thionamide therapy until the maternal immunoglobulins clear.

Hyperthyroidism and Breast Feeding

The thionamides are excreted into breast milk. The amounts are small and have not been shown to affect infant thyroid function or intellectual development (134-6). Nevertheless, thionamides should be given in divided doses and administered after feedings (108,137). Maternal thyroid hormone levels should be monitored frequently to facilitate thionamide dose adjustment. Monitoring of thyroid function in breast-fed infants is not necessary, so long as infant development proceeds normally and maternal doses do not exceed methimazole 20 mg/day or PTU 450 mg/day. Idiosyncratic reactions to these drugs have not been reported in breast-fed neonates (137).

Iodine is concentrated by the breast (138,139) and excreted into breast milk. Radioactive iodine is therefore contraindicated while the mother is breast feeding as therapeutic doses may be detected in the breast milk for several months (140). Even scanning doses may be found in the breast milk. In a description of an infant who breast-fed 4 hours after the mother received a dose of technecium-99, the infant received a total dose of 82.5 mCi, with the thyroid receiving 300 mRad, the upper large intestine 180 mRad, and other organs lower doses (141). If the infant had breast fed 30 minutes after the scanning dose, the estimated exposure would be 728 mCi. Therefore, bottle feeding should be instituted for 48 hours after a scanning dose before breast feeding may resume. Therapeutic doses of 131I dose should not be given for at least 3 months after breastfeeding is discontinued to avoid an excessive exposure to radiation in the lactating breasts that may potentially increase the risk of breast cancer (142).

Hypothyroidism

Hypothyroidism occurs in 2.5% of pregnancies (71,143). The incidence is higher in women with Type 1 diabetes who have microvascular complications (144). Women with hypothyroidism have a 2-fold greater risk of ovulatory infertility (145). They also appear to have higher rates of spontaneous abortion, congenital anomalies, preeclampsia, pregnancy-induced hypertension, placental abruption, premature birth, low birth weight, and stillbirth (146,147). Thyroid hormone replacement improves but does not eliminate the increased risk (147,153). It is not certain whether the poor pregnancy outcome is a result of the hypothyroidism, or is secondary to a more generalized autoimmune disturbance.

The initial development of the fetal brain occurs when the primary supply of thyroid hormone for the developing fetus is of maternal origin (153). Maternal hypothyroidism and low normal free T4 in the first half of gestation have been associated with irreversible neurologic deficits in the offspring (154-6), while later deficits cause less severe and partially reversible neuropsychologic impairment. The severity, timing of onset and duration of maternal hypothyroidism determine the impact on the neurologic development of the fetus. Even mild forms of maternal hypothyroidism appear to have an impact. As a result, some clinicians now recommend that pregnant women should be screened for hypothyroidism with a TSH and free T4 early in gestation. Detailed reviews of this subject have recently been published (94,153).

In order to reduce the duration a fetus is exposed to maternal hypothyroxinemia, pregnant women identified with hypothyroidism are generally started on levothyroxine at 1.9 mg/kg ideal body weight daily, with monitoring every 6 weeks until the TSH is normalized. Patients who are NPO should be given two thirds of the usual dose intravenously, as only 60-80% is available from the oral form.

Approximately 75-80% of patients previously treated with levothyroxine require an increased dose during pregnancy, with a median increment of 30-50% (71,157). Some of this may be due to the increased T4 turnover during pregnancy (99), while some may be due to intestinal complexing of T4 with the divalent cations, iron and calcium, which are components of prenatal vitamins (158,159). Patients should be advised to take their thyroid hormone prior to breakfast, and their prenatal vitamins at least 2 hours later. Serum TSH levels should be monitored every trimester to facilitate dose adjustment. Levothyroxine doses generally return to prepregnancy levels in the early postpartum period.

Myxedema Coma

Myxedema coma is extremely rare in pregnancy as it primarily affects older individuals. Severe hypothyroidism in younger patients is generally associated with hyperprolactinemia, anovulation, and infertility. When it does occur, it is a medical emergency with a 20% mortality. It is treated the same as in nonpregnant patients.

Postpartum Thyroiditis

Postpartum, subacute lymphocytic thyroiditis occurs in approximately 5-7% of women (160-2). This rate increases to 25% in women with Type 1 diabetes mellitus (163) and is associated with other autoimmune diseases. Postpartum thyroiditis is now conceived as an acute phase of autoimmune thyroid destruction in the setting of an ongoing process of thyroid autosensitization. Postpartum, there is a rebound reaction to the immune tolerance enjoyed during pregnancy. It is closely associated with the presence of thyroid antiperoxidase antibodies. A woman who tests positive for these antibodies early in gestation has a 30-52% risk of developing postpartum thyroiditis (164). An extensive review of the pathogenesis has been published recently (165).

Postpartum thyroiditis classically has a biphasic course of hyperthyroidism followed by hypothyroidism. Transient hyperthyroidism and hypothyroidism may occur in isolation. The onset is variable, with hyperthyroidism occuring 1-6 months' postpartum and lasting 1-2 months, followed by transient hypothyroidism 4-8 months' postpartum which resolves spontaneously in 4-6 months (162). The hyperthyroid phase is seen in two thirds of patients and may be asymptomatic. Many patients complain of fatigue, irritability, increased appetite, rapid weight loss, and palpitations (160-2). It is associated with a low radioactive iodine uptake.

Two thirds of all patients experience hypothyroidism. Some may develop hypothyroidism without preceding hyperthyroidism. They frequently have a painless, firm goiter. The hypothyroid phase may be asymptomatic or associated with complaints of fatigue, myalgias, arthralgias, loss of concentration, constipation, weight gain, and depression (162) and may be mistaken for "postpartum depression." The hypothyroidism resolves spontaneously in approximately 80% of cases but persists in 20% (162). High titers of antiperoxidase antibodies and the severity of the hypothyroidism predict persistent hypothyroidism (160).

As symptoms are generally nonspecific, a high index of suspicion is required for diagnosis. Patients with prior history of hypothyroidism may also develop postpartum thyroiditis (166), leading to a further decline in thyroid function. Because of the changing course of the condition, TSH and free T4 should be elevated at 4-8 week intervals. Patients with severe hyperthyroidism should have an 131I thyroid uptake (if not breast feeding) to distinguish postpartum thyroiditis from Graves' disease which may present in the first year postpartum with the altered immune status. Treatment is instituted for symptomatic cases. Thionamide drugs are not effective in postpartum thyroiditis, and b-blockers are

used for symptomatic relief. The hypothyroid phase should be treated with levothyroxine if symptomatic, with withdrawal or halving of the dose of thyroxine after 6 months to determine whether the condition was transient. Repeat TSH testing is done 6 weeks later. A number of patients continue to have positive antiperoxidase antibody titers and organification defects (167). Exposure to excess iodine in the form of radiocontrast media may precipitate hypothyroidism (167). These individuals are at high risk for future permanent hypothyroidism, with a rate of 48% within 7-9 years (168). Regular screening of thyroid status should be instituted so that intervention can occur early. Subclinical hypothyroidism has been associated with accelerated atherosclerosis (169) and deserves intervention. Postpartum thyroiditis recurs in future pregnancies in approximately 70%.

Thyroid Nodules and Thyroid Cancer

The incidence of thyroid nodularity does not increase with parity except in areas of marginal iodine intake (170). The risk of malignancy in a solitary thyroid nodule is approximately 10%. This risk dramatically increases with a history of prior head and neck irradiation (171). The effect of pregnancy on the natural history of thyroid carcinoma is controversial (172). Some have found no apparent effect (173-5), while other studies suggest there is an increased risk of malignancy in nodules which develop during pregnancy (176-8) and that the cancer may be more aggressive (179). The intrinsic TSH-like activity of hCG has been postulated to play a role in the progression of cancers found early in gestation (179).

In women of child-bearing years, approximately 65% of thyroid malignancies are papillary, 30% are follicular, 3% are medullary, 1% are anaplastic, and 1% are lymphoma or metastases to the thyroid (171). Diagnosis is made by fine needle aspiration. A diagnosis of medullary or anaplastic carcinoma or lymphoma warrants immediate surgery. Patients with well-differentiated thyroid malignancies could undergo a near total thyroidectomy in the second trimester or following delivery. Induction of hypothyroidism for adjuvant radioiodine therapy or scanning would then be delayed until the postpartum period to avoid the fetal risks associated with maternal hypothyroidism. Waiting until postpartum does not appear to alter the prognosis of thyroid carcinoma (171,180). If surgery is postponed until postpartum then thyroid hormone suppression therapy should be instituted until the surgery.

CALCIUM DISORDERS IN PREGNANCY

Calcium metabolism is dramatically altered by pregnancy and lactation. The normal fetal skeleton accumulates approximately 30g of calcium by term, proportional to the fetal weight. The largest proportion (80%) of that accretion occurs in the third trimester, at a rate of about 250-300 mg/day (181).

Total serum calcium levels fall early in pregnancy, due to hemodilution and the consequent decline in serum albumin (Figure 4). Ionized calcium levels and phosphate levels remain normal throughout pregnancy (181-5). PTH levels fall to 10-30% of the mean nonpregnant range in the first trimester but increase again to the midnormal range by term (185-7). Serum calcitonin levels increase during gestation (184,188), partly due to extrathyroidal synthesis in the placenta and breast. While PTH levels decline, total and free 1,25-dihydroxyvitamin D levels increase 2-fold in the first trimester, then remain constant until term (187,188). The maternal kidneys are the primary source for this increase in vitamin D secondary to up-regulation of the renal 1a-hydroxylase by PTHrP, with possibly small contributions from the maternal deciduas (189). PTHrP appears to increase early during pregnancy (190,191). The role of PTHrP is manifold. The amino-terminal portion stimulates renal 1a-hydroxylase and skeletal

calcium resorption (189). It can also inhibit acetylcholine-induced uterine contractions in the rat and is decreased acutely in the amnion and myometrium at the onset of labor in humans (192). The carboxy-terminal portion inhibits osteoclastic bone resorption ("osteostatin"), while the mid-portion stimulates placental calcium transfer (189). The roles of estradiol, progestins, prolactin, chorionic somatomammotropin, and IGF-1 are still under investigation.

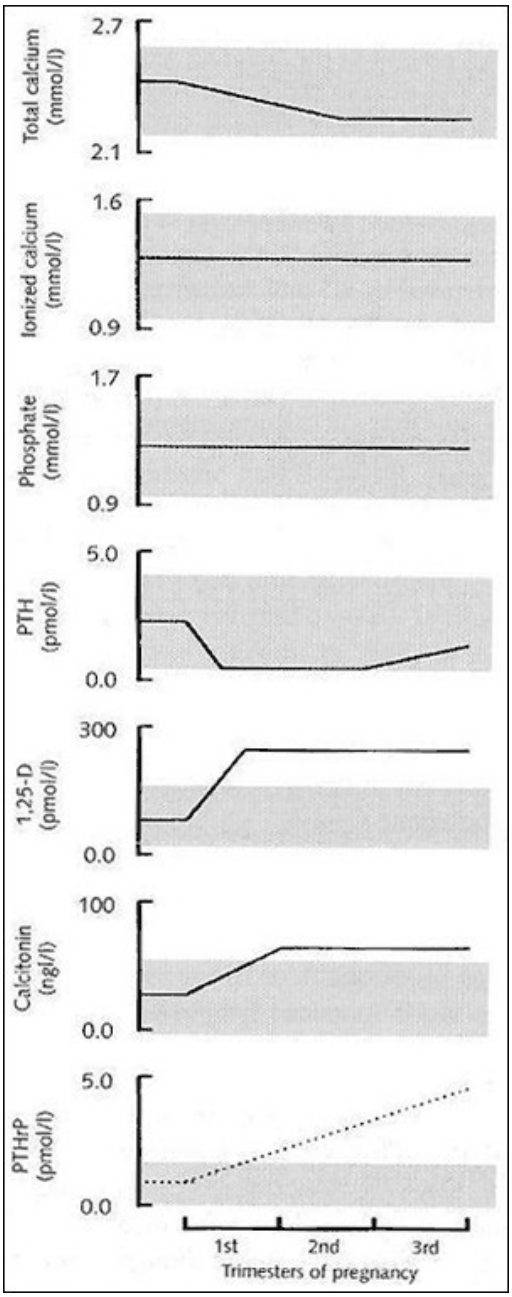

Figure 4.Schematic illustration of the longitudinal changes in calcium, phosphate, and calcitropic hormone levels that occur during human pregnancy. Normal adults ranges are indicated by the shaded areas. The progression in PTHrP levels has been depicted by a dashed line to reflect that the data are less complete.(From Kovacs CS, Kronenberg HM. Maternal-fetal calcium and bone metabolism during pregnancy, puerperium, and lactation. Endocrine Revs 1997;18:832.)

With the increase in 1,25-dihydroxyvitamin D, there is increased intestinal expression of the vitamin D-dependent calcium binding protein calbindin9K-D (189). This leads to a doubling in intestinal calcium

absorption by 12 weeks of gestation (187), and appears to be the major maternal adaptation to supply the fetal calcium requirements. Prolactin and somatomammotropin may also play roles in this increased calcium absorption (189). Animal models suggest that this increased calcium intake is stored in the maternal skeleton until required in the third trimester, but this has not been assessed in humans.

Urinary calcium excretion increases early in gestation secondary to an increased calcium load filtered by the kidneys and the increased glomerular filtration rate of pregnancy. The elevation of calcitonin levels may also contribute. Renal calcium excretion is low or normal in the fasted state (190).

In pregnant rat models, bone turnover is increased but bone mineral content is unchanged. Bone biopsies of women who underwent an elective termination of pregnancy in the first trimester revealed increased bone resorption, with increased resorption surface, increased number of resorption cavities, and decreased osteoid (193). This is not seen at term.

Most of the investigations of skeletal metabolism in pregnancy use bone markers and have a number of confounding variables including lack of prepregnancy baseline values, alterations in renal clearance, contributions from the gravid uterus, clearance by the placenta and hemodilution. Alkaline phosphatase is secreted by the placenta, and is not useful as a marker of bone formation in pregnancy. Urinary deoxypyridinoline, pyridinoline, and hydroxyproline increase in early to mid-pregnancy, suggesting bone resorption at that time (181). Bone formation markers osteocalcin and bone-specific alkaline phosphatase are decreased in early pregnancy and rise to normal or above by term (181). These findings suggest an increase in bone turnover in the first trimester but do not demonstrate a dramatic increase in the third trimester when most of the maternal-fetal calcium transfer occurs.

Studies of bone mineral density in pregnancy are limited because of the concerns regarding fetal radiation exposure and the confounding effects of altered maternal body composition and weight. Conflicting results have been obtained according to the method of bone density measurement used, the site examined, and the timing during gestation and postpartum. Ultrasonography at the os calcis suggests a decline in bone mineral density through gestation (194,195). Numerous studies of osteoporotic women do not demonstrate a significant association with parity (196), suggesting that any effect on bone metabolism is transient.

Osteoporosis

Transient, focal osteoporosis of the hip is a rare self-limited form of osteoporosis usually found in the third trimester or early postpartum. It generally presents as unilateral or bilateral hip pain, limp, and possible hip fracture. Bone mineral density is diminished at the femoral neck and head, with increased water content in the bone and the marrow. It generally resolves spontaneously within 2 to 6 months. There is no apparent association with the calcitropic hormones. Theories to explain this focal condition include femoral venous stasis secondary to compression by the gravid uterus, fetal pressure on the obturator nerve, marrow hypertrophy, immobilization, viral infection, trauma, and reflex sympathetic dystrophy (181).

Fragility fractures in pregnancy and the puerperium may also be due to preconception osteoporosis and increased bone turnover in pregnancy and lactation. Chronic therapy with heparin, corticosteroids, and anticonvulsants may cause secondary osteoporosis. Low dietary intake of calcium and vitamin D may cause excessive skeletal calcium resorption. Adequate calcium and vitamin D intake and exercise should be instituted when needed. Specific treatment with bisphosphonates or calcitonin is contraindicated because of possible adverse effects on the developing fetus.

Hypercalcemia

Hypercalcemia is generally mild and asymptomatic in pregnancy and is usually found on routine screening or on investigation of hypocalcemia in the neonate (197). Hypercalcemia occurs in 0.1-0.6% of the general population. In the child-bearing years, the most common etiology is hyperparathyroidism.

The diagnosis of mild hyperparathyroidism may be obscured by the pregnancy-induced fall in total calcium, the fall in intact PTH, and the rise in the 24-hour urinary excretion of calcium. In more severe forms of this condition, the risk of adverse pregnancy outcomes rises dramatically. Severe hypercalcemia may cause rapidly progressive anorexia, nausea, vomiting, weakness, fatigue, dehydration, and stupor. This requires emergency treatment as it may be fatal. Acute pancreatitis (182,197-9) may occur at rates 6 times that of the nonpregnant population, with significant risks for both mother and fetus. Patients with persistent vomiting must be hydrated rapidly to prevent worsening of the hypercalcemia from dehydration. As pregnancy tends to ameliorate hypercalcemia with the placental transfer of calcium to the fetus, maternal hypercalcemia may dramatically worsen postpartum (197-9).

Infants of mothers with severe hypercalcemia are at risk for spontaneous abortion (8%), premature birth (10%), stillbirth (2%), severe hypocalcemia with or without tetany (15-25%), and neonatal death (2%) (182,197-9). PTH does not cross the placenta, and the neonatal hypocalcemia is secondary to suppression of the fetal parathyroid glands by the placental transfer of elevated calcium levels, which stops at birth. The parathyroid gland suppression and hypocalcemia is transient, lasting up to 3-5 months, and can be managed with calcium and vitamin D supplements (182,197-9).

Because of the potential hazards to mother and child, all patients with known primary hyperparathyroidism should undergo surgery before conceiving. When hyperparathyroidism is diagnosed during pregnancy, parathyroidectomy is generally well-tolerated by mother and fetus. Of those pregnancies in which the hyperparathyroid mothers were treated expectantly or with oral phosphates, 40% of the neonates developed hypocalcemia. Hypercalcemia discovered late in gestation may be managed with oral phosphate (Fleet's Phospho-Soda, 15-50 cc/day in divided doses) (182,197-9). Calcium levels should be monitored every 2-4 weeks.

Initial therapy for patients with severe hypercalcemia (calcium > 14 mg/dl) includes rehydration with saline. Forced diuresis with furosemide may further increase urinary calcium excretion. However, loop diuretics readily cross the placenta and cause increased fetal urine production and polyhydramnios. Glucocorticoids and calcitonin may also be used, but the safety of bisphosphonates and other agents has not been established in pregnancy.

Hypocalcemia

The most common cause of hypocalcemia is hypoparathyroidism secondary to surgery for thyroid or parathyroid disease. Autoimmune, infiltrative, and idiopathic causes are uncommon. Vitamin D deficiency is very rare. During pregnancy, women with hypoparathyroidism generally have fewer hypocalcemic symptoms, with decreased dependence on supplemental calcitriol to maintain a normal serum calcium (189,200,201). This likely occurs because 1,25-dihydroxyvitamin D levels are less dependent on PTH production in pregnancy, but are also regulated by PTHrP, and possibly prolactin and chorionic somatomammotropin. In late pregnancy, hypercalcemia may occur unless the calcitriol dose is decreased below the prepregnancy level (200,201) This is more pronounced during breastfeeding, likely due to the large secretion of PTHrP at that time (see below).

Maternal hypocalcemia causes fetal hypocalcemia because of an inadequate transfer of calcium to the fetus. This results in fetal hyperparathyroidism with attendant skeletal demineralization, subperiostial bone resorption, osteitis fibrosa cystica and, rarely, death (202). 1,25-dihydroxyvitamin D is the preferred therapy because its rapid action allows precise modulation of serum calcium levels.

Lactation

Breast feeding causes a daily maternal calcium loss of 280-400 mg/day (196). This calcium seems to come primarily from the skeleton, with bone density losses of 1-3% per month, secondary to declining estrogen levels and high PTHrP. Ionized calcium levels increase to the high normal range (203). Phosphate levels may rise above the normal range, with increased renal reabsorption and skeletal resorption (184). PTH is reduced 50% in the first several months postpartum, and rises to above normal after weaning (187,189). Total and free levels of 1,25-dihydroxyvitamin D levels fall to normal within days postpartum (186). As 1,25-dihydroxyvitamin D levels fall to normal, intestinal calcium absorption decreases to the non-pregnant level. PTHrP levels are higher in lactating women than in nonpregnant controls, with a rise after suckling (203,204). PTHrP levels in breast milk may exceed 10,000 times that found in the serum of nonpregnant controls (205,206). PTHrP may regulate mammary development and mammary blood flow (189). It may also contribute to maternal skeletal calcium resorption, renal tubular reabsorption of calcium, and suppression of PTH. PTHrP levels correlate negatively with PTH levels and positively with the ionized calcium levels (181,203) and loss of bone mineral density in lactating women (207). The lactation influence on calcium homeostasis does not occur in women with pseudohypoparathyroidism who have resistance to the amino-terminal actions of PTH and PTHrP. Renal calcium excretion falls to 50 mg/24 hours with the decline in GFR to below prepregnant levels, and with increased tubular reabsorption of calcium.

Rat models reveal increased bone turnover with a 35% loss of bone mineral in 2-3 weeks of lactation. Urinary markers of bone resorption are higher than during pregnancy, and 2- to 3-fold higher than in nonpregnant controls. Bone formation markers are also higher than in pregnancy or the nonpregnant state (189). Bone density at trabecular sites declines at a rate of 1-3% per month, for a total of 3-10% lost within 2-6 months of lactation, with smaller losses at cortical sites (196). This loss correlates with the calcium lost in breast milk (208), and is not prevented by increasing calcium supplementation (209-12). The duration of amenorrhea, which corresponds to reduced estrogen levels and increased intensity of lactation and breast milk calcium losses, correlates positively with bone loss during lactation (207,210-12). The decline in bone density is greater than that seen in women with lower estrogen levels, increased urinary calcium excretion, and suppressed 1,25-dihydroxyvitamin D and PTH, induced by GnRH agonist therapy, who lose 1-4% of their trabecular bone density in 6 months (213). Lactating women have higher estrogen levels, reduced calcium excretion, and normal 1,25-dihydroxyvitamin D levels. PTHrP may be the added mechanism contributing to their higher bone loss at both cortical and trabecular sites. Postweaning, bone density increases by 0.5-2% per month, returning to normal in 3-6 months (196,211). PTH and 1,25-dihydroxyvitamin D levels increase after weaning (214), but the exact mechanism for rapid bone accretion is unstudied.

ADRENAL DISORDERS IN PREGNANCY

Pregnancy modifies adrenal steroid metabolism substantially. In contract to the effects on the hypothalamic-pituitary-adrenal axis, glucocorticoid levels provide a positive feedback on the placental corticosteroid axis. Placental CRH rises several hundred-fold during pregnancy, is extensively protein bound until term, and modulates both maternal and fetal pituitary-adrenal axes and may regulate

parturition (215). Both maternal and placental ACTH levels rise dramatically after 16-20 weeks' gestation (216)(Figure 5), with a final surge in ACTH and plasma cortisol during labor. Despite the increase in the placental hormones, the normal maternal circadian rhythm of ACTH secretion persists throughout pregnancy.

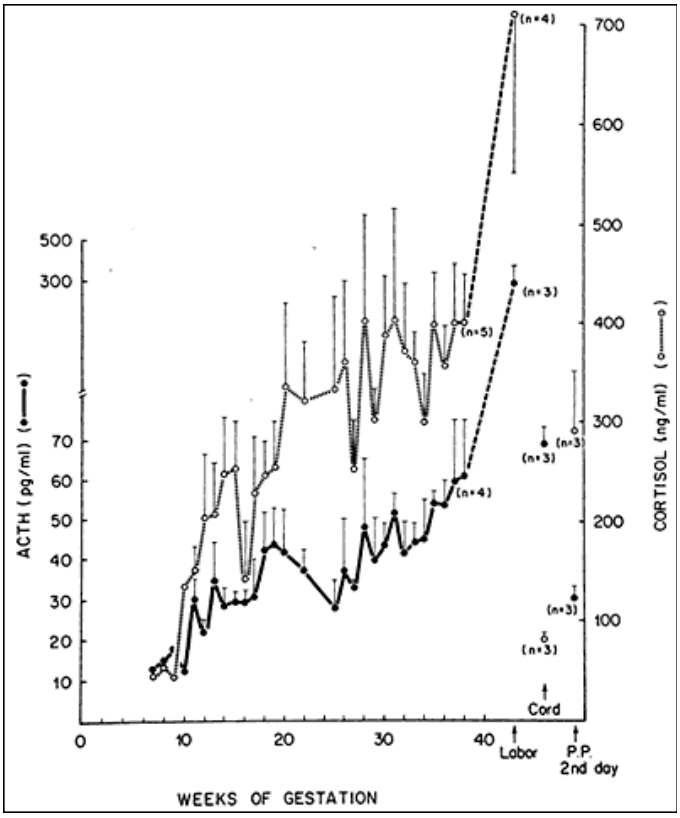

Figure 5.Plasma concentrations of adrenocortiotropic hormone (ACTH) and cortisol during normal pregnancy. Blood samples were obtained from five normal pregnant women weekly at 8:00 to 9:00 AM and from three women during labor and on the second postpartum day. In addition, umbilical cord plasma was obtained 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 adrenocortiotropin and cortisol relationships throughout human pregnancy. AM J Obstet Gynecol 1981;139:416)

The fetoplacental unit has a marked capacity for steroidogenesis. At the same time, maternal cortisol levels increase 2- to 3-fold throughout pregnancy (217,218) with an increase in the size of the maternal zona fasciculate (219). There is an estrogen-stimulated increase in circulating cortisol binding globulin levels, resulting in an increase in total cortisol levels and a decreased rate of cortisol clearance (220). With displacement of cortisol from CBG by progesterone, free cortisol levels also increase (217). Urine free cortisol levels rise 2-3 fold during gestation.

Numerous changes occur in the renin-angiotensin-aldosterone system as well. Plasma renin activity increases 4-fold and plateaus at 20 weeks' gestational age, despite the increase in plasma volume with pregnancy. Angiotensin II levels increase approximately 3-fold by term, although there is resistance to its pressor effects. Plasma mineralocorticoid levels increase 5- to 7-fold during gestation (218,221), but aldosterone secretion continues to respond normally to physiologic stimuli and varies inversely to changes in volume or dietary salt (222). The increase in aldosterone correlates with the pregnancy increase in GFR and in progesterone (223), which competitively inhibits sodium retention by

aldosterone at the distal renal tubules. Progesterone also demonstrates an anti-kaliuretic effect (222), with a report of amelioration of hypokalemia during pregnancy in a woman with primary aldosteronism (224).

Cushing's Syndrome During Pregnancy

Cushing's syndrome is uncommon, with an incidence of 2 in 1,000,000. Just over 100 cases have been reported in pregnancy to date, as fertility is generally reduced by altered gonadotropin secretion in pituitary disease, and increased adrenal androgen secretion in adrenal disease. Approximately 44% are secondary to a pituitary adenoma vs. an 80% rate expected in the nonpregnant woman. Of the remaining, 44% are adrenal adenomas, 11% adrenal carcinomas (225-31), and the remainer a mix of adrenonodular hyperplasia and ectopic ACTH (227). Recently, several cases of pregnancy-dependent Cushing's syndrome have been described, with no intrapartum adrenal steroid abnormalities noted (232,233). The increase in placental CRH rise apparently caused a pregnancy-induced exacerbation and recognition of the hypercortisolism in many cases, with occasional improvement in the symptoms postpartum (226,227).

It may be difficult to diagnose Cushing's syndrome during pregnancy because the typical symptoms of 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. The laboratory evaluation is confounded by the normal pregnancy rise in ACTH and cortisol levels. Normal pregnancy is also associated with "inadequate" suppression during the overnight dexamethasone suppression test (228). The elevated cortisol levels may be suppressed by the high dose dexamethasone suppression test, suggesting Cushing's disease (226). For all forms of Cushing's syndrome, ACTH levels are normal or high, likely from placental ACTH production or from the CRH-stimulated pituitary ACTH production (225-31). Thus, ACTH levels can not be used to distinguish between pituitary and adrenal etiologies.

The hypercortisolism of pregnancy continues to exhibit a normal circadian rhythm. This is absent in all forms of Cushing's syndrome (234). Petrosal sinus sampling has been performed during pregnancy with no ill effects (235), and patients with Cushing's disease apparently have the typical exaggerated ACTH response to CRH (229). CT or MRI are necessary for further characterization of pituitary or adrenal lesions.

Maternal complications of Cushing's syndrome include hypertension, diabetes, myopathy, postoperative wound infection and dehiscence. Fetal mortality of 25% from spontaneous abortion, stillbirth, and prematurity has been observed (225-31). Premature labor is common. The maternal hypercortisolemia may occasionally lead to fetal adrenal suppression (236), and the neonate should be tested for this and treated prophylactically until the results are known.

Rates of fetal loss and premature labor decrease, though are still increased, in patients who are treated during pregnancy (225,228). Medical therapy is generally ineffective (227,228,231), though metyrapone has proved efficacious in a few patients. Adrenal surgery may be performed through a flank incision or by laparoscopy. Because of the high rate of adrenal carcinoma, early surgery may improve the poor prognosis. Transsphenoidal surgery has also been used successfully (226). The risks of surgery to both mother and fetus are outweighed by the benefits of appropriately treating the Cushing's syndrome.

Adrenal Insufficiency

Primary adrenal insufficiency rarely presents in pregnancy (237). Secondary adrenal insufficiency, from pituitary neoplasms or glucocorticoid supression 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, and increased pigmentation. Addisonian hyperpigmentation may be distinguished from chloasma of pregnancy by its presence on the mucous membranes, on extensor surfaces, and over non-exposed areas. Weight loss together with these symptoms should prompt a clinical evaluation. If unrecognized, adrenal crisis may ensue at times of stress, such as a urinary tract infection or during labor (237). Fetal cortisol production may be protective, shielding the mother from severe adrenal insufficiency until postpartum (238).

The fetoplacental unit largely controls its own steroid milieu, so maternal adrenal insufficiency generally causes no problems with fetal development. Maternal antiadrenal autoantibodies may cross the placenta, but usually not in sufficient quantities to cause fetal or neonatal adrenal insufficiency (239). Although Osler observed intrauterine fetal growth restriction in offspring of women with Addison's disease (240), this observation has not been supported in most subsequent case series.

Adrenal insufficiency is associated with laboratory findings of hyponatremia, hyperkalemia, hypoglycemia, eosinophilia, and lymphocytosis. Plasma cortisol levels may fall in the normal "nonpregnant" range due to the increase in CBG concentrations, but will not be appropriately elevated for the stage of pregnancy. With primary adrenal insufficiency, ACTH levels will be elevated. 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.

Despite the normal increase in plasma cortisol during pregnancy, maternal replacement doses of corticosteroids usually are not different from those required in the non-pregnant state. Higher doses are needed at times of stress, such as during the course of "morning sickness" or during labor and delivery. Mineralocorticoid replacement requirements usually do not change during gestation, though some clinicians have decreased fludrocortisone intake in the third trimester in an attempt to treat Addisonian patients who develop preeclampsia (241).

Patients who have received glucocorticoids as antiinflammatory therapy are presumed to have adrenal axis suppression for at least one year (242). 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 syndrome, and their offspring are at risk for transient adrenal insufficiency. Although prednisone readily crosses the placenta (243), the maternal:fetal gradient is higher than with other available agents (244,245). Corticosteroid therapy during pregnancy is generally safe and suppression of neonatal adrenal function is uncommon (246). Glucocorticoid therapy during lactation is also safe, as minimal amounts of these medications are passed into breast milk.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia is 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 deficiency, seen in more than 90% of the CAH cases in pregnancy (247,248). 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 (248-50). The spontaneous abortion rate is twice that in the normal population (251), and congenital anomalies are more frequent. Cephalopelvic disproportion from an android pelvis may occur, sometimes complicated by the previous reconstructive surgery (252,253). 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 with glucocorticoid therapy (251). Often, however, ovulation induction is required to enable these patients to conceive children.

Fetal risk depends on the carrier status of the father. Unfortunately, ACTH stimulation testing to measure 17-OH progesterone demonstrates overlap between heterozygotes for CAH and the normal population (254). Virilization is not seen in the female fetus with nonclassic 21-hydroxylase deficiency (255), but occurs in a fetus with classic 21-hydroxylase deficiency unless fetal adrenal androgen production is adequately suppressed. Dexamethasone most readily crosses the placenta as it is not bound to CBG and is not metabolized by placental 11 b-hydroxysteroid dehydrogenase. It is commonly used at doses of 20 mg/kg maternal body weight per day to a maximum of 1.5 mg daily in 3 divided doses beginning before the 9th week of gestation (248,249). Maternal plasma and/or urinary estriol levels reflect fetal adrenal synthesis and are monitored to assess efficacy. Maternal cortisol and DHEA-S will determine maternal adrenal suppression. There is little effect on maternal 17-OH progesterone with therapy. 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.(247,249,256) The test itself is associated with a 1-4% risk of miscarriage and 2% risk of limb defects. 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.(256) 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 (249,257). 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 (257). Treatment by the 9th week of gestation is very effective in reducing the risk of virilization in the affected female fetus (249).

Primary Hyperaldosteronism During Pregnancy

Primary hyperaldosteronism rarely has been reported in pregnancy (258-61), and is most often caused by an adrenal adenoma. The elevated aldosterone levels found in patients are similar to those in normal pregnant women, but the plasma renin activity is suppressed (258-61).

Salt loading tests may be used to diagnose hyperaldosteronism. If baseline and suppression testing are equivocal, or radiologic scanning does not suggest unilateral disease, patients may be treated medically until delivery to allow more definitive investigations (260). Spironolactone, the usual nonpregnant therapy, is contraindicated in pregnancy as it crosses the placenta and is a potent antiandrogen which can cause ambiguous genitalia in a male fetus (261). Surgical therapy may be delayed until postpartum if hypertension can be controlled with agents safe in pregnancy, such as methyldopa, labetolol, and amiloride. As noted above, the hypokalemia may ameliorate in pregnancy because of the antikaliuretic effect of progesterone. Both hypertension and hypokalemia may exacerbate postpartum due to removal of the progesterone effect (262,263).

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 (264). 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. Extra-adrenal tumors which occur in 10%, such as in the organ of Zuckerkandl at the aortic bifucation, are particularly prone to hypertensive episodes with changes in position, uterine contractions, fetal movement, and Valsalva maneuvers (265). Unrecognized pheochromocytoma is associated with a maternal mortality rate of 50% at induction of anesthesia or during labor (266,267).

There is minimal placental transfer of catecholamines (268,269), likely due to high placental concentrations of catechol-O-methyltransferase and monoamine oxidase (268,270). Adverse fetal effects such as hypoxia are a result of catecholamine-induced uteroplacental vasoconstriction and placental insufficiency (271-3), and of maternal hypertension, hypotension, or vascular collapse.

As always, diagnosis of pheochromocytoma requires an index of suspicion. Preconception screening of families known to have MEN 2 with RET proto-oncogene is essential. Patients with MEN 2A are more likely to have paroxysmal hypertension and have higher rates of bilateral neoplasms than those with sporadic pheochromocytoma (274). Examination for associated evidence for MEN2 may be difficult in pregnancy, with the expected pregnancy alterations in calcium, PTH, and calcitonin. Clinical thyroid examination should be done, with fine needle aspiration of any nodules so that overt medullary carcinoma can be treated immediately. Individuals with neurofibromatosis (275), von Hipple-Lindau disease (276), or retinal angiomatosis should also be screened for pheochromocytomas prior to pregnancy.

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 anxiety, headaches, palpitations, 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 (272).

Laboratory diagnosis of pheochromocytoma is unchanged from the nonpregnant state as calecholamine metabolism is not altered by pregnancy per se (277). If possible, methyldopa and labetolol should be discontinued prior to the investigation as these agents may interfere with the quantification of the catecholamines and VMA (278). Provocative testing should be avoided because of the increased risk of maternal and fetal mortality. Tumor localization with MRI, with high intensity signals noted on T2-weighted images, provides the best sensitivity without fetal exposure to ionizing radiation. Metaiodobenzylguanidine scans are contraindicated in pregnancy, but may be necessary if other tumor localization methods fail.

Differentiation from preeclampsia is generally simple. The edema, proteinuria, and hyperuricemia found in preeclampsia are absent in pheochromocytoma. Plasma and urinary catecholamines may be modestly elevated in preeclampsia and other serious pregnancy complications requiring hospitalization, though they remain normal in mild preeclampsia and pregnancy-induced hypertension (279). Catecholamine levels are 2- to 4-times normal after an eclamptic seizure (280).

Initial medical management involves a-blockade with phenoxybenzamine, phentolamine, prazocin, 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 (272). Placental transfer of phenoxybenzamine occurs (281), but is generally safe (282,283). If hypertension remains inadequately

controlled, metyrosine has also been used successfully to reduce catecholamine synthesis in a pregnancy complicated by malignant pheochromocytoma (284), but may potentially adversely affect the fetus. Beta blockade is reserved for treating maternal tachycardia or arrhythmias which persists after full a-blockade and volume repletion. Beta blockers may be associated with fetal bradycardia and with intrauterine fetal growth restriction, when used early in pregnancy (277,285). 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 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 a-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 has been described in the 2nd trimester of pregnancy (286). 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 (287), 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 (288). Severe maternal hypertension may lead to placental ischemia and fetal hypoxia. However in the well-blocked patient, vaginal delivery may be possible with intensive pain management with epidural anesthesia and avoidance of mechanical compression, employing techniques of passive descent and instrumental delivery.

There is no available information regarding the impact of maternal use of phenoxybenzamine on the nursing neonate.

OBESITY IN PREGNANCY

Recent estimates reveal that in the US 18.5-38.3% of pregnant women are obese (289), a 30% increase in the last 10 years. Pregnancy complicated by maternal overweight (BMI 25-30 kg/m2) and obesity (BMI > 30 kg/m2) is associated with an increased risk for diabetes mellitus, hypertensive disorders, urinary tract infections, thrombophlebitis, and operative delivery (289-94). In turn, an operative delivery is associated with increased anesthetic and postoperative complications such as wound infection, dehiscence, and thromboembolic events. Respiratory complications include decreased lung volume related to chest wall and abdominal fat, mild hypoxia (295), and Pickwickian syndrome with hypoventilation and hypercapnia. These respiratory complications may be exacerbated by the expanding abdominal contents in pregnancy. Sleep disordered breathing, with increases in apnea/hypopnea, oxygen desaturation, and snoring times, is also more common in pregnancies complicated by obesity (296). This may predispose to intrauterine fetal growth restriction in the offspring, and hypertensive disorders and increased cardiovascular risk in the mothers.

Maternal overweight and obesity are associated with multiple complications in the offspring. These include macrosomia unrelated to gestational diabetes mellitus (289-91,297-9), intrauterine fetal growth restriction, congenital anomalies, and stillbirth. At one year, infants of obese mothers remain

significantly more obese than infants of nonobese mothers (293). There is a clear association between maternal obesity and spina bifida and other neural tube defects in the offspring (289,298). Several studies have also demonstrated an increase in cardiac defects in pregnancies complicated by obesity, with no reduction in rate when supplements are used (289,299). Overall, there is an increase in orofacial clefts, club foot, cardiac septal defects, and abdominal wall defects. Craniofacial and musculoskeletal defects are increased 3-fold when pregnancy is complicated by both obesity and diabetes mellitus. Stillbirth increases 2-fold in the presence of maternal obesity. Other delivery complications include meconium, late decelerations, and shoulder dystocia (294).

Weight gain guidelines have been established by the Institute of Medicine (300) (Table 3), and are discussed in the Diabetes in Pregnancy section below. Obese mothers are able to mobilize nutrients for adequate fetal growth without significant weight gain in pregnancy. Obese mothers who lose weight in pregnancy still deliver offspring with birth weights higher than the birth weights of term infants of normal weight mothers who gain the recommended amount of weight (301). Excessive weight gain in pregnancy has adverse impact on maternal complications, fetal/neonatal complications, and results in higher long-term maternal weight (302).

TABLE 3. Recommended Weight Gain for Pregnant Women by Prepregnancy Body Mass Index (BMI)

		Recommended weight gain	Weight gain/trimester	
Category	BMI (kg/m^2)	kg [lbs]	1st Trimester	2nd & 3rd Trimesters
Underweight	<19.8	12.5-18 [28-40]	2.3 [5]	0.5 [1]/week
Normal weight	19.8-26.0	11.5-16 [25-35]	1.6 [3.5]	0.4 [1]/week
Overweight	26.0-29.0	7-11.5 [15-25]	0.9 [2]	0.3 [0.7]/week
Severely obese	>29.0	~ 6.8 [15]*	—	—

* The recommended weight gain for morbidly obese women is at least 6.0 kg (accounting for the products of conceptus). This recognizes that many gain less weight with good pregnancy outcomes. Adapted from the recommendations of the Subcommittee on Nutritional Status and Weight Gain During Pregnancy, Food and Nutrition Board, Institute of Medicine: Nutrition During Pregnancy. National Academy Press, Washington, D.C., 1990.

DIABETES IN PREGNANCY

Insulin is the primary anabolic hormone of pregnancy. Early in gestation, progesterone in concert with estrogen has a direct tropic effect on the pancreatic b cells. Postprandial insulin concentrations rise in the presence of normal glucose tolerance, and contribute to an anabolic process of accretion of maternal subcutaneous fat and adipocyte enlargement. Animal models also demonstrate hepatic glycogen accumulation and an increase in lean body mass.

Insulin sensitivity appears to decline starting after 12-14 weeks of gestation, with progression to severe insulin resistance during the 3rd trimester (303), under the influence of rising placental hormones including human chorionic somatomammotropin, placental growth hormone variant, cortisol, prolactin, and progesterone. Marked hyperinsulinemia creates an anabolic state of maternal fuel storage during the fed state, which is offset by the catabolic effects of these insulin antagonists in the fasted state. Insulin resistance at the skeletal muscle and hepatocyte prolongs the accessibility of nutrients within the plasma compartment after feeding to allow a rapid transfer of stored nutrients to the fetal compartment in the second half of gestation, corresponding with the time of a geometric increase in the

fetal-placental mass (304). This system is disturbed when insulin secretion is inadequate, as with diabetes mellitus. All of the plasma substrates are affected, including fasting and postprandial glucose, FFA's, triglycerides, cholesterol, and branched-chain amino acids (305,306). These metabolic disturbances provide increased fuels to the fetal compartment, resulting in fetal hyperinsulinemia which mediates the adverse effects of diabetes mellitus on the offspring (307-10). The timing of the metabolic insult predicts the adverse outcome ("fuel-mediated teratogenesis"), with both perinatal and long-term consequences (307,308).

Complications

Disturbances in maternal metabolism at the time of conception increases the risk of congenital anomalies and spontaneous abortion (307,309,311). In patients with fair to good control at conception, the incidence of birth defects is approximately 5% (312,313), two times greater than that in the non-diabetic population. Further worsening of glycemic control is associated with dramatic increases in malformation rates (312). The risk of spontaneous abortion is directly proportional to the glycohemoglobin level in early pregnancy (312). Optimization of control prior to conception may reduce the congenital malformation rate to that of the non-diabetic population (314,315).

Macrosomia (birth weight above the 90th percentile for gestational age) is a frequent complication of both pregestational and gestational diabetes mellitus. Neonates may have almost twice as much adiposity as offspring of normal mothers (316), proportional to maternal metabolic control (317). The truncal obesity and asymmetric fetal growth associated with diabetes mellitus increase the risk of shoulder dystocia, birth trauma, and operative delivery. Fetal islet cell function, with b cell hypertrophy and hyperplasia and amniotic fluid hyperinsulinemia, is associated with maternal metabolic control, particularly that found in the second trimester (318,319). Once b cell hyperplasia occurs, the subsequent fetal hyperinsulinemia may further augment fetal growth in the absence of elevated maternal nutrients (318). Maternal postload glucose peaks may be blunted by exaggerated fetal glucose siphoning, which may cause false negative oral glucose tolerance test results (320). Early diagnosis and intervention are therefore critical to avoid complications in the offspring. Intrauterine fetal growth restriction is now rarely seen except in pregnancies complicated by hypertension or nephropathy (321).

There is an increase in the prevalence of obesity in the offspring of diabetic mothers (322). A direct correlation between maternal metabolic control and the development of childhood and adolescent obesity was seen in the Pima Indian study (323,324). Amniotic fluid insulin levels as a measure of stimulated fetal islet function also correlate positively with childhood obesity.(325).

Both animal and human studies demonstrate that disturbances in islet function during intrauterine life predispose the individual to impaired glucose tolerance (322). Pettitt et al examined offspring born to women from 3 risk groups: those who had diabetes during pregnancy ("diabetic"), those with a genetic predisposition to diabetes who had normal glucose tolerance during pregnancy but developed diabetes subsequently ("prediabetic"), and those who never developed diabetes ("nondiabetic"). Controlling for other confounding variables, Type 2 diabetes mellitus was present in 45.5% of those age 20-24 who were offspring of diabetic pregnancies, 8.6% of offspring of prediabetic mothers, and 1.4% of offspring of nondiabetic mothers.(326). Amniotic fluid insulin levels as a measure of fetal hyperinsulinemia are a strong predictor of impaired glucose tolerance in adolescence (327). These studies demonstrate the profound impact of an adverse metabolic environment on a genetic predisposition.

Diagnosis of Gestational Diabetes Mellitus

According to NHANES III, 2.9-17.3% of nonpregnant women age 20-49 have impaired glucose

tolerance or diabetes mellitus (328). Pregestational diabetes mellitus complicates up to 0.5% of pregnancies (329), although the prevalence of diabetes in younger age groups has dramatically increased in the last 10 years. Gestational diabetes mellitus (GDM), defined as "glucose intolerance with onset or first recognition during pregnancy," occurs in approximately 4% of pregnancies, with higher rates in at risk populations (330,331). The diagnosis does not exclude the possibility that unrecognized diabetes predated the pregnancy. Patients with GDM demonstrate features found in patients with Type 2 diabetes mellitus, including attenuated first phase and subsequent insulin release, adjusted for the level of insulin resistance (332,333). Therefore, the progressive insulin resistance of pregnancy reveals women at high risk for the development of Type 2 diabetes mellitus.

Women with GDM are generally asymptomatic, and detection requires an active screening program (Table 4). Low risk individuals, who do not need to be screened, include women with all of the following characteristics: member of a racial/ethnic group with a low prevalence of GDM; age < 25 years; normal weight (BMI < 25 kg/m2); no family history of diabetes; and no personal history of abnormal glucose metabolism or poor obstetric outcome. Those at particularly high risk for developing GDM (marked obesity, strong family history of Type 2 diabetes mellitus, personal history of GDM, glucose intolerance, or glucosuria) should be screened as soon as they present pregnant to allow early intervention (334). If GDM is not found, testing should be repeated at 24-28 weeks or at any time the patient develops symptoms suggestive of hyperglycemia. All others should be screened at 24-28 weeks' gestational age. The current recommendation is a 50 gram oral glucose challenge test without regard to the time of day or time of the last meal (335). Women with a one hour plasma glucose value > 140 mg/dl (7.8 mmol/L) require definitive evaluation with an oral glucose tolerance test. This involves approximately 14-18.5% of pregnant women,(330) with a sensitivity of 79% and a specificity of 87%. Decreasing the screening threshold to 130 mg/dl (7.2 mmol/L), increases the need for oral glucose tolerance tests to 20-25% of all pregnant women, but also increases the sensitivity to more than 90%. Blood glucose meters are inadequate for the screening process as they carry an intratest variability of 10-15% (334,336).

TABLE 4. Screening Strategy for the Detection of GDM

GDM risk assessment — Should be ascertained at the first prenatal visit.

Low risk	Blood glucose testing is not routinely required if all of the following characteristics are present: • Member of an ethnic group with a low prevalence of GDM • No known diabetes in first degree relatives • Age < 25 years • Weight normal before pregnancy (BMI < 26 kg/m2) • No history of abnormal glucose metabolism • No history of poor obstetric outcome
Average risk	Defined as a patient outside one or more of the above characteristics.Perform blood glucose testing at 24-28 weeks using either: • Two step procedure: 50 gm glucose challenge test (GCT)* followed by a diagnostic oral glucose tolerance test in those meeting the threshold value in the GCT. • One step procedure: Diagnostic oral glucose tolerance test performed on all

subjects.

Defined as a patient with one or more of the following characteristics:

- marked obesity (BMI >40 kg/m2)
- strong family history of Type 2 diabetes mellitus
- personal history of GDM, glucose intolerance, or glucosuria

High risk

Perform blood glucose testing as soon as feasible, using the procedures described above.

- If GDM is not diagnosed, blood glucose testing should be repeated at 24-28 weeks, or at any time a patient has symptoms or signs that are suggestive of hyperglycemia.

* 50 gram oral glucose load administered without regard to time of day or time of last meal. Venous plasma glucose is measured 1 hour later. A value of > 140 mg/dl [7.8 mmol/L] indicates the need for a full diagnostic glucose tolerance test.Adapted and reprinted with permission by Metzger BE: Summary and recommendations of the Fourth International Workshop Conference on Gestational Diabetes Mellitus. Diabetes Care 21 (Suppl2): B161, 1998.

A positive screening test is followed by a 100-gram oral glucose tolerance test. The original O'Sullivan and Mahan criteria for the diagnosis of GDM were developed to identify a population of pregnant women at high risk for the subsequent development of diabetes mellitus (337). Later modifications to the criteria were based on alterations in the glucose assay techniques. The current Carpenter and Coustan criteria (2 values at or above: fasting glucose 95 mg/dl, 1-hour 180 mg/dl, 2-hour 155 mg/dl, 3-hour 140 mg/dl) were adopted by the American Diabetes Association (335) because of evidence of perinatal morbidities similar to those found in pregnancies diagnosed with the earlier NDDG criteria (338-40). An international study funded by the NIH is currently underway to identify criteria using a 2-hour 75 gram glucose tolerance test to diagnose GDM based on perinatal outcome measures.

Maternal Complications of Pregestational Diabetes Mellitus

Diabetes in pregnancy is classified based on the severity of the metabolic disturbance and the presence and severity of maternal microvascular, neurologic, and macrovascular complications. These identify perinatal risk. In addition, pregnancy may alter the progression of these complications. Baseline retinopathic, renal, and neurologic function should be determined. Those identified with complications should be counseled regarding their perinatal risk and undergo intensive monitoring throughout pregnancy and postpartum using a team approach of specialists.

Retinopathy may progress during pregnancy secondary to poor glycemic control prior to pregnancy, rapid improvement in control during pregnancy, and concomitant hypertension (341,342). The Diabetes Control and Complications Trial (DCCT) demontrated that pregnancy itself adds independently to the risk of retinopathy progression (343). Patients with diabetes lack the autoregulation of retinal vessel constriction which normally protects the retina from the hyperdynamic changes of pregnancy (344). In addition, the potent angiogenic factor, fibroblast growth factor-2, is elevated in the second and third trimesters and correlate with glycohemoglobin levels (345). Retinopathy may continue to progress into the postpartum period (343,344,346), before it regresses.

Patients with diabetes mellitus have a four-fold increased risk of pregnancy-induced hypertension or preeclampsia (347), which may accelerate nephropathy. Other factors which increase the risk of

nephropathy progression include pregnancy-induced glomerular hyperfiltration, increased transmission of systemic pressure to the glomerulus in the presence of hypertension, increase in urinary tract infections, vesicoureteral reflux and physiological hydronephrosis, and inability to use ACE inhibitor therapy in pregnancy secondary to risk of fetal anephrism. Patients with mild diabetic nephropathy (microalbuminuria, proteinuria, and creatinine <1.4 mg/dl) generally exhibit a transient worsening during pregnancy (348,349). Patients with more severe degrees of nephropathy may have an accelerated decline in renal function with pregnancy (350,351).

The prevalence of diabetic neuropathy increases with the duration of diabetes mellitus, with rates up to 50% after 25 years. Autonomic neuropathy may adversely impact on maternal morbidity and pregnancy outcome (352,353). The irregular gastric emptying of gastroparesis causes erratic blood sugar control from a mismatch of insulin administration with the nutrient delivery to the small intestine. Postprandial emesis may be exacerbated by the "morning sickness" of early pregnancy and later by the mechanical compression of the stomach by an enlarging uterus. This can lead to intractable vomiting with maternal and fetal malnutrition, hypoalbuminemia, dehydration, and maternal aspiration. Incomplete bladder emptying may predispose to recurrent urinary tract infections and worsening renal function. Individuals with orthostatic hypotension, an infrequent finding in diabetic pregnancies, may have symptomatic improvement with the volume expansion of pregnancy (354) or may worsen with the normal pregnancy decline in blood pressure.

Macrovascular disease may progress in pregnancy. Cholesterol and triglyceride levels increase during gestation (see below). Diabetes is a risk factor for pregnancy-induced hypertension or preeclampsia (355,356). Microvascular disease may further increase the risk. The marked fluid shifts which occur postpartum increase the risk of myocardial infarction and congestive heart failure in women with coronary artery disease (357). Women who have had diabetes for more than 25 years should undergo stress testing prior to conception to allow intervention at that time if necessary.

Management

Monitoring

The goal of therapy is to maintain normal maternal pre- and postprandial glucose levels to avoid the immediate and long-term risks to the offspring. The trade-off of tight control is an increased risk for hypoglycemia. Hypoglycemia is frequent in patients with Type 1 diabetes mellitus, particularly in the first trimester (358), often during nocturnal hours. Intensive self-glucose monitoring is essential.

Patients with GDM and pregestational diabetes should monitor fasting urinary ketones to assess the adequacy of their nutritional intake and determine potential metabolic decompensation early in its development. Those with GDM on dietary therapy monitor fasting and one- or two-hour postprandial glucose levels to determine adequacy of therapy. Patients requiring insulin therapy may add premeal and bedtime glucose levels to facilitate insulin adjustment. Postmeal glucose levels demonstrate better correlation with birthweight than premeal glucose levels, reflecting fuel delivery to the fetus (359). Ongoing postprandial hyperglycemia despite normal preprandial glucose levels requires adjustment of meal size and frequency.

Diet

Diet is the cornerstone of therapy. Dietary prescriptions are individualized for ethnic and personal preferences, activity level, and prepregnancy BMI. The Institute of Medicine has published optimal weight gain guidelines during pregnancy based on associations between weight gain in pregnancy and perinatal morbidity (300)(Table 3, see above). Recommended weight gain is inversely proportional to maternal adiposity. A diet of 30-32 kcal/kg ideal body weight is prescribed in the first trimester, with an

increase to 35-38 kcal/kg ideal body weight in the second trimester, with adjustments to attain the desired weight gain. The calories include 50-55% carbohydrate, <30% fat, and 1.0-1.5 g/kg ideal body weight protein. Intake is spread throughout the day with the addition of a bedtime snack to avoid the predilection for accelerated starvation (360). Carbohydrate intake is limited at breakfast because of the increased insulin resistance at that time. Isocaloric dietary modifications which increase fat to reduce postprandial hyperglycemia (361) have undetermined impact on other maternal fuels, and the impact on the long-term outcome of the offspring has not been assessed. High fat diets are associated with altered vascular reactivity in the offspring of a rat model (362,363). Periconception supplementation with folic acid (0.8 mg/day) is recommended for diabetics, as it is for all women, to reduce the increased risk of neural tube defects.

Insulin

Patients with Type 1 diabetes mellitus lack endogenous insulin are deficient in some of the counterregulatory hormones and are predisposed to wide glucose excursions. As noted previously, intensive insulin therapy should be instituted prior to conception to reduce neonatal malformations and other morbidity. If patients with pregestational diabetes not undergoing intensive insulin therapy and under poor control are found to be pregnant, they should be hospitalized immediately for institution of intensive insulin therapy. Details of intensive therapy are beyond the scope of this discussion. This type of treatment generally involves giving basal insulin and premeal boluses of short-acting insulin either as multiple daily injections or using the insulin pump, with adjustments of insulin doses based upon pre- and post-meal glucose levels, meal size, and activity levels. Intensive insulin therapy must be closely monitored. Women with optimal glucose control at conception demonstrate little change in insulin requirement in the first trimester, with a modest decline at 10-14 weeks' gestation. Insulin requirements subsequently increase substantially to plateau late in the third trimester at total daily doses up to 3-fold above prepregnancy levels, and may decline modestly near term. A marked decline in insulin requirements suggests placental or renal dysfunction and warrants intensive maternal and fetal assessments. Patients with Type 2 diabetes mellitus should be treated with insulin prior to conception or at the first prenatal visit in an unplanned pregnancy.

There is no consensus regarding the level at which insulin therapy should be instituted in patients with GDM. Patients with fasting glucose > 105 mg/dl should receive insulin therapy. Rates of macrosomia have been reduced in settings where most of the patients with fasting glucose level < 105 mg/dl have received insulin therapy.(364) Attempts to use fetal ultrasound measurements of macrosomia to target patients for insulin intervention have resulted in a reduction in neonatal macrosomia (365-7), but may not reduce the long-term risks of obesity and glucose intolerance as these may occur in offspring with normal birth weights (324). Generally accepted targets of therapy are a fasting glucose <90-94 mg/dl, 1-hour postprandial glucose < 140 mg/dl, and 2-hour postprandial glucose < 120 mg/dl. Insulin doses of 0.5-2.0 units/kg are generally required to attain these goals.

Exercise

Exercise improves insulin sensitivity and peripheral glucose uptake. Moderate exercise has been used safely to improve glycemic control,(368,369) although previously inactive individuals may have an increased risk for uterine contractility, prematurity, fetal growth restriction, and fetal bradycardia (370).

Oral Agents

Oral agents have not been approved for use in pregnancy, as their safety has not been established during organogenesis (371,372). Adequacy of glycemic control to avoid short- and long-term complications must also be established. Studies are now underway to examine the use of oral agents in patients with GDM who fail dietary therapy (373).

Peripartum

The goal of therapy in the peripartum period is to maintain glucoses in the 70-120 mg/dl range. Oral carbohydrate is restricted, and intravenous dextrose is administered at rates of 5-8 g/hour. Glucose is monitored every 1 to 4 hours, and insulin is administered as necessary either as an intravenous infusion (0.01-0.04 U/kg actual body weight/hour)(374) or by subcutaneous injection of short-acting insulin every 3-6 hours (375). Labor may enhance glucose utilization (376), which may be modulated by the use of an epidural anesthetic. Insulin therapy to maintain euglycemia in labor is rarely required in GDM and may not be needed in many individuals with Type 2 diabetes mellitus.

Insulin requirements decline dramatically postpartum by up to 50-90%. Over the next few weeks, insulin requirements generally return to prepregnancy levels.

Breastfeeding

Breastfeeding increases the caloric requirements by 400-500 kcal/day. The benefits of breastfeeding are similar for the offspring of nondiabetic and diabetic women and should be encouraged. In addition, the epidemiologic study in the Pima Indians suggests additional long-term benefit in reducing the risk of developing Type 2 diabetes in this population (377). A recent study suggests that maternal hyperglycemia during breastfeeding may increase the risk of obesity in the offspring (378). Glycemic control therefore should not be neglected. Women with Type 2 diabetes who wish to breastfeed but require pharmacologic intervention postpartum are continued on insulin therapy until the child is weaned. Sulfonylureas may be secreted in breast milk and can cause hypoglycemia in the infant. The effects of other oral agents given to the mother during lactation on the neonate have not been determined and therefore should be avoided.

Postpartum Management

Postpartum reclassification of women with GDM is essential. An oral glucose tolerance test is performed at approximately 6 weeks' postpartum for reclassification, followed by postpartum counseling. Those with a family history of diabetes mellitus, non-Caucasian racial origin, obesity, early gestational age at diagnosis, and more marked hyperglycemia at diagnosis are at highest risk for progression to diabetes mellitus postpartum (379-81). A number of interventions have now been shown to reduce the risk of progression to diabetes in high-risk populations, especially those with impaired glucose tolerance. The Diabetes Prevention Program (DPP) demonstrated a 58% reduction in the progression to diabetes with diet, exercise, and a 7-10% weight loss (382). Pharmacologic therapy with metformin in the DPP provides a 31% reduction in diabetes (382), while troglitazone therapy demonstrated a 70% reduction in diabetes in a placebo-controlled trial in women with impaired glucose tolerance with prior GDM (383). Patients also may exhibit other features of the insulin resistance syndrome, such as hypertension, elevated triglycerides, and low HDL-C (384). These individuals may be at increased risk for premature vascular disease and should be monitored regularly and treated aggressively.

Patients should receive continuing follow-up with annual glucose testing and re-evaluation prior to any future pregnancies. Therapy should be initiated prior to conception to avoid the increased risk of congenital anomalies. Those with normal glucose tolerance before pregnancy should also be evaluated early in gestation, and if normal, again at the usual time of 24-28 weeks gestation. GDM recurs in more than half of subsequent pregnancies (385,386), though the risk of recurrence might be reduced by interpregnancy intervention (386).

Adequate contraception is vital to facilitate pregnancy planning. Low-dose oral contraceptives provide acceptable protection and do not exacerbate hyperlipidemia or glucose intolerance (387). Preparations containing the progestins norethindrone or desogestrel have also shown minimal metabolic effect. Patients treated with the thiazolidinedione derivatives such as pioglitazone need to be aware of possible loss of efficacy of contraception from low dose oral contraceptives.

LIPID DISORDERS IN PREGNANCY

Alterations in lipid metabolism in pregnancy favor fuel production for the developing fetus. Adipose tissue lipolysis increases, elevating the substrates for triglyceride synthesis, while lipoprotein lipase activity declines during the third trimester, reducing triglyceride clearance (388). The triglyceride:cholesterol ratio increases in all of the lipoprotein fractions with the first trimester decline in hepatic lipase (388). There is a consequent increase in triglycerides from the end of the first trimester, approaching levels 3 times greater than prepregnancy levels by term. This increase correlates with the rise in estrogen levels in pregnancy. This fat mobilization provides fuel for fetal development, and midtrimester triglyceride levels correlate with neonatal weight, independent of maternal glucose levels and obesity (389).

Lipoprotein apoB levels increase through gestation (390), and total and LDL cholesterol levels rise during the first trimester to peak at 150% above prepregnancy levels (391). HDL cholesterol increases 25-45% in the first trimester, then declines to near prepregnancy levels by term (391). The increase is secondary to elevations in HDL2b, with a decline in the HDL3a and HDL3b subfractions. The increase in triglycerides and fall in HDL are exaggerated when diabetes complicates pregnancy (391-3).

Postpartum, it generally takes months for the lipids to reach their prepregnancy levels, despite an initial fall in the triglycerides and cholesterol (391).

Patients with preexisting lipid abnormalities must discontinue pharmacologic therapy for pregnancy. HMG Co-A reductase inhibitors are contraindicated in pregnancy as they may impair fetal neural lipid synthesis. Niacin may cause hepatic toxicity and worsen insulin resistance, and its safety in pregnancy has not been studied. The fibrates have not been studied in pregnancy, although gemfibrozil is tumorigenic in rats. Bile acid binding resins are not absorbed. They may be used in pregnancy, but care should be taken to avoid fat-soluble vitamin deficiency.

Severe hypertriglyceridemia may occur in gestation in patients with lipoprotein lipase deficiency (394). Eruptive xanthomas have been seen in one patient during pregnancy (395). Of greater concern is the risk for pancreatitis and ARDS, with a 20% maternal mortality rate (394). Prevention requires drastic dietary fat restrictions. Total parenteral nutrition with no lipid component, or plasma exchange or lipoprotein apheresis may be used (394,396-8).

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