

The Hypothalamic-Pituitary-Adrenal Axis in Pregnancy: Challenges in Disease Detection and Treatment

John R. Lindsay and Lynnette K. Nieman

Reproductive Biology and Medicine Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892-1109

Pregnancy dramatically affects the hypothalamic-pituitary-adrenal axis leading to increased circulating cortisol and ACTH levels during gestation, reaching values in the range seen in Cushing's syndrome (CS). The cause(s) of increased ACTH may include placental synthesis and release of biologically active CRH and ACTH, pituitary desensitization to cortisol feedback, or enhanced pituitary responses to corticotropin-releasing factors. In this context, challenges in diagnosis and management of disorders of the hypothalamic-pituitary-adrenal axis in pregnancy are discussed.

CS in pregnancy is uncommon and is associated with fetal morbidity and mortality. The diagnosis may be missed because of overlapping clinical and biochemical features in

pregnancy. The proportion of patients with primary adrenal causes of CS is increased in pregnancy. CRH stimulation testing and inferior petrosal sinus sampling can identify patients with Cushing's disease. Surgery is a safe option for treatment in the second trimester; otherwise medical therapy may be used.

Women with known adrenal insufficiency that is appropriately treated can expect to have uneventful pregnancies. Whereas a fetal/placental source of cortisol may mitigate crisis during gestation, unrecognized adrenal insufficiency may lead to maternal or fetal demise either during gestation or in the puerperium. Appropriate treatment and management of labor are reviewed. (*Endocrine Reviews* 26: 775–799, 2005)

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I. Introduction

NORMAL HUMAN GESTATION dramatically affects the maternal hypothalamic-pituitary-adrenal (HPA) axis. Increasing placental production of estrogen stimulates hepatic corticosteroid-binding globulin (CBG) production, thus stimulating cortisol production and increasing circulating levels of bound cortisol. However, both circulating and urinary free cortisol levels also increase steadily during gestation, reaching values that are in the range seen in Cushing's syndrome (CS). Plasma ACTH levels parallel the rise in cortisol. The cause(s) of this increase in ACTH is not clear, but may include placental synthesis and release of biologically active CRH and ACTH, pituitary desensitization to cortisol feedback, or enhanced pituitary responses to corticotropin-releasing factors such as vasopressin and CRH. These possibilities will be discussed in the context of the decreased suppression of the HPA axis by exogenous glucocorticoids, blunted diurnal rhythm of cortisol and blunted response of ACTH to exogenous CRH, a normal response to stressors of venipuncture and labor, and the enhanced cortisol response to exogenous ACTH.

CS occurs rarely in pregnancy, with fewer than 150 cases in the world literature. When untreated, fetal mortality is nearly 20%; treatment reduces, but does not abolish, this adverse outcome. Maternal morbidity includes hypertension, hyperglycemia, and eclampsia.

The clinical diagnosis may be missed because of the overlapping features of weight gain, hypertension, fatigue, hyperglycemia, and emotional changes that occur in pregnancy. The biochemical diagnosis is difficult to establish because of the normal hypercortisolism of pregnancy. The proportion of patients with primary adrenal causes of CS is increased in pregnancy. This poses diagnostic problems be-

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Abbreviations: AI, Adrenal insufficiency; APS, autoimmune polyglandular syndrome; CBG, corticosteroid-binding globulin; CD, Cushing's disease; CRH-BP, CRH-binding protein; CRH-R, CRH receptor; CS, Cushing's syndrome; C-section, cesarean section; CT, computed tomography; DOC, desoxycorticosterone; HPA, hypothalamic-pituitary-adrenal; 11 β -HSD 2, 11 β -hydroxysteroid dehydrogenase 2; IPSS, inferior petrosal sinus sampling; ITT, insulin tolerance test; LCT, low-dose cosyntropin test; MRI, magnetic resonance imaging; 17-OHCS, 17-hydroxycorticosteroids; POMC, proopiomelanocortin; PRA, plasma renin activity; RAS, renin angiotensin system; SCT, standard cosyntropin test; UFC, urine free cortisol.

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cause the increased ACTH levels of normal pregnancy are not suppressed by the hypercortisolism; thus, in contrast to nonpregnant patients, an undetectable ACTH level cannot be used as a criterion for this diagnosis. We and others have used ovine CRH and inferior petrosal sinus sampling (IPSS) to identify patients with Cushing's disease (CD). Surgery is a safe option for treatment in the second trimester; otherwise, medical therapy may be used, which must be chosen carefully to avoid adverse maternal and fetal effects.

Women with known adrenal insufficiency (AI) that is appropriately treated can expect to have uneventful pregnancies of normal length without fetal compromise. However, if unrecognized, AI often leads to maternal or fetal demise either during gestation or in the puerperium. Emesis, fatigue, and altered food preferences of pregnancy contribute to a lack of clinical recognition of AI. Excessive emesis, hypoglycemia, and hyponatremia are important clues to its presence. Women are at increased risk for adrenal crisis postpartum, implying a potential contribution of a fetal/placental source of cortisol to prevention of crisis during gestation. Appropriate treatment, including increased sensitivity to mineralocorticoid replacement and management of labor, is reviewed.

II. HPA Axis Physiology in Normal Pregnancy

A. Circulating hormone levels and their origins

1. *Circulating and urinary glucocorticoids and CBG.* Pregnancy is associated with a state of increased HPA axis function (1, 2) as shown by elevations in urine free cortisol (UFC), plasma 17-hydroxysteroids [17-hydroxycorticosteroids (17-OHCS)], total and free plasma cortisol, and CBG values during pregnancy (3–10). It is assumed that increased circulating estrogens from the placenta stimulate hepatic production of CBG, which remains elevated until at least the 12th postpartum day (10). Presumably, free cortisol concentrations drop transiently, as CBG increases, reducing negative feedback and increasing ACTH stimulation so that cortisol production increases to maintain a normal free cortisol level. However, as described below, free cortisol levels also are elevated, particularly in the second and third trimesters (5, 7, 8, 10, 11).

Total and free plasma cortisol concentrations rise in parallel across gestation (11, 12), with plasma cortisol reported as 2- to 3-fold elevated compared with nonpregnant controls (5, 13). The increases in plasma cortisol are noted as early as the 11th week of gestation (12). In one series there was an almost 5-fold increment between the first trimester and delivery (Fig. 1) (3). As shown by Mukherjee and Swyer (14), there is a wide range of normal variation in the third trimester plasma cortisol from 16.3–55 $\mu\text{g/dl}$ (450–1518 nmol/liter). The circadian rhythm of cortisol is preserved, although it may be partly blunted (3–5, 10, 14, 15).

Plasma free cortisol elevations of 2- to 4-fold were reported across several studies, suggesting greater tissue exposure to glucocorticoids during pregnancy (4, 7, 16, 17). The greatest increase in free cortisol index appears between the first and second trimesters, reaching a plateau in the third trimester (7). Salivary cortisol, another measure of plasma free cortisol,

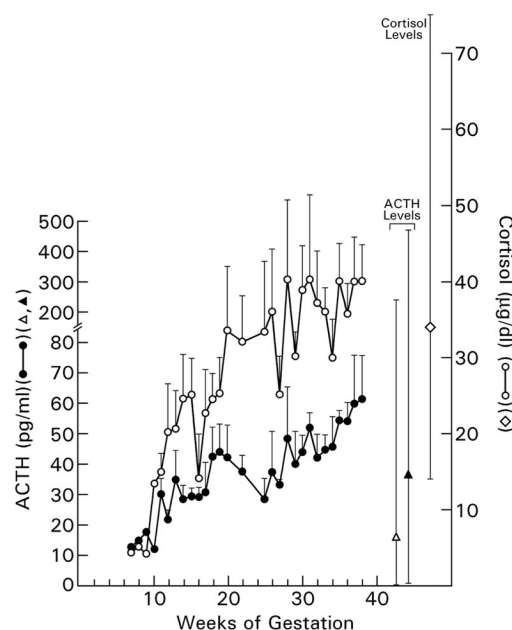


FIG. 1. Serial increases in serum cortisol (\circ) and ACTH (\bullet) during pregnancy in normal controls throughout pregnancy. This graph was modified from the series of five normal pregnant women from the series by Carr *et al.* (3) in 1981. The bars adjacent to the right axis are summary data derived from a recent series (173) to denote the range of serum cortisol observed in CS in pregnancy (\diamond , median and range; $n = 52$); ACTH values for CD (\blacktriangle , median and range; $n = 18$) and adrenal CS (\triangle , median and range; $n = 17$). [Reprinted and modified with permission from B. R. Carr *et al.*: *Am J Obstet Gynecol* 139: 416–422, 1981 (3). © Elsevier.]

is more than 2-fold increased compared with nonpregnant controls in the third trimester (10, 17).

Urine cortisol and its metabolites also increase in parallel with cortisol throughout gestation. In 1953, Gemzell (1) demonstrated that 17-OHCS levels were elevated 4-fold in pregnancy; this increase is mainly due to increased cortisol (9). Mean 24-h UFC is elevated at least 180% during gestation compared with nonpregnant levels (4). The aforementioned elevations in cortisol and its metabolites are consistent with a hypothesis that the maternal adrenals and the fetal-placental unit, in addition to estrogen-stimulated CBG elevations, all contribute to hypercortisolism in pregnancy (10, 18).

One explanation for the elevation in free cortisol is that pregnancy may represent a state refractory to cortisol action (7). Allolio *et al.* (17) demonstrated significant correlations between serum progesterone and salivary cortisol during late pregnancy. They suggested that elevated free plasma cortisol levels may result from antiglucocorticoid effects of elevated progesterone concentrations in pregnancy (17). Other theories include an altered set point to the negative feedback mechanism controlling ACTH secretion (4, 5). An alternate hypothesis is that placental ACTH represents an autonomous continuous source that is superimposed upon normal pituitary ACTH production (4).

The fetus is protected in early gestation from the effects of maternal hypercortisolism by placental 11- β hydroxysteroid dehydrogenase 2 (11 β -HSD 2), which converts active glucocorticoids, cortisol, and corticosterone to their inactive 11-

keto metabolites (19, 20). The enzyme is located in the syncytial trophoblastic cells. The capacity of placental 11 β -HSD 2 is sufficient to ensure that fetal cortisol levels are much lower than maternal levels (19). Whereas fetal cortisol concentrations are affected by 11 β -HSD 2 enzyme activity, approximately three fourths of fetal cortisol originates from fetal adrenal gland production in term infants (21–23). Dexamethasone, in contrast, is a poor substrate for 11 β -HSD 2 and can cross the placenta readily (20). In nonpregnant subjects conversion of cortisol to cortisone predominates; however, in late gestation there is a reversal of this reaction in the uterus, which favors production of the active hormone (24). These effects may favor late fetal development, including lung maturation (24). Altered 11 β -HSD 2 activity has been implicated in fetal programming, and this role has been a focus of research in the pathogenesis of adult disease, including the metabolic syndrome (20, 25, 26). Impaired activity of the enzyme and possible excessive fetal glucocorticoid exposure are observed in intrauterine growth retardation and preeclampsia, which are commonly associated with preterm infants (22).

2. Plasma ACTH. ACTH is a 39-amino acid peptide normally derived, in the pituitary corticotropes, from successive cleavage of a larger precursor peptide, proopiomelanocortin (POMC). This reaction gives rise to a series of related peptides including β -endorphin and α -MSH (27). Parallel rises in plasma ACTH, β -endorphin, and β -lipotropin are observed through pregnancy, consistent with their origin from POMC (28). A placental source of ACTH was postulated for many years before the demonstration of ACTH and immunoreactive β -endorphin and lipotropin within the placenta in the 1970s (29–31). Demura *et al.* (32) later showed the presence of equimolar concentrations of ACTH and β -endorphin in trophoblastic tissues consistent with their origin from a common precursor. Short mRNA related to the gene encoding POMC was subsequently detected in human placenta (33), and trophoblastic cells synthesize POMC-derived peptides *in vitro* (34, 35). Whether POMC itself has a specific action in pregnancy is unknown (3).

In one series, plasma POMC was undetectable in nonpregnant women but became detectable by the third month and then steadily increased toward midgestation (36). Plasma POMC correlated with plasma CRH but showed no diurnal variation, was not suppressed by glucocorticoid administration, and did not correlate with plasma ACTH or cortisol (36).

Plasma ACTH levels rise through pregnancy, reaching maximal levels during labor and delivery (Fig. 1); in one study, levels increased almost 3-fold from the end of the first to the third trimester (23–59 pg/ml measured by RIA; 5–13 pmol/liter) (3). Compared with healthy nongravid women, basal plasma ACTH levels in pregnancy have been variably reported as low (3, 14) or high (37) using RIA. Diurnal patterns of plasma ACTH and β -endorphin concentrations parallel each other and are preserved throughout pregnancy, and circulating cortisol and ACTH levels are strongly correlated (14, 15, 17). The elevated ACTH levels observed in late pregnancy suggest that a source of ACTH exists that is not subject to normal feedback control (3). Placentally de-

rived ACTH may be a significant contributor to hypercortisolism in pregnancy. *In vitro* stimulation of ACTH production from superfused human placenta was first described in 1986 (38), and release of bioactive ACTH has been demonstrated in early and late gestation (39). Petraglia *et al.* (40) demonstrated that CRH modulates release of placental ACTH.

3. Plasma CRH and CRH-binding protein (CRH-BP). CRH was isolated from human placenta in 1988 by Sasaki *et al.* (41) and is identical to hypothalamic CRH in structure, immunoreactivity, bioactivity, and transcriptional sites (42). It has since been demonstrated in extracts of placenta and in fetal plasma and amniotic fluid (43–46). Placental CRH mRNA was identified between wk 7 and 40 of gestation; it increased more than 20-fold in the 5 wk preceding parturition in parallel with rising plasma CRH concentrations (47, 48).

Plasma CRH levels rise exponentially by 1000-fold as gestation progresses (49), beginning around 8 wk gestation (50, 51). At the 35th week there is a sharp increase to a peak of 4000 pg/ml at 40 wk gestation (5, 52) (Fig. 2), with normalization to nonpregnant values within 24 h of delivery (53–56). CRH levels are significantly lower (20-fold) in umbilical cord plasma than in the maternal circulation and are close to the nonpregnant reference range (45). These data suggest that the placenta is the source of elevated circulating CRH during gestation (44, 45, 57, 58).

The regulation of placental CRH production is not well understood. In one study circulating values were not changed by administration of betamethasone, 12 mg (59), whereas others found increased CRH concentrations in maternal and fetal plasma and amniotic fluid after betamethasone (60). There was no apparent circadian rhythm in plasma CRH despite preservation of circadian patterns of ACTH and cortisol (15). One hypothesis is that placental CRH drives the maternal HPA axis in a constitutive, noncircadian, and nonpulsatile fashion (15). Placental CRH mRNA is up-regulated

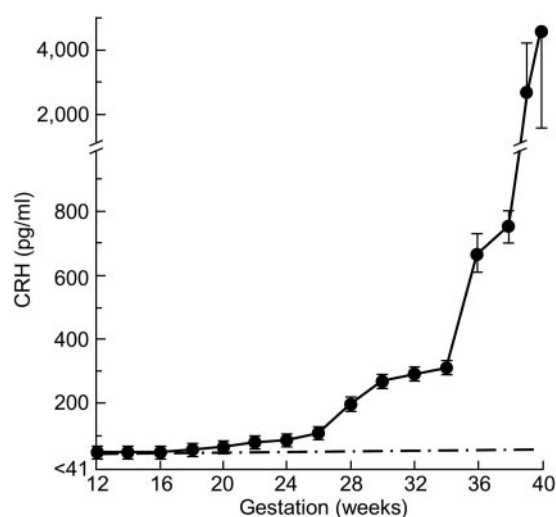


FIG. 2. Mean plasma CRH concentrations in seven women throughout pregnancy. Sequential samples were obtained at 1- to 2-wk intervals beginning at 12 wk gestation. [Reprinted with permission from R. S. Goland *et al.*: *Am J Obstet Gynecol* 159:884–890, 1988 (52). © Elsevier.]

by glucocorticoids, in contrast to negative feedback effects of cortisol on hypothalamic CRH (61, 62). Robinson *et al.* (61) suggested that the rise in CRH preceding parturition could result from stimulation by elevated fetal glucocorticoids. Increased placental CRH might stimulate a further rise in fetal glucocorticoids via ACTH, leading to a positive feed-forward loop (61).

Systemic maternal effects of elevated CRH in pregnancy are thought to be limited due to binding of free bioactive CRH to CRH-BP, a 322-amino acid glycoprotein (63). Whereas CRH-BP has been demonstrated primarily in the brain in mammals, in the human it is also present in the liver and placenta (64). Human CRH-BP binds to human but not ovine CRH (65). Circulating CRH-BP levels in early and midgestation are similar to nonpregnant levels, suggesting that, in contrast to CBG, CRH-BP is not stimulated by elevated estrogen levels in pregnancy (66). Between wk 34 and 35 of gestation, CRH-BP concentrations fall by around 60%, leading to elevations in free CRH (66) (Fig. 3). When given *in vitro* with CRH, at typical gestational concentrations, CRH-BP reduces the amount of ACTH released by the placenta but not the corticotrope, thereby potentially maintaining the maternal stress response during the third trimester (67).

CRH receptors (CRH-Rs) are present in reproductive tissues, such as the placenta and endometrium, and also are widely distributed throughout the central nervous system, heart, lung, skeletal muscle, skin, and lymphatic organs (68). CRH-Rs are located in nonpregnant myometrium, and CRH during pregnancy may regulate myometrial contractility via a direct effect on myometrial cells (49, 69). Two different isoforms of these receptors exist, CRH-R1 and CRH-R2, which share 70% sequence homology. In one recent study, myometrium and choriodecidua expressed mRNA and protein for both receptors, whereas placenta expressed predominantly CRH-R2 (68). CRH causes ACTH release from primary culture of human placental cells, suggesting that it is an important regulator of ACTH levels in gestation (51). The

exact role of differential expression of CRH-Rs in the pregnant state and during uterine quiescence is currently an area of active research (68).

There is no correlation between plasma CRH and ACTH or total or free cortisol, suggesting either that placental CRH is not the sole regulator of the maternal pituitary-adrenal axis, or that regulation occurs in a paracrine fashion within the placenta (17, 45). These findings may be consistent with the concept that HPA axis function remains intact in normal pregnancy despite observations consistent with desensitization of maternal pituitary corticotrophs. The primary stimulus for the increase in activity of the HPA axis in the third trimester appears to be placental CRH.

Although CRH is a significant regulator of maternal and fetal HPA axes in pregnancy, it also plays a more general role in female reproduction (Table 1) (53). There is evidence that CRH facilitates decidualization, implantation, and ovarian function (53). Locally produced embryonic and endometrial CRH impedes rejection during implantation by inducing apoptosis in activated leukocytes carrying Fas ligand, thereby protecting the fetus from the maternal immune system (54, 70). Maternal CRH acts as a biological clock that determines the length of gestation (55, 71), and premature or accelerated activation of the placental CRH system may be associated with earlier onset of labor and delivery (72). Placental CRH may also be a marker of antepartum risk for preterm delivery (72). CRH is generally higher in women with spontaneous labor compared with those requiring induction, consistent with a central role in the onset of parturition (73, 74).

The possible role of urocortin 1 and 2 in human reproduction has recently been examined. Table 2 illustrates the putative effects of the urocortins and CRH described in a recent review (75). The urocortins are members of the CRH peptide family and share between 35 and 43% sequence homology with CRH. In late ovine pregnancy, cortisol stimulates pituitary urocortin mRNA, suggesting that urocortin may be partly responsible for the mechanism of sustained activation of the HPA axis (76). Urocortin stimulates increases in ACTH in rat pituitary cell cultures and in plasma with similar or greater potency than CRH (56, 76, 77). The pituitary is the site with the highest immunoreactive urocortin in man (78). Human placenta, chorion, and amnion also express urocortin 1 (75). However, plasma urocortin 1 levels do not change through gestation until labor, when

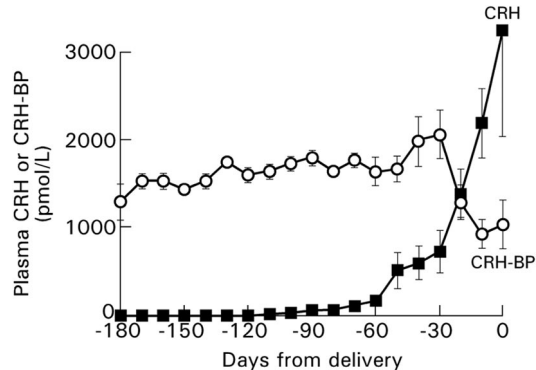


FIG. 3. Comparison of the molar concentrations of CRH (■) and CRH-BP (○) in maternal plasma during the final 180 d of gestation in pregnancies ending in spontaneous term labor (37–42 wk gestation). Each point represents the mean (\pm SEM) of samples grouped by 10-d intervals calculated retrospectively from the day of delivery (mean of 59 samples at each time point). CRH and CRH-BP concentrations are significantly different ($P < 0.002$) at all points except at the intersection of the two curves, 20 d before delivery. [Reprinted with permission from M. McLean *et al.*: *Nat Med* 1:460–463, 1995 (71). © Nature Publishing Group (<http://www.nature.com/>).]

TABLE 1. Reproductive roles of CRH

Reproductive CRH	Potential roles
Uterine CRH	Decidualization Blastocyst implantation and early maternal tolerance
Placental CRH	Maintaining proper fetoplacental circulation Fetal adrenal steroidogenesis Onset of parturition
Ovarian CRH	Inhibition of female sex steroid production Follicular maturation Ovulation Luteolysis

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TABLE 2. Urocortins and urocortin-related peptides expression, established functions, and putative effects in the different reproductive tissues

	Peptides and receptors expressed	Functions
Ovary	Urocortin 1; CRH; CRH1 and CRH2(a) receptors	Putative: ovarian steroidogenesis (luteal regression)
Endometrium	Urocortin 1; CRH; CRH1(a), CRH1(b), and CRH2(a) receptors	Putative: cell growth; decidualization; implantation; local hormonogenesis and blood flow
Placenta	Urocortin 1; CRH; CRH1(a), CRH-Rc, and CRH2(b) receptors; CRH1(a)	Established: ACTH, prostaglandins (PGs), and activin A secretion; placental vasculature relaxation
Myometrium	Urocortin 1 and urocortin 2; CRH; CRH1(a), CRH1(b), CRH2(a), and CRH2(b) receptors	Putative: control of labor Established: stimulation (urocortins) and inhibition (CRH) of contractility
Prostate	Urocortin 1; CRH receptors (rat)	Putative: control of vascular tone Putative: PGs secretion; influence on sperm transport; myometrial contractility; local blood flow

CRH-RC, CRH spliced variant receptor C; CRH1, CRH type 1 receptor; CRH2(a), CRH type 2a receptor; CRH1(a), CRH type 1a receptor; CRH 1(b), CRH type 1b receptor; CRH 2(b), CRH type 2b receptor; PGs, prostaglandins. [Reproduced with permission from P. Florio *et al.*: *Peptides* 25:1751–1757, 2004 (75). © Elsevier].

levels increase (79, 80). Recent *ex vivo* studies are consistent with a role for promotion of myometrial contractility (81). Urocortin 1 causes relaxation of placental vasculature; it stimulates prostaglandin E₂ release *in vitro* (82) and may thus enhance prostaglandin release *in vivo*. Urocortin has a stimulatory effect on ACTH release equimolar to CRH (81) and may maximize placental release of ACTH. Recent studies demonstrate that urocortin 2 interacts with myometrial CRH-R2s to stimulate myometrial contractility (83). Whereas the urocortins probably stimulate contractility of the myometrium, CRH acts in an inhibitory fashion via its effects on a nitric oxide synthase-dependent pathway (75, 84). The urocortins and CRH are bound to CRH-BP with similar avidity, and their biological activity is significantly dependent upon the free hormone availability.

4. Mineralocorticoids. Normal pregnancy is characterized by adaptation of the renin-angiotensin system (RAS) to increased demands upon the maternal circulation. Normal gestation is associated with increased vascular distensibility and reduced peripheral vascular resistance (85). Whereas the intravascular volume in gravid subjects increases by approximately 45%, blood pressure falls despite an increment of 25–50% in cardiac output (86, 87). Pregnancy is associated with increases in glomerular filtration rate by 50% and an increase in filtered sodium load of 5,000–20,000 mEq (88, 89). Normal pregnant women retain 200–300 mEq of sodium; in addition there is an increase in extracellular fluid by 4–6 liters (86).

Plasma progesterone concentrations increase progressively throughout pregnancy to between 100 and 300 ng/ml in parallel with increases in plasma estradiol levels (87, 90). Acting as a mineralocorticoid receptor antagonist, progesterone reduces sodium reabsorption; it also contributes to reduced systemic vascular resistance, causing smooth muscle relaxation (91, 92). Conversely, increased estradiol and estradiol levels in pregnancy are associated with elevated renin concentrations and up-regulation of the RAS (87, 93).

Against this backdrop of normal physiological changes occurring in pregnancy, elevations in mineralocorticoid levels appear necessary to maintain normal sodium balance and volume homeostasis. Although the RAS is markedly stimulated during pregnancy, both renin and aldosterone respond physiologically, albeit at an altered set point. Blockade

of the mineralocorticoid receptor in animal models demonstrates that aldosterone and the RAS are of critical importance to fetal growth and development (94).

a. RAS. The RAS comprises a cascade of events that proceeds from renin-mediated cleavage of the decapeptide angiotensinogen to angiotensin I, which is rate limiting. Angiotensin I can then be cleaved by angiotensin-converting enzyme to the octapeptide angiotensin II, which promotes aldosterone synthesis and secretion. Whereas renin is produced predominantly in the kidneys, the RAS is up-regulated during pregnancy, and the fetal-placenta unit is an important additional site of RAS activity (95, 96).

Plasma renin activity (PRA) increases early in the first trimester of normal pregnancy, reaching values almost 3- to 7-fold greater than the normal range by the third trimester (87, 96, 97) (Fig. 4). Approximately 50% of this increase is attributable to increased plasma renin substrate, and the changes observed in pregnancy are independent of sodium or potassium (87). A positive correlation exists between plasma renin substrate and plasma estradiol and estradiol, supporting the view that increases are mediated by elevated estrogens during pregnancy (87, 93). Increased concentrations of renin are demonstrated within uterus, placenta, and amniotic fluid (95, 98–101). The ovary produces renin and

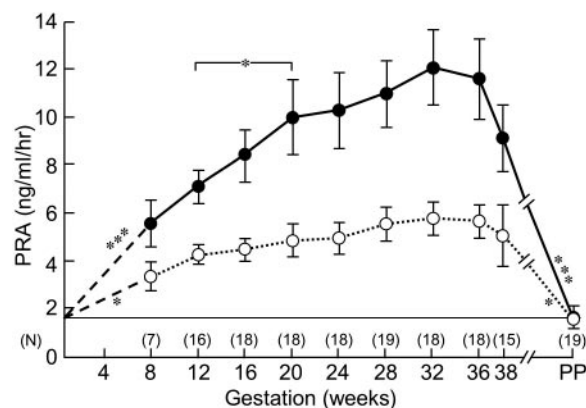


FIG. 4. Sequential changes in PRA (●) and in PRA normalized to the postpartum (PP) substrate values (○) (mean ± SE) throughout pregnancy (*, $P < 0.05$; ***, $P < 0.001$). [Reprinted with permission from M. Wilson *et al.*: *Am J Med* 68:97–104, 1980 (87). © Elsevier.]

prorenin (102, 103). However, other factors, including changes in salt intake, blood pressure, effects of progesterone, increased renin substrate concentration, and the fetoplacental unit, influence the plasma renin concentration (87, 95, 104, 105). The response of plasma renin to posture or saline loading in pregnancy is similar in direction and magnitude compared with nonpregnant subjects, consistent with intact physiological regulation (106). However, urinary excretion of sodium before and after saline infusion is lower in pregnancy, in keeping with an increased sodium requirement for homeostasis (106).

Angiotensinogen is the substrate for renin that releases angiotensin I. Increases in plasma angiotensinogen are similar to those of renin, reaching a plateau by the 20th week of gestation (96), and are also presumed related to increased estrogen exposure (107). Angiotensinogen has been demonstrated in homogenates of human placenta, amnion, chorion, and endometrium (95). In addition to immunohistochemistry, PCR techniques have confirmed angiotensinogen mRNA in human placenta and decidua (95). In pregnancy, an increased proportion of angiotensinogen exists as a high molecular weight form (108), the exact role of which is unknown (88). It is increased in pregnancy-associated hypertension and potentially could reduce the formation of angiotensin II due to conformational changes (109). However, these changes are usually accompanied by inversely proportional changes in renin secretion in normal physiology, thereby limiting the effect on blood pressure (110, 111).

b. Aldosterone regulation. In normal pregnancy, plasma and urinary aldosterone increase, in association with enlargement of the zona fasciculata (18, 86, 112). Plasma aldosterone concentrations are elevated 5- to 7-fold during the first trimester (18) and continue to increase until the 38th week of gestation when 10 to 20-fold elevations are reached (18, 86, 113). In contrast to desoxycorticosterone (DOC) and cortisol, aldosterone is not bound substantially to plasma proteins (113). There exists a disproportionate rise in plasma aldosterone concentrations compared with the magnitude of renin secretion, suggesting a possible increase of some other unknown pregnancy-associated factor that contributes to plasma aldosterone concentrations in pregnancy (97, 114).

The diurnal rhythm of plasma aldosterone concentrations is preserved during pregnancy (115). Aldosterone responses to salt loading, posture, diuretics, volume depletion, and administration of mineralocorticoid suggest that the RAS is under tight physiological control (85, 116, 117). Furthermore, serum potassium levels remain constant in pregnancy despite increased plasma aldosterone, perhaps because of the mineralocorticoid antagonist effects of progesterone (96). Evidence in favor of a hypothesis that elevations in aldosterone levels are not excessive includes the observation of natriuresis after administration of an aldosterone inhibitor (118). Significantly, aldosterone levels are reduced in pregnancy-associated hypertension (96). Women with pregnancy-induced hypertension have a 2-fold greater increase in plasma aldosterone-plasma renin ratio compared with normal pregnant women (97), whereas in primary hyperaldosteronism, plasma aldosterone is increased in association with reduced renin (119).

c. Other mineralocorticoids. Corticosterone, deoxycortisol, and cortisone parallel the 2- to 3-fold rise seen in cortisol during gestation (18). Plasma DOC, a potent mineralocorticoid, increases from 2-fold normal during the first trimester to peak levels of 60–100 ng/100 ml in the third trimester (120–122) and may contribute to sodium retention in pregnancy. Early studies showed increased responsiveness of urinary measures of DOC to ACTH stimulation during the first and second trimesters compared with nonpregnant controls; these observations suggest that DOC represents a substantial nonsuppressible source of mineralocorticoid that is relatively independent of the RAS (123). In the third trimester, whereas total DOC levels are unchanged after ACTH stimulation, free DOC levels are elevated, possibly due to displacement of free DOC from CBG-binding sites (121, 123, 124). Similarly, during the third trimester, DOC levels are not suppressed by salt intake or dexamethasone (121), lending credence to the hypothesis that DOC may promote sodium retention (107). The fetoplacental unit probably contributes to circulating DOC levels, as increased concentrations of DOC have been demonstrated in mixed cord blood (125). Noltén *et al.* (120) have speculated that placental progesterone might be converted to DOC by the fetal adrenals. Further support for this hypothesis is provided by the observation that DOC sulfate has been found in high concentrations in umbilical cord blood.

B. Regulation of the HPA axis

1. ACTH stimulation of cortisol secretion. It was known as early as 1955 that, during late pregnancy, the adrenal glands have increased responsiveness to ACTH compared with nonpregnant women (126–128). Subsequent studies measuring urinary 17-oxogenic steroids or 11-hydroxycorticosteroids or plasma cortisol after im tetracosactin, corticotropin gel, or synthetic ACTH demonstrated 1- to 2-fold elevations in normal pregnancy compared with nonpregnant subjects (129). There was speculation that the apparent increased responsiveness might be due, in part, to delayed clearance of cortisol (126), because of a delayed peak response at 120 min. There also is a greater absolute rise in the unbound cortisol response, which increases as pregnancy advances (7).

A recent study examined aldosterone and cortisol responses to low-dose ACTH stimulation in normal pregnancy and preeclampsia (2, 3, 5, and 7 $\mu\text{g/h}$ for 80 min), demonstrating a similar pattern of enhanced responsiveness of cortisol release in the third trimester of pregnancy compared with nonpregnant women (130). The mean maximum cortisol response in pregnancy was 34.9 $\mu\text{g/dl}$ (963 nmol/liter) compared with 18.4 $\mu\text{g/dl}$ (507 nmol/liter) in a group of nonpregnant controls, despite administration of lower doses (1, 2, 3, and 5 $\mu\text{g/h}$) to the control women to account for their lower relative plasma volume (130).

McKenna *et al.* (131) examined responses of six healthy women to 1 μg ACTH during the 24th to 34th weeks of gestation. The mean peak cortisol response was 44 $\mu\text{g/dl}$ (1215 nmol/liter) (99% CI, 33.2–55.6 $\mu\text{g/dl}$; 917–1535 nmol/liter) and was attained at a mean of 27 min after cortrosyn.

2. Stimulation of ACTH secretion by CRH and vasopressin. Exogenous human CRH, 1 $\mu\text{g/kg}$, failed to increase plasma

cortisol or ACTH in seven pregnant women 1 wk before their expected delivery date (132). Although two women experienced transient flushing, no other maternal or fetal side effects were noted (132). In contrast, in the same women studied at 4–5 wk postpartum, there was a prompt ACTH response to administered CRH. Other investigators using a higher dose (2 $\mu\text{g}/\text{kg}$) during third trimester pregnancies demonstrated ACTH and cortisol increments that were similar to those of nonpregnant women (133). Whereas diminished CRH responsiveness may be due to effects of CRH-BP, *in vitro* studies of pituitary columns continuously perfused with CRH demonstrated initially brisk responses of β -endorphin secretion, which gradually declined to baseline after a period of hours (134). These observations are consistent with a hypothesis proposed by Schulte *et al.* (132) that blunting of the CRH response may arise due to high endogenous cortisol concentrations with desensitization of the pituitary corticotrophs.

As noted earlier, plasma CRH levels are relatively nonvariant during the third trimester (17), suggesting that circadian and pulsatile secretion of ACTH from the corticotrope may be driven by another secretagogue (15). Arginine vasopressin has been postulated to fill this role, as it is secreted in a pulsatile fashion with a circadian increase in amplitude (15). Goland *et al.* (135) suggested that chronic placental CRH stimulation of the pituitary-adrenal axis during pregnancy leads to enhanced responsiveness to vasopressin and down-regulation of the response to exogenous CRH.

3. The stress response. An individual's ability to mount an appropriate stress response during the antenatal period is preserved in normal pregnancy (136). ACTH and cortisol levels are subsequently increased during the stress of labor (see below).

4. Suppression of the axis by glucocorticoids. The HPA axis response to exogenous glucocorticoids during pregnancy is blunted. A range of reported dosing protocols and end points make interpretation of dexamethasone suppression tests more difficult in normal pregnancy. Early studies of human pregnancies showed suppression of urinary 17-OHCS of approximately 55% after 4–6 mg dexamethasone (129). Women in the third trimester treated with high-dose glucocorticoids (dexamethasone, 24 mg) before delivery exhibit suppressed ACTH levels within the first 24 h postpartum compared with untreated controls (137), but these effects are short lived (138). After iv administration of 4 mg dexamethasone to women in the second trimester with congenital adrenal hyperplasia, approximately 60% suppression of plasma cortisol was noted within 2 h that continued for up to 8 h. Up to 90% suppression was achieved after 12 mg dexamethasone given in a divided dose (139).

Odagiri *et al.* (13) demonstrated a 40% vs. 87% suppression of plasma cortisol and similar effects on UFC after 1 mg dexamethasone in normal second- to third-trimester pregnancy compared with nongravid controls (Fig. 5). Whereas the majority of nonpregnant women showed a consistent suppression of plasma cortisol, there was a wide range of variation in responses in pregnant women. Advancing gestation was associated with increasing loss of suppressibility

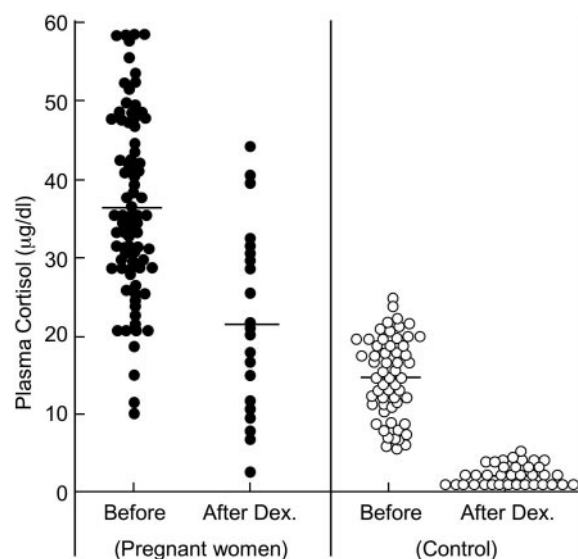


FIG. 5. Change in plasma cortisol before and after the administration of 1 mg of dexamethasone (Dex.) in pregnant women (●). Blood was drawn at 0800 h. A single dose of dexamethasone was administered orally at 2300 h, and blood was drawn at 0800 h on the following day. [Reprinted from E. Odagiri *et al.*: *Endocrinol Jpn* 35:685–690, 1988 (13). © Endocrine Society of Japan.]

after 1 mg dexamethasone (13). This decrease in the suppressive action of dexamethasone has been attributed to CBG effects on cortisol, tissue refractoriness to glucocorticoids, or resetting of the maternal HPA feedback mechanism (13). Other theories posit that antiglucocorticoid effects of progesterone might contribute to tissue resistance (13, 140). Other confounding factors, such as extrapituitary sources of ACTH and CRH, probably also contribute. Although pregnancy may alter the absorption of dexamethasone, there are contradictory reports examining its bioavailability. In one series, bioavailability via the oral route was 72% of the im route (141). In another series, the bioavailability of an 8-mg oral dose was similar to 6-mg im dosing (142).

5. The HPA axis during parturition. Plasma CRH, ACTH, and plasma cortisol concentrations increase severalfold with the onset of labor and delivery (3, 45, 143). Peak CRH levels occur within 48 h before delivery and fall during labor, consistent with a preeminent role for CRH in parturition (73). Whereas CRH levels fall during delivery, ACTH secretion is maximal during labor and delivery, demonstrating that the axis is not completely suppressed (73). Labor and childbirth are situations of acute stress, and peripheral maternal plasma ACTH levels are 10-fold elevated during labor compared with nonpregnant individuals (144). ACTH does not cross the placenta (137), and there is a 2-fold gradient in plasma ACTH in cord blood compared with higher levels in maternal blood during delivery (14, 144). In one early study, vaginal delivery was associated with higher plasma cortisol than during cesarean section (C-section) (14). A subsequent study demonstrated ACTH, β -endorphin, and β -lipotropin levels that were highest immediately after vaginal delivery compared with those after C-section; although both groups fell rapidly to the normal range, ACTH levels were highest in the C-

section group at 30 min post delivery, reflecting surgical stress (28).

In the immediate postpartum period, plasma CRH, ACTH, and cortisol levels fall rapidly toward the nonpregnant range, consistent with their biological half-lives (145). Both CRH and ACTH normalize within 2 h from delivery whereas normalization of plasma cortisol levels is more protracted (58). In one series, mean postpartum 24-h plasma cortisol levels were 5.4 $\mu\text{g/dl}$ (149 nmol/liter) compared with the second (18.8 $\mu\text{g/dl}$; 518 nmol/liter) and third trimesters (20.3 $\mu\text{g/dl}$; 560 nmol/liter) (4). Diurnal patterns of ACTH are present in the postpartum period (14, 15, 17).

In the immediate postpartum period 82% of women in one series did not have normal cortisol suppression after 1 mg dexamethasone (146). This abnormality may persist for up to 2–3 wk in a significant proportion of women (147). Owens *et al.* (147) observed normal responses to dexamethasone by the fifth postpartum week.

III. Cushing’s Syndrome (CS) in Pregnancy

A. Frequency

CS is rarely associated with pregnancy, probably because hypercortisolism prevents normal follicular development and ovulation. The first description of CS occurring in pregnancy was reported by Hunt and McConahey (148) in 1953. Since then, at least 136 pregnancies have been reported in 122 subjects as individual cases and small case series (149–171). Multiple pregnancies occurred in about 10% of the patients (151, 172). The mean gestational age at diagnosis is approximately 18 wk (173).

B. Maternal and fetal morbidity and mortality

CS is associated with significant maternal morbidity and mortality in approximately 70% of cases. The most common complications in pregnancy are hypertension and diabetes or impaired glucose tolerance (158, 164, 174). In smaller numbers of cases, pregnancies were associated with poor wound healing, osteoporosis, fracture, severe psychiatric complications, maternal cardiac failure, and death (154, 156, 175, 176) (Table 3). Maternal death is rare: one death was reported in the month after delivery as a result of cerebrovascular disease and disseminated intravascular coagulation caused by pheochromocytoma (177). Another woman died due to complications from adrenalectomy and C-section (160).

Regarding fetal outcome, in a series of 136 pregnancies

complicated by CS there were 107 (79%) live births (173). Forty-three percent of births were premature. There were eight stillbirths, six intrauterine deaths/spontaneous abortions, and one ectopic pregnancy. Six therapeutic abortions were undertaken, and in three cases the outcome was uncertain. One infant died from respiratory distress and hyaline membrane disease (171). Intraventricular hemorrhage caused another infant death (178). Fetal AI occurs rarely, and signs of glucocorticoid excess have not been reported, suggesting that placental degradation of cortisol protects the fetus (171).

C. Causes

The causes of CS can be broadly divided into excessive ACTH secretion by a corticotrope or ectopic tumor or autonomous adrenal hypersecretion of cortisol that is independent of ACTH (Table 4). Adrenal adenomas underlie a disproportionately high proportion of CS cases, accounting for approximately 40–50% of cases in pregnancy, compared with about 15% in nonpregnant women (149, 159). Conversely, CD appears to be less common in pregnancy, with rates of 58–70% in the general population compared with 33% in 122 pregnant women (149, 159, 179). Ectopic ACTH secretion has been reported to cause CS in four patients, two of whom had a diagnosis of pheochromocytoma (174, 177). Pheochromocytoma also was associated with one case of apparent ACTH-independent hypercortisolism in pregnancy (180). There was at least one case of CS where remission was observed during pregnancy (181). The increased incidence of adrenal CS in pregnancy is not understood. It is possible that women with CD are less ovulatory than those with primary adrenal disease, perhaps because they are more hyperandrogenic (182). Most patients with ectopic ACTH secretion have severe hypercortisolism and amenorrhea, which probably accounts for the reduced prevalence of this condition in pregnancy (158, 174, 177).

D. Screening and diagnosis

1. *Clinical features.* Pregnant women with CS have clinical features similar to those who are not pregnant, except that the pregnant women report preservation of menses until conception. Typically, women show weight gain, hypertension, bruising, and hirsutism. Unfortunately, CS is often not detected until 12–26 wk gestation (149, 157), possibly partially because changes in physical appearance are ascribed to pregnancy rather than CS (3).

TABLE 3. Frequency of maternal and fetal complications arising in CS during pregnancy

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

IUGR, Intrauterine growth retardation; IUD, intrauterine death.
[Reprinted from J. R. Lindsay *et al.*: *J Clin Endocrinol Metab* 90:3077–3083, 2005 (173). © The Endocrine Society.]

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TABLE 4. Etiology of CS in pregnancy

Etiology	Cases [n (%)]
CD	40 (33)
Adrenal adenoma	56 (46)
Carcinoma	12 (10)
Carney's complex	1 (0.8)
Pheochromocytoma	1 (0.8)
ACTH-independent hyperplasia	4 (3)
Ectopic CS	4 (3)
Unspecified	4 (3)

2. *Screening tests.* In nonpregnant women, screening tests for CS establish enhanced cortisol production or a deranged diurnal rhythm, or document blunted suppression of cortisol after dexamethasone suppression. The normal gestational changes in the HPA axis alter these parameters and complicate the screening process for CS (3, 13, 133) (Fig. 1). As reviewed above, these changes include estrogen-dependent increases in CBG, increases in plasma cortisol and ACTH, and a 2- to 3-fold increase in plasma free cortisol and UFC (3, 133).

The mean morning plasma cortisol level of 37 $\mu\text{g}/\text{dl}$ in pregnant women with CS is similar to the range observed by Carr and Simpson (3) in normal pregnancy (Fig. 1). Thus, as in the nonpregnant individual, morning plasma cortisol concentrations generally do not establish the diagnosis of CS.

The nocturnal nadir of plasma cortisol is lost in CS but is preserved in pregnancy, albeit with a higher absolute value (3–5, 176, 183, 184). An elevated midnight or evening plasma cortisol has helped to confirm hypercortisolism in some pregnant women (153, 161, 164, 179). However, no studies have developed a diagnostic threshold for interpretation of the test in pregnant patients. Similarly, salivary cortisol levels reflect serum levels and are elevated in patients with CS (185). However, there is only one case report that documents the potential utility of this noninvasive measure in pregnancy (185).

In nonpregnant women, UFC increases above 4-fold normal are virtually diagnostic of CS. Whereas UFC excretion is normal in the first trimester, it increases up to three times the upper limit of normal during the second and third trimesters. There is a mean 8-fold increase of UFC in pregnant CS patients (range, 2- to 22-fold) (173). This overlap of UFC values in pregnant women with and without CS suggests that only UFC values in the second and third trimester greater than three times the upper limit of normal can be taken to indicate CS (186). However, most studies characterized relatively few pregnant women using measurement of UFC by RIA. The current “gold standard” techniques for UFC measurement are structural assays such as mass spectroscopy, which have lower normative ranges than do antibody-based assays. Thus, it would be very helpful to have additional information on normative data using these modern methodologies.

As discussed earlier, suppression of both plasma and urinary free cortisol by dexamethasone is blunted in pregnancy (4, 29). Thus, the 1-mg dexamethasone suppression test has more limited utility in pregnancy than in the general population because of increased risk for false-positive results.

In summary, standard screening is likely to yield a higher proportion of false-positive diagnoses unless pregnancy-

specific cutoff points are developed for UFC and the 1-mg dexamethasone suppression test. Midnight plasma or salivary cortisol may be better, but require further study.

3. *Tests for the differential diagnosis.* Hypercortisolism, regardless of the cause, inhibits ACTH secretion by normal corticotropes. As a result, plasma ACTH levels are suppressed in nonpregnant patients with autonomous adrenal disorders and are inappropriately normal or increased in those with tumoral ACTH production. In such patients, a two-site immunoradiometric assay reliably discriminates low (<10 pg/ml; 2.2 pmol/liter) or suppressed (<5 pg/ml; 1.1 pmol/liter) ACTH levels (187) to identify ACTH-independent primary adrenal causes of CS. In that setting no further biochemical testing is needed, and imaging of the adrenal glands will localize the abnormality to a unilateral adrenal adenoma or carcinoma or bilateral adrenal disorders.

However, pregnant patients with adrenal causes of CS do not consistently have suppressed plasma ACTH values, probably reflecting effects of placental CRH that is not suppressed by hypercortisolism (see above). As a result, the recommended diagnostic ACTH thresholds for adrenal CS in the general population are not valid in pregnancy and may lead to missed diagnoses (187).

In nonpregnant individuals, the 8-mg overnight dexamethasone suppression test distinguishes CD from ectopic ACTH secretion with a sensitivity ranging from 60–80% and a specificity of more than 80% when a cutoff point of plasma cortisol suppression above 80% is used (187, 188). However, some authors advocate abandoning the test altogether; although it can detect patients with CD with relatively high sensitivity, it does not accurately exclude those with ectopic ACTH secretion due to a wide range of suppression of plasma cortisol for each diagnosis (188). The efficacy of the 8 mg dexamethasone suppression test for the differential diagnosis of ectopic ACTH secretion in pregnancy is unknown due to the limited number of reported cases (161, 163, 171, 178, 179, 189–191). The test may help discriminate adrenal forms of CS from CD, which may be useful given the difficulties in interpretation of plasma ACTH and the increased prevalence of adrenal disorders in pregnancy. In a recent systematic review, no patient with a primary adrenal cause of CS showed suppression, whereas four of seven patients with CD did (173).

In nonpregnant individuals with CD, the tumor corticotropes retain ACTH (and hence cortisol) responsiveness to CRH stimulation, whereas adrenal tumors and the majority of ectopic ACTH-producing tumors do not respond (192). Ovine CRH (the analog available in the United States) is a Food and Drug Administration (FDA) category C drug, recommended for use in pregnancy only when absolutely clinically indicated. Animal studies showed no teratogenic or adverse behavioral effects after 100 μg human CRH during organogenesis (193). Plasma ACTH responses to human CRH, 1 $\mu\text{g}/\text{kg}$, were reduced in third-trimester normal pregnancies (132). Although the CRH stimulation test has not been systematically studied in CS in pregnancy, in reports in the literature (and from our personal experience from three patients tested), there was a substantial rise in plasma cortisol (44–130%), consistent with surgically confirmed CD (161,

164, 165), and no adverse effects were observed (161, 164, 165).

For those pregnant women with CRH and dexamethasone test responses consistent with CD, and pituitary lesions larger than at least 6 mm, usually no additional testing is necessary, just as in the nonpregnant population. For others, IPSS may be warranted. The test involves catheterization of the petrosal sinuses draining the pituitary gland and simultaneous sampling from these and a peripheral vein for ACTH measurement before and after administration of CRH. The central-to-peripheral ACTH gradient in patients with CD is not found in other causes of CS, providing a very high diagnostic accuracy in the differential diagnosis of ACTH-dependent CS in the nonpregnant population (194). CS in pregnancy may represent one spectrum of disease in which the test may have special value given the difficulties with differentiation of normal physiological changes of pregnancy. The perceived risk of ionizing radiation probably has limited its use in pregnancy, reflected by only one published case in the literature using IPSS (165). Two additional cases have since been undertaken at our institution, indicating that the test can be used safely and effectively in a center with clinical expertise (173). Specific precautions, including a direct jugular approach for catheter insertion and use of additional lead barrier protection, are necessary during pregnancy. We advocate that IPSS should only be considered during pregnancy after completion of careful noninvasive assessment and only in centers with special expertise using the technique. Also, because it is not known whether pregnant patients with adrenal disease have complete pituitary suppression, the usual criteria for interpretation may not exclude these patients.

In summary, although no diagnostic algorithm has been developed prospectively, we recommend a combination of UFC and assessment of midnight salivary cortisol for screening of CS in pregnancy. In patients with confirmed CS, a low ACTH should prompt imaging of the adrenals. However, in cases with borderline ACTH, a combination of the 8-mg dexamethasone suppression test and CRH stimulation testing is suggested to establish the presence of, and distinguish between, the ACTH-dependent forms. IPSS may be necessary in a portion of cases with discordant biochemical or imaging findings.

4. Imaging

a. Adrenal. Early reports of patients with adrenal CS were characterized by either the absence of imaging or reliance on x-ray tomography or pyelography (154, 169, 195). In other patients imaging was deferred until the postpartum period (196). Despite inadequate tumor definition using these modalities, several women had successful localization and surgery (148, 170). In more recent reports, about 50% of women had detailed ultrasound imaging, which is safe and effective in most. However, ultrasound appears to be less sensitive at smaller tumor size so that several cases required additional modalities for tumor localization (166). Magnetic resonance imaging (MRI) and computed tomography (CT) have been used effectively, although the former is preferred during pregnancy due to the risk of ionizing radiation (153, 180, 198). Specific precautions for the use of MRI are detailed below.

b. Pituitary. Pituitary MRI should be obtained in all nonpregnant patients with ACTH-dependent CS (187). A recent consensus statement concluded that pituitary MRI may provide a definitive diagnosis in the setting of responses to CRH and dexamethasone consistent with CD when a greater than 6-mm pituitary adenoma is identified (187). However, the use of MRI is not routine in pregnant women because of safety issues. Because of potential (but unproven) teratogenic effects of MRI in the first trimester during organogenesis, it is considered contraindicated at that time, but is considered safe after 32 wk gestation. Between 12 and 32 wk, the potential and largely unknown risks of MRI must be balanced with the potential benefit, recognizing that MRI will detect an incidental tumor (≤ 6 mm) in up to 10% of healthy individuals. Evidence of a size criterion for pituitary incidentaloma stems from nonpregnant series (199). However, as the normal pituitary increases in size up to 2-fold by the third trimester, there may be an increased number of incidentalomas identified in pregnancy using these criteria compared with the nonpregnant population. The use of the contrast agent gadopentetate dimeglumine (gadolinium) is contraindicated in pregnancy, because it is FDA category C. In one series of nonpregnant individuals, the sensitivity of MRI for detection of CD decreased from 52% with contrast to 38% without (200). Pituitary MRI alone correctly identified an adenoma during pregnancy in five of eight patients with CD, three of whom had macroadenomas (161, 163–165, 171). This was not sufficiently sensitive for detection of microadenomas (171). Of interest, pituitary macroadenomas, reported in about half of those with reporting of imaging or operative findings, are overrepresented compared with nonpregnant series (163, 165, 191, 201, 202).

E. Treatment of CS

As cited previously, untreated CS is associated with significant maternal morbidity, including diabetes, hypertension, heart failure, and preeclampsia (191, 196, 203), and adverse fetal outcomes, including premature births, spontaneous abortions, stillbirth, perinatal death, and intrauterine growth retardation (149, 159). It is assumed that these outcomes could be prevented by reducing UFC excretion to the upper part of the range observed in normal pregnancy (186, 204, 205). However, treatment for pregnant patients with CS tends to have been implemented sporadically, generally late in the course of the pregnancy. As a result, the ability of treatment to prevent adverse outcomes is not well established. We recently reviewed 136 pregnancies in which treatment outcomes were available. When no active treatment was given, there were 59 live births (76%) compared with 50 live births (89%) in women in whom treatment was instituted at a mean gestational age of 20 ± 1 wk (173). Even in cases with apparent remission after successful treatment, the progression to eclampsia and premature delivery in a case treated at our institution illustrates that successful treatment may not prevent adverse outcomes (173).

Most patients underwent adrenalectomy for adrenal adenomas, although several had adrenal carcinoma (153, 157, 174). The live birth rate after unilateral or bilateral adrenalectomy is approximately 87%; although the patient group is

heterogeneous, adrenalectomy appears beneficial (149, 157, 158, 173).

Forty women, including four who were treated at our institution, have been reported with CD. Approximately 20% underwent transsphenoidal surgery (164). The remainder received medical therapy and/or adrenalectomy, and one case of unrecognized pregnancy had external pituitary irradiation (148, 158, 206–208). A high proportion, either presenting late in pregnancy or before modern management, was left untreated (209, 210). In contrast to medical therapy, which is discussed below, surgery seems to be more uniformly successful (161, 163, 164, 179).

Primary medical therapy was given to 20 women, usually to prolong pregnancy or to prepare for delivery (171, 211). Metyrapone, which seems generally well tolerated, has been used most often (155, 204) and has had no adverse effects on maternal hepatic functioning or fetal development in the small number of cases reported to date. There is one report of fetal hypoadrenalism after metyrapone (151). However, although metyrapone is effective, there is the potential for exacerbation of hypertension and progression to preeclampsia, which may limit its use (155, 178). Ketoconazole has been used successfully without adverse event in three anecdotal reports of pregnancies (211–213), including in an individual who had discontinued contraception while using ketoconazole, 600–1000 mg, for CD (211). Despite known antiandrogenic effects through inhibition of aromatase activity, a normal male infant was delivered at 37 wk (211). In the rat, ketoconazole crosses the placenta and is teratogenic and abortifacient, so that the drug is FDA category C. Although ketoconazole has been advocated recently as a potential option in patients requiring medical therapy, we recommend its use only in individuals who are intolerant of metyrapone and are in need of emergency medical therapy. Cyproheptadine appeared safe in three women, but is not effective (214–216). Aminoglutethimide is avoided because it can induce fetal masculinization (217). Similarly, mitotane is contraindicated as it has teratogenic effects (202).

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

IV. Adrenal Insufficiency in Pregnancy

A. Overview

Although AI in pregnancy is uncommon, it is important to recognize it to optimize maternal and fetal outcomes. AI can present acutely or with a more insidious set of chronic symptoms. Primary AI (so-called Addison's disease) refers to intrinsic adrenal pathology with atrophy of the adrenal cortex and insensitivity to ACTH and angiotensin II stimulation,

resulting in impairment of aldosterone and/or cortisol secretion. Urinary and plasma cortisol and aldosterone levels are low or undetectable (218). Plasma aldosterone-to-renin ratios are reduced in association with elevated PRA (218, 219). Secondary or tertiary AI arises from impaired ACTH or CRH secretion due to hypothalamic or pituitary disease or, more commonly, as a result of exogenous corticosteroid administration. However, secondary AI is not associated with mineralocorticoid deficiency, as the zona glomerulosa remains responsive to the action of the RAS.

B. Frequency

The prevalence of primary AI in the predominantly Caucasian nonpregnant population is estimated to range between 39 and 117 per million (220–222). Although the majority of cases of primary AI affect women (~92%) (223), the exact prevalence of AI occurring in association with pregnancy is unknown. By 1953, there were approximately 50 cases of AI in pregnancy reported, and since then a similar number have been published (148, 224, 225). In one of the largest series, during a 12-yr period between 1976 and 1987 in Tromsø, Norway, five women with AI gave birth to six children. From this series of 15,700 deliveries, the estimated incidence of pregnancy in women with AI was 1:3000 births per 12-yr period (225). In 1968, Mason *et al.* (221) estimated one case of AI in pregnancy per 12,000 gestations.

C. Causes

The presentation and causes of AI have been reviewed extensively (226, 227). Autoimmune adrenalitis is the most common cause of primary AI in developed countries, whereas tuberculosis is a more common etiology worldwide. Whereas the glands are small in autoimmune primary adrenal disease, they are large in tuberculous or fungal infection, bilateral metastases, hemorrhage, or infarction. A recent Italian survey illustrated the current prevalence and etiology in a group of 322 patients with AI presenting between 1969 and 1999. Most patients were female, and 83% of them had an autoimmune cause for AI. The mean age at presentation was 30 yr and, although tuberculosis was relatively uncommon (12%), that condition was more prevalent in males who had a mean age of presentation of 53 yr (227). The association of AI with type 1 diabetes mellitus has been well described in the general population and in pregnancy (228–231).

At least seven pregnancies in association with autoimmune polyglandular syndrome (APS) type 2 or Schmidt's syndrome (primary autoimmune hypoadrenalism, type 1 diabetes mellitus, thyroid autoimmune disease), have been reported since the syndrome was originally described in 1926 (225, 232–237). This condition is more common in women and is more common than the other forms of APS. APS 2 has a complex inheritance pattern with varying degrees of genetic susceptibility. A high index of clinical suspicion should be present for the diagnosis in offspring of individuals with APS (232, 233, 238). The prevalence of APS 2 is probably overrepresented in the literature of AI in pregnancy, because it is a unique multisystem endocrine disease. Three cases with APS presented as a new diagnosis of AI during preg-

nancy (233, 234, 236). An awareness of the association of type 1 diabetes or thyroid disease with AI is necessary to ensure adequate screening and recognition of APS before or during pregnancy. In addition to the morbidity associated with AI, untreated hypothyroidism is associated with higher incidence of infertility and miscarriage as well as gestational hypertension and low birth weight (235, 236). Macrosomia and eclampsia are common complications of uncontrolled gestational diabetes, and appropriate management poses a particular challenge beyond that of isolated hypoadrenalism in APS 2 (232).

The most common cause of secondary AI in the adult population is administration of exogenous corticosteroids for conditions such as asthma and inflammatory bowel and dermatological or rheumatic diseases (239, 240). The adverse effects of exogenous steroids and their contribution to fetal growth retardation, suppression of the fetal HPA axis, and effects on neurological functioning have previously been reviewed extensively in both animal models and in humans (241–245). The true prevalence of AI after long-term glucocorticoid replacement in either the nonpregnant or pregnant population is unknown. An assessment of the HPA axis is warranted for women receiving at least 5 mg prednisone or equivalent per day for more than 3 wk (246). In these cases glucocorticoid reserve should be tested formally before discontinuing a tapering regimen (see below), and stress dosing of glucocorticoids should be administered as clinical suspicion arises. These patients are at particular risk in times of stress and may be at increased risk during pregnancy.

Asthma complicates approximately 4% of pregnancies, and current guidelines support the use of inhaled or systemic corticosteroids for treatment in pregnancy (247). Although chronic oral or high-dose corticosteroid use for asthma in pregnancy is associated with gestational diabetes, preterm labor, and preeclampsia, there have been few reports of adrenal crisis in pregnancy (248). Similarly, whereas steroid dependency is common in up to 36% of patients with Crohn's disease, there have been only isolated cases presenting in adrenal crisis (249). In contrast, recent series highlight the potential risks of maternal adrenal suppression in women treated with standard short-term doses of betamethasone for preterm delivery (131, 250).

Postpartum pituitary necrosis (Sheehan's syndrome) is a well-recognized complication of pregnancy, which results after obstetric shock and usually presents with failure to lactate or to resume normal menses in the postpartum period (251). The diagnosis should be considered in postpartum women with hypoglycemia or coma or in stable cases at longer-term follow-up (252). Approximately 20% of cases of Sheehan's syndrome arise due to antepartum hemorrhage (253). Although it is the most widely cited cause of hypopituitarism in association with pregnancy, this condition has become less common with improved obstetric care (253, 254).

Lymphocytic hypophysitis has considerable overlap in clinical presentation with Sheehan's syndrome, and these two conditions are the primary differential diagnoses for postpartum hypopituitarism (255). Lymphocytic hypophysitis was first described in 1962 by Goudie and Pinkerton (197), and since then at least 130 cases have been described (256). Approximately 90% of cases present in the last trimester

of pregnancy or in the early postpartum period. Lymphocytic hypophysitis is characterized by inflammatory lesions of the pituitary, which simulate a pituitary space-occupying lesion, and often is diagnosed at biopsy of what was considered to be a tumor. The presentation may occur with symptoms of hypoadrenalism or hypothyroidism or other autoimmune conditions, such as pernicious anemia, and may be responsive to glucocorticoids in a proportion of cases.

Other causes of primary hypopituitarism in the adult population are pituitary or other intracranial neoplasms and their associated treatments. In one large series of hypopituitarism in the United Kingdom, 77% had been treated with surgery and 35% with pituitary radiotherapy (257). Iatrogenic causes of secondary AI are important, given the potential for early identification. Careful follow-up after transphenoidal surgery or pituitary irradiation is recommended. In macroadenomas, ACTH deficiency usually occurs late, in association with a progressive decline in GH, gonadotropin reserve, and TSH production. These all contribute to diminished reproductive function, ensuring that pregnancy is rare except in cases undergoing assisted reproduction. However, since the availability of ovulation induction with gonadotropins, women with established hypopituitarism can expect near normal fecundity, although their pregnancies are considered high risk (258).

D. Maternal and fetal morbidity and mortality

Early reports of AI in pregnancy highlighted the potential risks of mortality (259, 260). Cohen (261) reported a 35% mortality rate for AI in pregnancy in the 70 yr before 1930, which decreased to 18% between 1940 and 1947. In one of the largest early series, Brent (224) observed high rates of adrenal crisis and mortality (45%) in 39 cases of AI in pregnancy before 1946. In contrast, Hendon and Melick (262) subsequently found only one death in 14 cases in 1955. Indeed, more recent series demonstrate the potential for successful maternal outcome after the availability of cortisone in the 1950s. There have been no reported maternal deaths since the 1950s (219, 263). Several subsequent cases have illustrated the potential for safe outcomes for both mother and fetus in previously undiagnosed and untreated cases, probably reflecting less severe AI and improved obstetric care (225, 235, 264). Significantly, unrecognized cases may be protected by transplacental passage of cortisol from fetus to mother. Primate studies showed that up to 60% of fetal cortisol is normally transmitted to the mother, representing 6.6% of total maternal cortisol under normal conditions (236). Consequently, the need for treatment of AI may be recognized only in the immediate postpartum period (236). In cases with AI during pregnancy, careful attention to management of glucocorticoid replacement is required to enhance maternal outcomes and avoid adrenal crisis. Unfortunately, adrenal crisis can occur despite appropriate titration of glucocorticoid replacement, emphasizing the importance of close and careful clinical follow-up (225). Whereas maternal hypotension is a presentation of adrenocortical failure, side effects of treatment for AI include hypertension and exacerbation of preeclampsia (225, 265). It is also important to recognize that,

whereas the early emphasis is on careful antenatal care, follow-up in the distant postpartum period is critical given a report of late maternal death at 8 months postpartum (225).

Intrauterine growth retardation and low birth weight are the most commonly reported adverse effects for the fetus from mothers with untreated AI. Osler and Pedersen (228) demonstrated the association of fetal growth retardation with AI in a series of 15 cases in 1962; their observations have since been confirmed in a series of additional case reports by ultrasound (228, 236, 266, 267). In contrast, a later series of 34 pregnancies by Hilden and Ronnike (268) showed no discrepancy in gestational age or fetal weight compared with the general population. Careful treatment of AI with physiological glucocorticoid replacement in pregnancy can lead to successful pregnancy outcomes, including birth weights appropriate for gestational age (269).

The true prevalence of fetal mortality occurring in AI in pregnancy is unknown, and reported cases may be biased toward publication of successful pregnancy outcomes. However, there have been multiple reports of intrauterine death occurring in AI in pregnancy (265, 270, 271). Many of these reported cases occurred in previously unrecognized cases or before the availability of modern glucocorticoid regimens (265, 270, 271). Although there have been several reports of women with AI presenting during gestation with previous recurrent or subsequent abortions, there does not appear to be an increased risk from AI alone, when appropriately treated (229, 272–274). Of note, several such cases were associated with positive anticardiolipin antibodies or circulating lupus anticoagulant (272–274). Furthermore, adverse effects of associated conditions, including diabetes, likely contributed to fetal morbidity or mortality in other reports (228). There is no evidence of an increased prevalence of congenital defects resulting from AI (229).

Pregnancies in women with panhypopituitarism should be viewed as high risk. One single center series reported 18 patients with live births in 61%, miscarriage in 28%, midtrimester uterine death rate in 11%, and a high rate of fetal loss in twin pregnancy (258).

E. Diagnosis

1. Clinical and laboratory features. The majority of cases of AI in pregnancy already have a confirmed diagnosis at presentation. However, some patients present in the third trimester of pregnancy and may be unmasked during the stress of labor or intercurrent illness (266). A search for a possible new diagnosis of AI in pregnancy should be prompted by classic symptoms of excessive fatigue, malaise, weight loss, vomiting, or biochemical disturbance (264, 265). In women with hypoglycemia, testing of the HPA axis should be done before excluding other causes arising in pregnancy, and this symptom may be exacerbated by GH deficiency in those with secondary AI (275, 276). Patients may present with seizures or mental confusion that may require intensive care management (275).

Normal pregnancy is associated with a small reduction in serum sodium (5 mEq or less); if hyponatremia is more severe, primary AI should be excluded (264, 265). Notably, hyponatremia and metabolic acidosis are associated with a

poor fetal outcome (270). Hyperkalemia was absent in several cases of newly diagnosed primary AI and may not reflect the severity of adrenocortical dysfunction (264, 270). Exclusion of AI should be considered in cases with unexplained orthostasis or hypotension, even in the postpartum period (264, 273, 277). Signs of mineralocorticoid deficiency may signal impending adrenal crisis, which has a potentially high mortality in unrecognized cases in the community (260). However, patients with secondary AI do not often exhibit orthostasis and hypotension or hyperkalemia. As a result, absence of these features cannot be used to exclude AI.

We advocate a low threshold for consideration of AI (primary) in patients with a personal or family history of autoimmune disease or other relevant clinical features (264, 270, 278). The presence of other potentially associated organ-specific autoimmune disease, such as type 1 diabetes or vitiligo, should raise clinical suspicion of AI in the presence of typical symptoms (228–231, 265). Severe abdominal pain associated with increased pigmentation (melanoderma) may herald the onset of AI, and the possibility of acute adrenal hemorrhage should be considered (274). In some cases the presentation is associated with persistent vomiting that can be associated with or confused with hyperemesis gravidarum, potentially leading to a fatal outcome if left undiagnosed (264). Indeed one woman presented with severe weakness and psychotic behavior reflecting the diverse range of symptoms attributable to adrenocortical dysfunction (236).

Most patients with secondary AI have been identified before pregnancy, particularly if they have had previous glucocorticoid treatment as detailed above. It is less common for new-onset hypopituitarism to occur during pregnancy (256, 279).

Apart from the preservation of mineralocorticoid secretion, the principal differences in secondary AI compared with primary adrenal disease arise due to local effects from space-occupying lesions at the pituitary, such as headache or visual field disturbance, as well as associated hypopituitarism (225, 256, 279, 280). Significantly, due to the typical sequence of loss of pituitary reserve, ACTH deficiency is usually a late presentation of a primary pituitary etiology, and the patient is likely to have presented with earlier signs of pituitary dysfunction. A presentation with disturbed gonadotropin function resulting in amenorrhea is a frequent initial presentation in nonpregnant women. A failure of lactation or resumption of menses in the postpartum period may be the first sign of hypopituitarism. Involution of normal breast tissue may occur due to loss of prolactin reserve. Symptoms of fatigue and cold intolerance as well as skin or hair changes suggest thyroid dysfunction (279). Diabetes insipidus should prompt a search for large tumors such as craniopharyngiomas or lymphocytic hypophysitis (279). However, mild diabetes insipidus may coexist even in association with Sheehan's syndrome (252).

2. Screening tests for the diagnosis of AI. The diagnostic approach for evaluation of possible AI depends on the degree of clinical suspicion and pretest probability. Empirical treatment with glucocorticoids is recommended when the clinical suspicion for adrenal crisis is high due to the potential associated morbidity and mortality (265). In this setting it is

important to obtain samples for measurement of plasma cortisol and plasma ACTH levels while gaining iv access immediately before emergency treatment. Testing is first divided into assessment of the functional integrity of the HPA axis followed by a search for the underlying cause of AI. A variety of approaches, including random plasma cortisol or dynamic testing with ACTH stimulation, the insulin tolerance test (ITT), the metyrapone test, and lastly the CRH stimulation test, are available for confirmation of AI. However, most of these tests of HPA reserve have not been validated in pregnancy.

a. Random cortisol. In the nonstressed general population and pregnancy, an undetectable early morning plasma cortisol ($<3.0 \mu\text{g/dl}$; 83 nmol/liter) confirms AI in the setting of a typical clinical presentation (131). In the first and early second trimesters the diagnosis can be excluded if the patient is clinically stable when basal plasma cortisol levels are greater than $19 \mu\text{g/dl}$ (525 nmol/liter) (131, 281). Whereas a basal plasma cortisol greater than $19 \mu\text{g/dl}$ (525 nmol/liter) may be adequate for exclusion of AI in the nonstressed nonpregnant population, a normal nonpregnant reference range plasma cortisol is insufficient to exclude AI in the third trimester of pregnancy (281).

Figure 1 illustrates the normal physiological 3-fold rise in plasma cortisol observed during the third trimester of normal pregnancy (3, 120, 131, 282). In nongravid women, an elevated plasma ACTH level in the setting of normal plasma cortisol is considered presumptive evidence of subclinical AI, and further testing is indicated. Measurement of plasma ACTH is usually reserved for determination of the cause of AI; however, it may have more utility for diagnosis in pregnancy if it is elevated or undetectable, as levels stay within the normal range during gestation.

Patients with a clinical presentation consistent with AI and an indeterminate plasma cortisol ($3\text{--}30 \mu\text{g/dl}$; $83\text{--}828 \text{ nmol/liter}$) during gestation, and particularly during the third trimester, require formal dynamic testing of the HPA axis if the clinical suspicion is high (278). Unfortunately, as with plasma cortisol, the dynamic tests of adrenal reserve and their diagnostic cutoff points have not been validated during pregnancy.

b. Standard or high-dose cosyntropin stimulation test. Administration of cosyntropin (1–24 corticotropin) is the most commonly employed test used for the diagnosis of AI. The standard cosyntropin test (SCT) is performed by administering a supraphysiological dose of $250 \mu\text{g}$ im or iv and measuring plasma cortisol levels after 30 and 60 min. The test may be performed at any time of the day, and the 30-min cutoff point is considered the most consistent measure for diagnosis (283). The standard test performs well in patients with primary AI with high sensitivity and specificity (97 and 95%, respectively) (284) but is less sensitive for detection of early hypopituitarism (285). Defining cutoff points for a normal response to cosyntropin has been the focus of many previous series, and much debate, but published criteria are limited to the nonpregnant population (283). Discrepancies between results from the SCT and the ITT have also been a recent matter of debate given a number of nonpregnant patients

who may pass the SCT but fail an ITT (285–287). Conversely, higher cutoff points for the diagnosis based on ITT criteria may result in a higher proportion of normal subjects misdiagnosed.

Cosyntropin is licensed by the FDA as a category C drug for administration in pregnancy only when clearly indicated. Animal reproduction studies have not been conducted, and it is not conclusively known whether it can cause fetal harm when administered to pregnant women or can affect reproduction (package insert, Amphastar Pharmaceuticals). A plasma cortisol value of less than $18 \mu\text{g/dl}$ (497 nmol/liter) after cosyntropin, $250 \mu\text{g}$, was used for the diagnosis of AI in previous case reports (275, 288). However, these criteria are probably not accurate for use in pregnancy, given increased plasma cortisol responses to $250 \mu\text{g}$ ACTH ranging between 60 and 80% above nonpregnant responses in the second and third trimesters of normal pregnancy (120). Due to the lack of data in pregnancy on the plasma cortisol response to SCT, existing thresholds for the plasma cortisol response may be no more useful than basal cortisol levels used alone. In several series, basal cortisol levels were undetectable before an abnormal plasma cortisol after ACTH stimulation in confirmed AI during pregnancy (233, 270).

SCT seems the most cost-effective, safe, and reliable dynamic test for use in suspected primary AI in pregnancy (289–291). There is insufficient information to recommend specific cutoff points during pregnancy. However, based on previously reported 0800 h third trimester plasma cortisol levels and on results from low-dose cosyntropin stimulation testing (see below), we would exclude AI if basal and/or stimulated plasma cortisol levels in the third trimester after SCT are at least $30 \mu\text{g/dl}$ (828 nmol/liter) (131).

c. Low-dose cosyntropin stimulation test. Whereas the SCT has good reliability for detection of moderate or severe AI, it has limited utility in early AI, probably because mild adrenal dysfunction can be overcome by the supraphysiological ACTH dose. The $1 \mu\text{g}$ low-dose cosyntropin test (LCT) has been extensively studied in nonpregnant subjects and has sensitivity approaching 93% using cortisol criteria of $18.1\text{--}20.0 \mu\text{g/dl}$ ($500\text{--}550 \text{ nmol/liter}$) (283, 292, 293). The test is conducted by administering $1 \mu\text{g}$ ACTH(1–24) iv, with sampling for plasma cortisol at baseline and at intervals until 60 min. There has been controversy as to whether the LCT test offers additional sensitivity for detection of secondary AI (284, 292, 294, 295). A recent meta-analysis addressed this issue and found a sensitivity of 61% at a specificity of 95% using receiver operating curve analysis for nonpregnant patients taking glucocorticoids or with pituitary disease (284). Significantly, the SCT and LCT summary measures were no different at similar measures of sensitivity and specificity. Added to these issues the LCT has disadvantages compared with the SCT with regard to preparation, dilution, and ensuring an accurate dose administration. The LCT, however, has recently been examined in secondary AI in pregnancy (131).

McKenna *et al.* (131) examined responses to LCT during the 24th–34th wk of gestation. This prospective case-control trial enrolled 18 pregnant women at risk of preterm labor, who were receiving antenatal corticosteroids, and six healthy

controls with low-risk pregnancies. The women who had received at least two weekly courses of two doses of 12 mg betamethasone, 24 h apart, were assessed after a median of 3 d from betamethasone administration. The six normal pregnant women had a mean peak cortisol response of 44 $\mu\text{g/dl}$ (1215 nmol/liter) (99% confidence interval, 33.2–55.6 $\mu\text{g/dl}$; 917–1535 nmol/liter), which was attained at 27 min after LCT. In the corticosteroid-treated group, the peak cortisol was delayed at 37 min and did not exceed the normal unsuppressed response, 30 $\mu\text{g/dl}$ (828 nmol/liter). Only one subject had a peak cortisol greater than the nonpregnant cutoff of 18–20 $\mu\text{g/dl}$ (497–552 nmol/liter) used for the nonpregnant population (131). These preliminary observations suggest that a diagnosis of AI is confirmed using existing nonpregnant thresholds in the majority of cases. Using a threshold above 30 $\mu\text{g/dl}$ (828 pmol/liter) after LCT, the test will have increased sensitivity for the diagnosis of AI. Significantly, this study demonstrated that in most cases the diagnosis could be predicted by 0800 h plasma cortisol because only 17% of subjects with a subnormal LCT had basal plasma cortisol greater than 3 $\mu\text{g/dl}$ (82.8 nmol/liter) (131).

d. ITT. The ITT has been considered the “gold standard test” for assessment of the HPA axis in the general population, and the most accurate dynamic test for secondary AI. However, there are no reports to support its use in pregnancy, which should probably be considered a relative contraindication, given the potential risks for the fetus. The ITT may be considered a useful adjunct to testing with cosyntropin in the postpartum period for more formal assessment of HPA and GH reserve. The test is conducted by administering 0.1–0.15 U/kg iv and measuring glucose and cortisol at intervals until 60 min. The traditional cutoff point for normal responses in the nonpregnant population is 18 $\mu\text{g/dl}$ (497 nmol/liter), in the setting of confirmed hypoglycemia (40 $\mu\text{g/dl}$; <2.2 mmol/liter). However, the diagnostic accuracy is not 100%, and a range of diagnostic cutoff points has been used (283).

e. Metyrapone stimulation test. The metyrapone test was developed to assess the functional integrity of the HPA axis. Metyrapone blocks the *CYP11B1* (11- β hydroxylase) enzyme, thereby inhibiting the final step in cortisol synthesis with a consequent build up in the cortisol precursor 11-deoxycortisol, which is relatively devoid of glucocorticoid activity. As a result, there is a stimulus for production of ACTH and an increase in 11-deoxycortisol. The overnight metyrapone stimulation test is conducted by administering metyrapone, 30 mg orally, with a snack at midnight (296). Cortisol and 11-deoxycortisol are measured at 0800 h the following morning. AI is confirmed in the nonpregnant population with an 11-deoxycortisol level less than 7 $\mu\text{g/dl}$ (193 nmol/liter), in the setting of cortisol levels 2–7.5 $\mu\text{g/dl}$ (55–207 nmol/liter) (281). We do not recommend using the metyrapone test in pregnancy due to the risk of precipitating adrenal crisis.

f. CRH stimulation test. The CRH stimulation test has utility for differentiation of tertiary *vs.* secondary AI in nonpregnant subjects (132). Whereas in patients with secondary AI there is little or no ACTH response, those with tertiary disease usually have an exaggerated and prolonged ACTH response

(246). However, in pregnancy the normal cortisol and ACTH response is typically reduced, and therefore this test probably has limited utility for the diagnosis of AI (132). In addition to the need for further validation in the general and pregnant population, the test is expensive and requires multiple sampling time points. For these reasons we do not recommend the CRH test for the diagnosis of AI in pregnancy.

3. Differentiation of primary and secondary AI. Cases of primary AI must be distinguished from Sheehan’s syndrome or other secondary causes in view of their associated anterior pituitary hormone deficiencies (297–299). Plasma ACTH levels differentiate primary (elevated) from secondary adrenal failure (low or normal) and can help to confirm primary AI in nonpregnant patients with borderline plasma cortisol levels. It is for this reason that simultaneous plasma cortisol and plasma ACTH levels should be drawn in the initial workup for AI, immediately before empirical treatment of adrenal crisis. ACTH levels are normally within the reference range in the absence of AI. An ACTH level above 100 pg/ml (22 pmol/liter) is generally consistent with primary AI, even in late pregnancy (281). In primary AI in pregnancy, elevated ACTH levels in the range of 400–2000 pg/ml (88–440 pmol/liter) have been reported (219, 264, 274). However, ACTH levels fluctuate widely day to day, and a single value cannot be relied upon for diagnosis of either primary or secondary AI (266). It is prudent to measure ACTH on multiple occasions to improve diagnostic accuracy. To avoid falsely low results, it is important to collect the sample in prechilled EDTA tubes, with transport in an ice bath and prompt refrigerated centrifugation and plasma separation.

Approximately 90% of nonpregnant patients with “idiopathic” AI are positive for 21-hydroxylase antibodies, and antibodies to 17 α -hydroxylase and side chain cleavage enzymes are positive in approximately 30% (300, 301). Positive adrenal antibodies predict the development of AI and may be elevated in other forms of organ-specific autoimmune disease (302). In one series of 123 women, positive testing for adrenal antibodies detected subclinical AI in 3.2% of cases (302). The presence of adrenal antibodies provides confirmatory evidence for an autoimmune etiology but cannot be relied upon for diagnosis of AI, given a 10% prevalence of negative testing in patients with proven AI. Positive adrenal antibodies should prompt a search for other endocrine deficiencies that might require treatment.

The presence of mineralocorticoid deficiency is highly suggestive of primary AI arising from adrenocortical atrophy. Although formal dynamic testing of mineralocorticoid reserve is not usually required, a failure of plasma aldosterone to reach 5 ng/ml (0.14 nmol/liter) at 30 min after cosyntropin supports a diagnosis of primary AI in nonpregnant subjects (283, 303). Whereas plasma aldosterone levels and PRA are elevated in normal pregnancy, there are no data on these values in patients with AI (87), and cutoff points for AI in pregnancy have not been established.

Patients with secondary AI should undergo additional testing to determine the extent of hypopituitarism; GH testing *may be* especially useful as it usually antedates other loss of other pituitary hormone reserve.

4. *Retesting in the postpartum period.* Formal retesting of the HPA axis should be considered when a diagnosis has been made during gestation, particularly in cases of adrenal hemorrhage, which may manifest as reversible AI (273, 275). However, formal retesting should not be considered in the immediate postpartum period because biochemical values do not usually return to prepregnancy levels until at least 7 d after delivery (304).

5. *Imaging.* Patients with positive adrenal antibodies have an autoimmune etiology and do not require imaging. Imaging of the adrenal glands can detect the large glands associated with tuberculous or fungal infection, bilateral metastases, hemorrhage, or infarction (274, 277, 305). Ultrasound imaging is safe but may have limited resolution. MRI without gadolinium administration is preferred to CT in pregnancy. Although MRI provides excellent soft tissue enhancement and has improved resolution compared with ultrasound (306, 307), during the differential diagnosis we recommend deferment of adrenal imaging until the postpartum period, provided that the patient is clinically stable (277).

Pituitary MRI without gadolinium administration should be considered early in the evaluation of secondary AI to exclude a pituitary macroadenoma or space-occupying lesion (279, 308, 309). As it has limited specificity for differentiation of lymphocytic hypophysitis from other pituitary masses, a biopsy may be required (but is rarely necessary) for a definitive diagnosis (256, 310). In Sheehan's syndrome, a CT scan may reveal absence of pituitary enhancement, consistent with pituitary ischemia (252). At longer-term follow-up, an empty sella may be seen (252). However, because documentation of this diagnosis is not needed for treatment, we recommend that CT scans be deferred to the postpartum period to reduce exposure to radiation.

F. Treatment

Patients with primary or secondary AI are best managed by a multidisciplinary clinic that includes an endocrinologist and an obstetrician who have access to an experienced pituitary surgeon. The primary focus for endocrinology is directed at diagnosis and monitoring the adequacy of mineralocorticoid and/or corticosteroid replacement therapy in the antenatal period, during crisis and labor, and for continuity during the postpartum period. The team must decide on the optimal timing for surgical removal of craniopharyngiomas or other large intracranial neoplasms; although surgery may be left to the postpartum period in selected cases, the second trimester is widely believed to be the optimal time for surgery during gestation (279).

Glucocorticoid and mineralocorticoid treatment is not associated with teratogenicity or increased fetal loss (311). In a large early report of women in 260 pregnancies treated with pharmacological doses of corticosteroids, there were eight stillbirths, 15 premature infants, and seven congenital abnormalities, two of which were cleft palate (312). Walsh and Clark (313) described the potential for successful pregnancy with normal labor and fetal outcome, in the absence of increased congenital birth defects, maternal infections, poor wound healing, or hemorrhage in patients on long-term cor-

ticosteroids. They also demonstrated normal progress and development up to age 6 yr during screening of a limited number of children whose mothers were treated with pharmacological corticosteroids in pregnancy (313). Due to the potential for fetal adrenal hypoplasia, we recommend careful monitoring of the mother during the antenatal period, and of the infant in the early postpartum period, in cases treated with pharmacological corticosteroid doses (314).

1. *Glucocorticoid replacement.* Corticosteroid therapy became available for treatment of AI in the 1950s and was associated with improved outcomes in pregnancy. The early use of DOC was subsequently replaced by cortisone (17-hydroxy-11-dehydrocorticosterone) (315, 316). The aim of treatment in pregnancy is to achieve a physiological glucocorticoid replacement dose to enhance maternal and fetal outcomes (262). The most dangerous periods during pregnancy are in undiagnosed cases during the first trimester when symptoms of adrenal crisis can be mistaken for pregnancy-associated emesis, and during the stress of labor and delivery (270). With adequate replacement there is often prompt resolution of buccal hyperpigmentation in newly diagnosed cases (262). During the first and second trimesters, careful monitoring and titration of therapy is required to avoid corticosteroid overreplacement and the potential for inducing symptoms or signs of CS (267) and, in women with coexisting type 1 diabetes, to prevent recurrent hypoglycemia (229).

Several glucocorticoid preparations are available for chronic replacement during pregnancy. Hydrocortisone is our preferred choice at a replacement dose of 12–15 mg/m² of body surface area (253). The daily dose is usually divided in two: two thirds given on wakening and the remaining one third of daily requirement in the afternoon, to mimic the normal diurnal variation. Stable isotope studies indicate a normal adult cortisol secretion rate of 4–8 mg/m² · d, and present replacement regimens for the nonpregnant population may lead to overreplacement in a proportion of cases (317). It is interesting to note that the replacement doses of hydrocortisone in women with AI, when taking the oral contraceptive pill, are not higher than those of a similar weight not on the pill. Consistent with these observations, glucocorticoid doses rarely need to be increased during pregnancy, even in the third trimester. One series described the natural history of five pregnancies in patients undergoing treatment for AI in pregnancy (225). Adverse effects included psychosis, personality change, and increased pigmentation. The hydrocortisone dose was increased in two women; two required an increase in mineralocorticoid dose, two remained stable, and one commenced therapy during pregnancy (225).

Other choices for glucocorticoid replacement include prednisone, prednisolone, or cortisone acetate. Prednisone and cortisone acetate are both inactive and require reduction of a ketone group to a hydroxyl group on carbon 11. Although they may be used for chronic therapy, they should not be considered for treatment of adrenal crisis. Whereas cortisol (hydrocortisone) and cortisone acetate have relatively short biological half-lives (8–12 h), prednisone and prednisolone have longer half-lives of 24–72 h (318). Therefore, although these agents are more useful in pharmaco-

logical doses for inflammatory conditions, hydrocortisone may be a more useful physiological replacement therapy. Furthermore, the fetus is relatively protected from excessive glucocorticoid exposure by the enzyme 11 β -HSD 2. Glucocorticoids can cross the placenta. In contrast to hydrocortisone, dexamethasone is not degraded by 11 β -HSD 2. Thus, we recommend hydrocortisone for use in pregnancy in terms of its efficacy and safety profile.

2. Mineralocorticoid replacement. Mineralocorticoids are required only in primary AI and are usually initiated at the time of diagnosis of AI. Before the availability of 9 α -fluoro-hydrocortisone, salt tablets (3–6 g sodium chloride given orally) were used for treatment of mineralocorticoid deficiency (262, 315). Modern regimens use oral fludrocortisone at a usual daily dose of 0.1 mg, which can range between 0.05 and 0.2 mg (318). Mineralocorticoid dosages are usually stable through pregnancy; however, in some cases doses are reduced during the third trimester to avoid side effects of edema or exacerbation of hypertension (319). In contrast, other women with primary AI have had a stable clinical course in the absence of mineralocorticoid treatment (229). This may be explained, in part, by the mineralocorticoid action of hydrocortisone. Ongoing careful clinical assessment will detect potential side effects of treatment during the various stages of pregnancy (319). Low plasma aldosterone in the setting of elevated PRA may have utility for assessment of the adequacy of mineralocorticoid replacement therapy, but this has not been formally validated in pregnancy.

3. Education. The management of AI in pregnancy relies upon education of the patient at diagnosis with reinforcement of the basic principles of management regularly at follow-up. As in the nonpregnant population, an individual's adherence to the prescribed treatment regimen may avoid adrenal crisis, which is a particular challenge, given the frequency of nausea or vomiting during the first trimester. Consequently, prepregnancy counseling should be conducted to ensure that women with planned or unplanned pregnancy know to present themselves to endocrinology and obstetric care early in gestation, given the inherent risks associated with delayed management. It is important to advise patients to continue the replacement dose of corticosteroid even in the presence of nausea. Women should be taught to give hydrocortisone, 100 mg im, in the event of emesis or other gastrointestinal symptoms that preclude effective absorption of an oral dose and should be advised to seek parenteral therapy in the setting of protracted nausea or vomiting. Women should be encouraged to present early during systemic illness for iv hydrocortisone treatment. All patients with AI, particularly during pregnancy, should be advised to wear a medic alert bracelet or necklace so that they may be identified in an emergency (MedicAlert Foundation International, 2323 Colorado Avenue, Turlock, CA 95382; telephone, 888-633-4298 or www.medicalert.org).

4. During labor. Normal vaginal delivery is a reasonable expectation for women with AI. Indications for delivery by C-section are similar to those in a nonpregnant individual (225). Routine replacement therapy can be continued until the onset of labor. During labor the patient's normal dose of

hydrocortisone is doubled, provided that oral intake is tolerated. Alternatively, a parenteral dose of 50 mg hydrocortisone may be given during the second stage of labor, with further dosing dependent on the progress of labor (219). Before C-section, stress doses of hydrocortisone, 100 mg iv or im, are given at the onset and continued at 6- to 8-h intervals after delivery (253). The doses of hydrocortisone then can be tapered over 48 h to a regular replacement dose (253, 318). Physiological glucocorticoid replacement can continue during breast feeding, as less than 0.5% of the absorbed dose is excreted per liter of breast milk (266, 311).

5. Acute treatment for adrenal crisis diagnosed during pregnancy. During pregnancy an undiagnosed patient with AI may tolerate the first, second, or third trimesters but experience an acute deterioration during the labor and delivery. Alternatively, an associated urinary tract infection, hyperemesis, preeclampsia, or significant antepartum hemorrhage may precipitate an adrenal crisis in gestation. The presentation of adrenal crisis, as in the general population, is often associated with hypotension, hypoglycemia, or coma (320). Acute treatment of AI includes prompt rapid glucocorticoid replacement with hydrocortisone, 100–200 mg, given iv as a single bolus. Thereafter, 50–100 mg boluses are given every 6–8 h during the acute period, based on maximal cortisol production rates of 200–400 mg/d (265). Women with hypoglycemia should receive 5% dextrose infusions (321), and those with hypotension should receive normal saline. Fludrocortisone is not indicated in the acute period and has been associated with pulmonary edema due to salt and water retention (265). Treatment with cortisone or prednisone, which has been associated with a poor maternal outcome in individual cases, is not recommended for adrenal crisis due to the requirement for metabolism to the active forms (259). A transfer to routine oral therapy is warranted when acute symptoms have settled or when the patient is tolerating oral fluids.

6. Postpartum. After delivery all women should recommence mineralocorticoid and/or corticosteroid replacement, usually at the dose they received before gestation, within the first 24–48 h after delivery. In a limited number of cases, stress coverage may be required during recovery from surgery or intercurrent illness. Assessment of the HPA axis in infants from mothers with AI who received appropriate physiological glucocorticoid replacement is usually not necessary. However, infants born to mothers receiving pharmacological doses of agents that cross the placenta require more formal assessment to exclude AI.

V. Summary

In conclusion, the HPA axis plays an important physiological role in normal pregnancy, contributing to regulation of maternal fertility, parturition, blood pressure control, and sodium balance. Although disorders of the HPA axis are rare, CS and adrenocortical hypofunction, when untreated, are associated with significant maternal and fetal morbidity and potential mortality. This review illustrates some of the difficulties in interpretation of diagnostic testing in pregnancy

and provides a framework for the management of CS and hypoadrenalism occurring in pregnancy.

Acknowledgments

Address all correspondence and requests for reprints to: L. K. Nieman, M.D., Reproductive Biology and Medicine Branch, National Institute of Child Health and Human Development, National Institutes of Health, Building 10, Clinical Research Center, Room 1-3140, 10 Center Drive, Bethesda, Maryland 20892-1109. E-mail: niemanl@mail.nih.gov

References

- Gemzell CA 1953 Blood levels of 17-hydroxycorticosteroids in normal pregnancy. *J Clin Endocrinol* 13:898–902
- Bayliss RI, Browne JC, Round BP, Steinbeck AW 1955 Plasma 17-hydroxycorticosteroids in pregnancy. *Lancet* 268:62–64
- Carr BR, Parker Jr CR, Madden JD, MacDonald PC, Porter JC 1981 Maternal plasma adrenocorticotropin and cortisol relationships throughout human pregnancy. *Am J Obstet Gynecol* 139:416–422
- Cousins L, Rigg L, Hollingsworth D, Meis P, Halberg F, Brink G, Yen SS 1983 Qualitative and quantitative assessment of the circadian rhythm of cortisol in pregnancy. *Am J Obstet Gynecol* 145:411–416
- Nolten WE, Lindheimer MD, Rueckert PA, Oparil S, Ehrlich EN 1980 Diurnal patterns and regulation of cortisol secretion in pregnancy. *J Clin Endocrinol Metab* 51:466–472
- Patrick J, Challis J, Natale R, Richardson B 1979 Circadian rhythms in maternal plasma cortisol, estrone, estradiol, and estril at 34 to 35 weeks' gestation. *Am J Obstet Gynecol* 135:791–798
- Nolten WE, Rueckert PA 1981 Elevated free cortisol index in pregnancy: possible regulatory mechanisms. *Am J Obstet Gynecol* 139:492–498
- Wilson EA, Finn AE, Rayburn W, Jawad MJ 1979 Corticosteroid-binding globulin and estrogens in maternal and cord blood. *Am J Obstet Gynecol* 135:215–218
- Martin JD, Mills IH 1958 The effects of pregnancy on adrenal steroid metabolism. *Clin Sci (Lond)* 17:137–146
- Scott EM, McGarrigle HH, Lachelin GC 1990 The increase in plasma and saliva cortisol levels in pregnancy is not due to the increase in corticosteroid-binding globulin levels. *J Clin Endocrinol Metab* 71:639–644
- Meulenberg PM, Hofman JA 1990 The effect of oral contraceptive use and pregnancy on the daily rhythm of cortisol and cortisone. *Clin Chim Acta* 190:211–221
- Demey-Ponsart E, Foidart JM, Sulon J, Sodozoy JC 1982 Serum CBG, free and total cortisol and circadian patterns of adrenal function in normal pregnancy. *J Steroid Biochem* 16:165–169
- Odagiri E, Ishiwatari N, Abe Y, Jibiki K, Adachi T, Demura H, Shizume K 1988 Hypercortisolism and the resistance to dexamethasone suppression during gestation. *Endocrinol Jpn* 35:685–690
- Mukherjee K, Swyer GI 1972 Plasma cortisol and adrenocorticotrophic hormone in normal men and non-pregnant women, normal pregnant women and women with pre-eclampsia. *J Obstet Gynaecol Br Commonw* 79:504–512
- Magiakou MA, Mastorakos G, Rabin D, Margioris AN, Dubbert B, Calogero AE, Tsigos C, Munson PJ, Chrousos GP 1996 The maternal hypothalamic-pituitary-adrenal axis in the third trimester of human pregnancy. *Clin Endocrinol (Oxf)* 44:419–428
- Burke CW, Roulet F 1970 Increased exposure of tissues to cortisol in late pregnancy. *Br Med J* 1:657–659
- Allolio B, Hoffmann J, Linton EA, Winkelmann W, Kusche M, Schulte HM 1990 Diurnal salivary cortisol patterns during pregnancy and after delivery: relationship to plasma corticotrophin-releasing-hormone. *Clin Endocrinol (Oxf)* 33:279–289
- Dorr HG, Heller A, Vermold HT, Sippell WG, Herrmann M, Bidlingmaier F, Knorr D 1989 Longitudinal study of progestins, mineralocorticoids, and glucocorticoids throughout human pregnancy. *J Clin Endocrinol Metab* 68:863–868
- Fowden AL, Forhead AJ 2004 Endocrine mechanisms of intrauterine programming. *Reproduction* 127:515–526
- Seckl JR, Cleasby M, Nyirenda MJ 2000 Glucocorticoids, 11 β -hydroxysteroid dehydrogenase, and fetal programming. *Kidney Int* 57:1412–1417
- Beitins IZ, Bayard F, Ances IG, Kowarski A, Migeon CJ 1973 The metabolic clearance rate, blood production, interconversion and transplacental passage of cortisol and cortisone in pregnancy near term. *Pediatr Res* 7:509–519
- Kajantie E, Dunkel L, Turpeinen U, Stenman UH, Wood PJ, Nuutila M, Andersson S 2003 Placental 11 β -hydroxysteroid dehydrogenase-2 and fetal cortisol/cortisone shuttle in small preterm infants. *J Clin Endocrinol Metab* 88:493–500
- Quinkler M, Oelkers W, Diederich S 2001 Clinical implications of glucocorticoid metabolism by 11 β -hydroxysteroid dehydrogenases in target tissues. *Eur J Endocrinol* 144:87–97
- Murphy BE 1977 Conversion of cortisol to cortisone by the human uterus and its reversal in pregnancy. *J Clin Endocrinol Metab* 44:1214–1217
- Phillips DI, Barker DJ, Fall CH, Seckl JR, Whorwood CB, Wood PJ, Walker BR 1998 Elevated plasma cortisol concentrations: a link between low birth weight and the insulin resistance syndrome? *J Clin Endocrinol Metab* 83:757–760
- Phillips DI 2001 Programming of adrenocortical function and the fetal origins of adult disease. *J Endocrinol Invest* 24:742–746
- Waddell BJ 1993 The placenta as hypothalamus and pituitary: possible impact on maternal and fetal adrenal function. *Reprod Fertil Dev* 5:479–497
- Raisanen I 1988 Plasma levels and diurnal variation of β -endorphin, β -lipotropin and corticotropin during pregnancy and early puerperium. *Eur J Obstet Gynecol Reprod Biol* 27:13–20
- Rees LH, Burke CW, Chard T, Evans SW, Lettichworth AT 1975 Possible placental origin of ACTH in normal human pregnancy. *Nature* 254:620–622
- Odagiri E, Sherrell BJ, Mount CD, Nicholson WE, Orth DN 1979 Human placental immunoreactive corticotropin, lipotropin, and β -endorphin: evidence for a common precursor. *Proc Natl Acad Sci USA* 76:2027–2031
- Nakai Y, Nakao K, Oki S, Imura H, Li CH 1978 Presence of immunoreactive β -endorphin in plasma of patients with Nelson's syndrome and Addison's disease. *Life Sci* 23:2293–2298
- Demura R, Odagiri E, Yoshimura M, Jibiki K, Adachi T, Shirota M, Demura H, Shizume K, Oouchi H 1982 Placental secretion of prolactin, ACTH and immunoreactive β -endorphin during pregnancy. *Acta Endocrinol (Copenh)* 100:114–119
- Chen CL, Chang CC, Krieger DT, Bardin CW 1986 Expression and regulation of proopiomelanocortin-like gene in the ovary and placenta: comparison with the testis. *Endocrinology* 118:2382–2389
- Liotta A, Osathanondh R, Ryan KJ, Krieger DT 1977 Presence of corticotropin in human placenta: demonstration of *in vitro* synthesis. *Endocrinology* 101:1552–1558
- Liotta AS, Krieger DT 1980 *In vitro* biosynthesis and comparative posttranslational processing of immunoreactive precursor corticotropin/ β -endorphin by human placental and pituitary cells. *Endocrinology* 106:1504–1511
- Raffin-Sanson ML, Massias JF, Ankotche A, Coste J, de Keyzer Y, Oliver C, Dumont C, Cabrol D, Ferre F, Bertagna X 1999 High precursor level in maternal blood results from the alternate mode of proopiomelanocortin processing in human placenta. *Clin Endocrinol (Oxf)* 50:85–94
- Genazzani AR, Petraglia F, Parrini D, Nasi A, Angioni G, Facchinetti F, Facchini V, Volpe A 1984 Lack of correlation between amniotic fluid and maternal plasma contents of β -endorphin, β -lipotropin, and adrenocorticotrophic hormone in normal and pathologic pregnancies. *Am J Obstet Gynecol* 148:198–203
- Mulder GH, Maas R, Arts NF 1986 *In vitro* secretion of peptide hormones by the human placenta. I. ACTH. *Placenta* 7:143–153
- Waddell BJ, Burton PJ 1993 Release of bioactive ACTH by perfused human placenta at early and late gestation. *J Endocrinol* 136:345–353
- Petraglia F, Sawchenko PE, Rivier J, Vale W 1987 Evidence for local stimulation of ACTH secretion by corticotropin-releasing factor in human placenta. *Nature* 328:717–719

41. Sasaki A, Tempst P, Liotta AS, Margioris AN, Hood LE, Kent SB, Sato S, Shinkawa O, Yoshinaga K, Krieger DT 1988 Isolation and characterization of a corticotropin-releasing hormone-like peptide from human placenta. *J Clin Endocrinol Metab* 67:768–773
42. Magiakou MA, Mastorakos G, Webster E, Chrousos GP 1997 The hypothalamic-pituitary-adrenal axis and the female reproductive system. *Ann NY Acad Sci* 816:42–56
43. Sasaki A, Liotta AS, Luckey MM, Margioris AN, Suda T, Krieger DT 1984 Immunoreactive corticotropin-releasing factor is present in human maternal plasma during the third trimester of pregnancy. *J Clin Endocrinol Metab* 59:812–814
44. Goland RS, Wardlaw SL, Stark RI, Brown Jr LS, Frantz AG 1986 High levels of corticotropin-releasing hormone immunoactivity in maternal and fetal plasma during pregnancy. *J Clin Endocrinol Metab* 63:1199–1203
45. Campbell EA, Linton EA, Wolfe CD, Scraggs PR, Jones MT, Lowry PJ 1987 Plasma corticotropin-releasing hormone concentrations during pregnancy and parturition. *J Clin Endocrinol Metab* 64:1054–1059
46. Sasaki A, Shinkawa O, Yoshinaga K 1990 Immunoreactive corticotropin-releasing hormone in amniotic fluid. *Am J Obstet Gynecol* 162:194–198
47. Frim DM, Emanuel RL, Robinson BG, Smas CM, Adler GK, Majzoub JA 1988 Characterization and gestational regulation of corticotropin-releasing hormone messenger RNA in human placenta. *J Clin Invest* 82:287–292
48. Petraglia F, Tabanelli S, Galassi MC, Garuti GC, Mancini AC, Genazzani AR, Gurpide E 1992 Human decidua and *in vitro* decidualized endometrial stromal cells at term contain immunoreactive corticotropin-releasing factor (CRF) and CRF messenger ribonucleic acid. *J Clin Endocrinol Metab* 74:1427–1431
49. Hillhouse EW, Grammatopoulos DK 2002 Role of stress peptides during human pregnancy and labour. *Reproduction* 124:323–329
50. Madhappan B, Kempuraj D, Christodoulou S, Tsapikidis S, Boucher W, Karagiannis V, Athanassiou A, Theoharides TC 2003 High levels of intrauterine corticotropin-releasing hormone, urocortin, tryptase, and interleukin-8 in spontaneous abortions. *Endocrinology* 144:2285–2290
51. Sorem KA, Smikle CB, Spencer DK, Yoder BA, Graveson MA, Siler-Khodr TM 1996 Circulating maternal corticotropin-releasing hormone and gonadotropin-releasing hormone in normal and abnormal pregnancies. *Am J Obstet Gynecol* 175:912–916
52. Goland RS, Wardlaw SL, Blum M, Tropper PJ, Stark RI 1988 Biologically active corticotropin-releasing hormone in maternal and fetal plasma during pregnancy. *Am J Obstet Gynecol* 159:884–890
53. Kalantaridou SN, Makriganakis A, Mastorakos G, Chrousos GP 2003 Roles of reproductive corticotropin-releasing hormone. *Ann NY Acad Sci* 997:129–135
54. Mastorakos G, Ilias I 2003 Maternal and fetal hypothalamic-pituitary-adrenal axes during pregnancy and postpartum. *Ann NY Acad Sci* 997:136–149
55. Smith R 1998 Alterations in the hypothalamic pituitary adrenal axis during pregnancy and the placental clock that determines the length of parturition. *J Reprod Immunol* 39:215–220
56. Ozawa M, Oki Y, Watanabe F, Iino K, Masuzawa M, Iwabuchi M, Yoshimi T 1998 Effect of urocortin and its interaction with adrenocorticotropin (ACTH) secretagogues on ACTH release. *Peptides* 19:513–518
57. Fadalti M, Pezzani I, Cobellis L, Springolo F, Petrovec MM, Ambrosini G, Reis FM, Petraglia F 2000 Placental corticotropin-releasing factor. An update. *Ann NY Acad Sci* 900:89–94
58. Okamoto E, Takagi T, Makino T, Sata H, Iwata I, Nishino E, Mitsuda N, Sugita N, Otsuki Y, Tanizawa O 1989 Immunoreactive corticotropin-releasing hormone, adrenocorticotropin and cortisol in human plasma during pregnancy and delivery and postpartum. *Horm Metab Res* 21:566–572
59. Tropper PJ, Goland RS, Wardlaw SL, Fox HE, Frantz AG 1987 Effects of betamethasone on maternal plasma corticotropin releasing factor, ACTH and cortisol during pregnancy. *J Perinat Med* 15:221–225
60. Marinoni E, Korebrits C, Di Iorio R, Cosmi EV, Challis JR 1998 Effect of betamethasone *in vivo* on placental corticotropin-releasing hormone in human pregnancy. *Am J Obstet Gynecol* 178:770–778
61. Robinson BG, Emanuel RL, Frim DM, Majzoub JA 1988 Glucocorticoid stimulates expression of corticotropin-releasing hormone gene in human placenta. *Proc Natl Acad Sci USA* 85:5244–5248
62. Blumenfeld Z, Jaffe RB 1986 Hypophysiotropic and neuromodulatory regulation of adrenocorticotropin in the human fetal pituitary gland. *J Clin Invest* 78:288–294
63. Potter E, Behan DP, Fischer WH, Linton EA, Lowry PJ, Vale WW 1991 Cloning and characterization of the cDNAs for human and rat corticotropin releasing factor-binding proteins. *Nature* 349:423–426
64. Thomson M 1998 Does the CRH binding protein shield the anterior pituitary from placental CRH? *Endocrine* 9:221–226
65. Orth DN, Mount CD 1987 Specific high-affinity binding protein for human corticotropin-releasing hormone in normal human plasma. *Biochem Biophys Res Commun* 143:411–417
66. Linton EA, Perkins AV, Woods RJ, Eben F, Wolfe CD, Behan DP, Potter E, Vale WW, Lowry PJ 1993 Corticotropin releasing hormone-binding protein (CRH-BP): plasma levels decrease during the third trimester of normal human pregnancy. *J Clin Endocrinol Metab* 76:260–262
67. Linton EA, Behan DP, Saphier PW, Lowry PJ 1990 Corticotropin-releasing hormone (CRH)-binding protein: reduction in the adrenocorticotropin-releasing activity of placental but not hypothalamic CRH. *J Clin Endocrinol Metab* 70:1574–1580
68. Sehlinger B, Zahradnik HP, Simon M, Ziegler R, Noethling C, Schaefer WR 2004 mRNA expression profiles for corticotrophin-releasing hormone, urocortin, CRH-binding protein and CRH receptors in human term gestational tissues determined by real-time quantitative RT-PCR. *J Mol Endocrinol* 32:339–348
69. Jones SA, Challis JR 1989 Local stimulation of prostaglandin production by corticotropin-releasing hormone in human fetal membranes and placenta. *Biochem Biophys Res Commun* 159:192–199
70. Makriganakis A, Zoumakis E, Kalantaridou S, Coutifaris C, Margioris AN, Coukos G, Rice KC, Gravanis A, Chrousos GP 2001 Corticotropin-releasing hormone promotes blastocyst implantation and early maternal tolerance. *Nat Immunol* 2:1018–1024
71. McLean M, Bisits A, Davies J, Woods R, Lowry P, Smith R 1995 A placental clock controlling the length of human pregnancy. *Nat Med* 1:460–463
72. Wadhwa PD, Porto M, Garite TJ, Chic-DeMet A, Sandman CA 1998 Maternal corticotropin-releasing hormone levels in the early third trimester predict length of gestation in human pregnancy. *Am J Obstet Gynecol* 179:1079–1085
73. Ochedalski T, Zylinska K, Laudanski T, Lachowicz A 2001 Corticotrophin-releasing hormone and ACTH levels in maternal and fetal blood during spontaneous and oxytocin-induced labour. *Eur J Endocrinol* 144:117–121
74. Sasaki A, Shinkawa O, Yoshinaga K 1989 Placental corticotropin-releasing hormone may be a stimulator of maternal pituitary adrenocorticotropin hormone secretion in humans. *J Clin Invest* 84:1997–2001
75. Florio P, Vale W, Petraglia F 2004 Urocortins in human reproduction. *Peptides* 25:1751–1757
76. Holloway AC, Howe DC, Chan G, Clifton VL, Smith R, Challis JR 2002 Urocortin: a mechanism for the sustained activation of the HPA axis in the late-gestation ovine fetus? *Am J Physiol Endocrinol Metab* 283:E165–E171
77. Asaba K, Makino S, Hashimoto K 1998 Effect of urocortin on ACTH secretion from rat anterior pituitary *in vitro* and *in vivo*: comparison with corticotropin-releasing hormone. *Brain Res* 806:95–103
78. Iino K, Sasano H, Oki Y, Andoh H, Shin RW, Kitamoto T, Totsune K, Takahashi K, Suzuki H, Nagura H, Yoshimi T 1997 Urocortin expression in human pituitary gland and pituitary adenoma. *J Clin Endocrinol Metab* 82:3842–3850
79. Clifton VL, Gu Q, Murphy VE, Schwartz J, Madsen G, Smith R 2000 Localization and characterization of urocortin during human pregnancy. *Placenta* 21:782–788
80. Glynn BP, Wolton A, Rodriguez-Linares B, Phaneuf S, Linton EA 1998 Urocortin in pregnancy. *Am J Obstet Gynecol* 179:533–539

81. Petraglia F, Florio P, Benedetto C, Marozio L, Di Blasio AM, Ticconi C, Piccione E, Luisi S, Genazzani AR, Vale W 1999 Urocortin stimulates placental adrenocorticotropin and prostaglandin release and myometrial contractility *in vitro*. *J Clin Endocrinol Metab* 84:1420–1423
82. Muramatsu Y, Sugino N, Suzuki T, Totsune K, Takahashi K, Tashiro A, Hongo M, Oki Y, Sasano H 2001 Urocortin and corticotropin-releasing factor receptor expression in normal cycling human ovaries. *J Clin Endocrinol Metab* 86:1362–1369
83. Karteris E, Hillhouse EW, Grammatopoulos D 2004 Urocortin II is expressed in human pregnant myometrial cells and regulates myosin light chain phosphorylation: potential role of the type-2 corticotropin-releasing hormone receptor in the control of myometrial contractility. *Endocrinology* 145:890–900
84. Aggelidou E, Hillhouse EW, Grammatopoulos DK 2002 Up-regulation of nitric oxide synthase and modulation of the guanylate cyclase activity by corticotropin-releasing hormone but not urocortin II or urocortin III in cultured human pregnant myometrial cells. *Proc Natl Acad Sci USA* 99:3300–3305
85. Gabbe SG 2002 Obstetrics—normal and problem pregnancies, 4th ed. New York, Edinburgh, London, and Philadelphia: Churchill and Livingston
86. Ehrlich EN 1978 Mineralocorticoids in normal and hypertensive pregnancies. *Semin Perinatol* 2:61–71
87. Wilson M, Morganti AA, Zervoudakis I, Letcher RL, Romney BM, Von Oeyon P, Papera S, Sealey JE, Laragh JH 1980 Blood pressure, the renin-aldosterone system and sex steroids throughout normal pregnancy. *Am J Med* 68:97–104
88. Ehrlich EN, Nolten WE, Oparil S, Lindheimer MD 1976 Mineralocorticoids in normal pregnancy. *Perspect Nephrol Hypertens* 5:189–201
89. Sims EA, Krantz KE 1958 Serial studies of renal function during pregnancy and the puerperium in normal women. *J Clin Invest* 37:1764–1774
90. Laidlaw JC, Ruse JL, Gornall AG 1962 The influence of estrogen and progesterone on aldosterone excretion. *J Clin Endocrinol Metab* 22:161–171
91. Lindheimer MD, Katz AI, Nolten WE, Oparil S, Ehrlich EN 1977 Sodium and mineralocorticoids in normal and abnormal pregnancy. *Adv Nephrol Necker Hosp* 7:33–59
92. Quinkler M, Meyer B, Oelkers W, Diederich S 2003 Renal inactivation, mineralocorticoid generation, and 11β -hydroxysteroid dehydrogenase inhibition ameliorate the antimineralocorticoid effect of progesterone *in vivo*. *J Clin Endocrinol Metab* 88:3767–3772
93. Helmer OM, Griffith RS 1952 The effect of the administration of estrogens on the renin-substrate (hypertensinogen) content of rat plasma. *Endocrinology* 51:421–426
94. Mirshahi M, Ayani E, Nicolas C, Golestaneh N, Ferrari P, Valamenes F, Agarwal MK 2002 The blockade of mineralocorticoid hormone signaling provokes dramatic teratogenesis in cultured rat embryos. *Int J Toxicol* 21:191–199
95. Nielsen AH, Schauer KH, Poulsen K 2000 Current topic: the uteroplacental renin-angiotensin system. *Placenta* 21:468–477
96. Brown MA, Wang J, Whitworth JA 1997 The renin-angiotensin-aldosterone system in pre-eclampsia. *Clin Exp Hypertens* 19:713–726
97. Brown MA, Zammit VC, Mitar DA, Whitworth JA 1992 Renin-aldosterone relationships in pregnancy-induced hypertension. *Am J Hypertens* 5:366–371
98. Lumbers ER 1995 Functions of the renin-angiotensin system during development. *Clin Exp Pharmacol Physiol* 22:499–505
99. Downing GJ, Poisner AM, Barnea ER 1995 First-trimester villous placenta has high prorenin and active renin concentrations. *Am J Obstet Gynecol* 172:864–867
100. Hanssens M, Vercruysse L, Keirse MJ, Pijnenborg R, Van Assche FA 1995 Identification of 'renin'-containing cells in the choriodecidua. *Placenta* 16:517–525
101. Hagemann A, Nielsen AH, Poulsen K 1994 The uteroplacental renin-angiotensin system: a review. *Exp Clin Endocrinol* 102:252–261
102. Itskovitz J, Sealey JE 1987 Ovarian prorenin-renin-angiotensin system. *Obstet Gynecol Surv* 42:545–551
103. Kim S, Shinjo M, Fukamizu A, Miyazaki H, Usuki S, Murakami K 1987 Identification of renin and renin messenger RNA sequence in rat ovary and uterus. *Biochem Biophys Res Commun* 142:169–175
104. Oparil S, Ehrlich EN, Lindheimer MD 1975 Effect of progesterone on renal sodium handling in man: relation to aldosterone excretion and plasma renin activity. *Clin Sci Mol Med* 49:139–147
105. Brown MA, Nicholson E, Gallery ED 1988 Sodium-renin-aldosterone relations in normal and hypertensive pregnancy. *Br J Obstet Gynaecol* 95:1237–1246
106. Weinberger MH, Kramer NJ, Grim CE, Petersen LP 1977 The effect of posture and saline loading on plasma renin activity and aldosterone concentration in pregnant, non-pregnant and estrogen-treated women. *J Clin Endocrinol Metab* 44:69–77
107. Morgan L, Crawshaw S, Baker PN, Broughton Pipkin F, Kalsheker N 2000 Polymorphism in oestrogen response element associated with variation in plasma angiotensinogen concentrations in healthy pregnant women. *J Hypertens* 18:553–557
108. Tewksbury DA, Dart RA 1982 High molecular weight angiotensinogen levels in hypertensive pregnant women. *Hypertension* 4:729–734
109. Ramaha A, Celerier J, Patston PA 2003 Characterization of different high molecular weight angiotensinogen forms. *Am J Hypertens* 16:478–483
110. Skinner SL, Lumbers ER, Symonds EM 1969 Alteration by oral contraceptives of normal menstrual changes in plasma renin activity, concentration and substrate. *Clin Sci* 36:67–76
111. Azizi M, Hallouin MC, Jeunemaitre X, Guyene TT, Menard J 2000 Influence of the M235T polymorphism of human angiotensinogen (AGT) on plasma AGT and renin concentrations after ethinylestradiol administration. *J Clin Endocrinol Metab* 85:4331–4337
112. Gibson M, Tulchinsky D 1980 Maternal-fetal endocrinology. Philadelphia: Saunders; 129–143
113. Nolten WE, Ehrlich EN 1980 Sodium and mineralocorticoids in normal pregnancy. *Kidney Int* 18:162–172
114. Brown MA, Broughton Pipkin F, Symonds EM 1988 The effects of intravenous angiotensin II upon blood pressure and sodium and urate excretion in human pregnancy. *J Hypertens* 6:457–464
115. Lindheimer MD, del Greco F, Ehrlich EN 1973 Postural effects on Na and steroid excretion, and serum renin activity during pregnancy. *J Appl Physiol* 35:343–348
116. Ehrlich EN, Lindheimer MD 1972 Effect of administered mineralocorticoids or ACTH in pregnant women. Attenuation of kaliuretic influence of mineralocorticoids during pregnancy. *J Clin Invest* 51:1301–1309
117. Boonshaft B, O'Connell JM, Hayes JM, Schreiner GE 1968 Serum renin activity during normal pregnancy: effect of alterations of posture and sodium intake. *J Clin Endocrinol Metab* 28:1641–1644
118. Ehrlich EN 1971 Heparinoid-induced inhibition of aldosterone secretion in pregnant women. The role of augmented aldosterone secretion in sodium conservation during normal pregnancy. *Am J Obstet Gynecol* 109:963–970
119. Okawa T, Asano K, Hashimoto T, Fujimori K, Yanagida K, Sato A 2002 Diagnosis and management of primary aldosteronism in pregnancy: case report and review of the literature. *Am J Perinatol* 19:31–36
120. Nolten WE, Lindheimer MD, Oparil S, Ehrlich EN 1978 Desoxycorticosterone in normal pregnancy. I. Sequential studies of the secretory patterns of desoxycorticosterone, aldosterone, and cortisol. *Am J Obstet Gynecol* 132:414–420
121. Nolten WE, Lindheimer MD, Oparil S, Rueckert PA, Ehrlich EN 1979 Desoxycorticosterone in normal pregnancy. II. Cortisol-dependent fluctuations in free plasma desoxycorticosterone. *Am J Obstet Gynecol* 133:644–648
122. Brown JJ, Fraser R, Lever AF, Robertson JJ 1972 Hypertension with aldosterone excess. *Br Med J* 2:391–396
123. Ehrlich EN, Biglieri EG, Lindheimer MD 1974 ACTH-induced sodium retention in pregnancy. Role of desoxycorticosterone and corticosterone. *J Clin Endocrinol Metab* 38:701–705
124. Schambelan M, Biglieri EG 1972 Desoxycorticosterone production and regulation in man. *J Clin Endocrinol Metab* 34:695–703
125. Brown RD, Strott CA, Liddle GW 1972 Plasma desoxycorticosterone in normal and abnormal pregnancy. *J Clin Endocrinol Metab* 35:736–742

126. Jailer JW, Christy NP, Longson D, Wallace EZ, Gordon WE 1959 Further observations on adrenal cortical function during pregnancy. *Am J Obstet Gynecol* 78:1–10
127. Smith PE 1955 The endocrine glands in hypophysectomized pregnant rhesus monkeys (*Macaca mulatta*) with special reference to the adrenal glands. *Endocrinology* 56:271–284
128. Johnstone FD, Campbell S 1974 Adrenal response in pregnancy to long-acting tetracosactrin. *J Obstet Gynaecol Br Commonw* 81:363–367
129. Maeyama M, Nakagawa T 1970 Effects of ACTH, metopirone and dexamethasone on maternal urinary steroid excretion in late pregnancy. *Steroids* 15:267–273
130. Brown MA, Thou ST, Whitworth JA 1995 Stimulation of aldosterone by ACTH in normal and hypertensive pregnancy. *Am J Hypertens* 8:260–267
131. McKenna DS, Wittber GM, Nagaraja HN, Samuels P 2000 The effects of repeat doses of antenatal corticosteroids on maternal adrenal function. *Am J Obstet Gynecol* 183:669–673
132. Schulte HM, Weisner D, Allolio B 1990 The corticotrophin releasing hormone test in late pregnancy: lack of adrenocorticotrophin and cortisol response. *Clin Endocrinol (Oxf)* 33:99–106
133. Suda T, Iwashita M, Ushiyama T, Tozawa F, Sumitomo T, Nakagami Y, Demura H, Shizume K 1989 Responses to corticotropin-releasing hormone and its bound and free forms in pregnant and nonpregnant women. *J Clin Endocrinol Metab* 69:38–42
134. Thomson M, Chan E-C, Falconer J, Madsen G, Smith R 1990 Desensitization of superfused isolated ovine anterior pituitary cells to human corticotropin-releasing factor. *J Neuroendocrinol* 2:181–187
135. Goland RS, Wardlaw SL, MacCarter G, Warren WB, Stark RI 1991 Adrenocorticotropin and cortisol responses to vasopressin during pregnancy. *J Clin Endocrinol Metab* 73:257–261
136. Raisanen I, Salminen K, Laatikainen T 1990 Response of plasma immunoreactive β -endorphin and corticotropin to isometric exercise in uncomplicated pregnancy and in pregnancy-induced hypertension. *Eur J Obstet Gynecol Reprod Biol* 35:119–124
137. Allen JP, Cook DM, Kendall JW, McGilvra R 1973 Maternal-fetal ACTH relationship in man. *J Clin Endocrinol Metab* 37:230–234
138. Kauppila A, Jouppila P, Karvonen P, Tuimala R, Ylikorkala O 1976 Effect of dexamethasone on blood levels of ACTH, cortisol, progesterone, estradiol and estriol during late pregnancy. *Int J Gynaecol Obstet* 14:177–181
139. Charnvise S, Fencel MD, Osathanondh R, Zhu MG, Underwood R, Tulchinsky D 1985 Adrenal steroids in maternal and cord blood after dexamethasone administration at midterm. *J Clin Endocrinol Metab* 61:1220–1222
140. Abou Samra AB, Loras B, Pugeat M, Tourniaire J, Bertrand J 1984 Demonstration of an antilucocorticoid action of progesterone on the corticosterone inhibition of β -endorphin release by rat anterior pituitary in primary culture. *Endocrinology* 115:1471–1475
141. Elliott CL, Read GF, Wallace EM 1996 The pharmacokinetics of oral and intramuscular administration of dexamethasone in late pregnancy. *Acta Obstet Gynecol Scand* 75:213–216
142. Egerman RS, Pierce IV WF, Andersen RN, Umstot ES, Carr TL, Sibai BM 1997 A comparison of the bioavailability of oral and intramuscular dexamethasone in women in late pregnancy. *Obstet Gynecol* 89:276–280
143. Sasaki A, Shinkawa O, Margioris AN, Liotta AS, Sato S, Murakami O, Go M, Shimizu Y, Hanew K, Yoshinaga K 1987 Immunoreactive corticotropin-releasing hormone in human plasma during pregnancy, labor, and delivery. *J Clin Endocrinol Metab* 64:224–229
144. Costa A, De Filippis V, Voglino M, Giraudi G, Massobrio M, Benedetto C, Marozio L, Gallo M, Molina G, Fabris C, Bertino E, Licata D 1988 Adrenocorticotrophic hormone and catecholamines in maternal, umbilical and neonatal plasma in relation to vaginal delivery. *J Endocrinol Invest* 11:703–709
145. Carr BR, Simpson ER 1981 Synthesis of cholesterol in the human fetus: 3-hydroxy-3-methylglutaryl coenzyme A reductase activity of liver microsomes. *J Clin Endocrinol Metab* 53:810–812
146. Greenwood J, Parker G 1984 The dexamethasone suppression test in the puerperium. *Aust NZ J Psychiatry* 18:282–284
147. Owens PC, Smith R, Brinsmead MW, Hall C, Rowley M, Hurt D, Lovelock M, Chan EC, Cubis J, Lewin T 1987 Postnatal disappearance of the pregnancy-associated reduced sensitivity of plasma cortisol to feedback inhibition. *Life Sci* 41:1745–1750
148. Hunt AB, McConahey CW 1953 Pregnancy associated with diseases of the adrenal glands. *Am J Obstet Gynecol* 66:970–987
149. Buescher MA, McClamrock HD, Adashi EY 1992 Cushing syndrome in pregnancy. *Obstet Gynecol* 79:130–137
150. Sheeler LR 1994 Cushing's syndrome and pregnancy. *Endocrinol Metab Clin North Am* 23:619–627
151. Wallace C, Toth EL, Lewanczuk RZ, Siminoski K 1996 Pregnancy-induced Cushing's syndrome in multiple pregnancies. *J Clin Endocrinol Metab* 81:15–21
152. Lubin V, Gautier JF, Antoine JM, Beressi JP, Vexiau P 2002 [Cushing's syndrome during pregnancy]. *Presse Med* 31:1706–1713
153. Doshi S, Bhat A, Lim KB 2003 Cushing's syndrome in pregnancy. *J Obstet Gynaecol* 23:568–569
154. Tajika T, Shinozaki T, Watanabe H, Yangawa T, Takagishi K 2002 Case report of a Cushing's syndrome patient with multiple pathologic fractures during pregnancy. *J Orthop Sci* 7:498–500
155. Shaw JA, Pearson DW, Krukowski ZH, Fisher PM, Bevan JS 2002 Cushing's syndrome during pregnancy: curative adrenalectomy at 31 weeks gestation. *Eur J Obstet Gynecol Reprod Biol* 105:189–191
156. Reschke K, Klose S, Mohnike K, Buhtz P, Roessner A, Lehnert H 2002 [Manifestation of Cushing syndrome and osteoporotic fractures in pregnancy in a patient with Carney complex]. *Med Klin (Munich)* 97:91–95
157. Pricolo VE, Monchik JM, Prinz RA, DeJong S, Chadwick DA, Lamberton RP 1990 Management of Cushing's syndrome secondary to adrenal adenoma during pregnancy. *Surgery* 108:1072–1077; discussion 1077–1078
158. Aron DC, Schnall AM, Sheeler LR 1990 Cushing's syndrome and pregnancy. *Am J Obstet Gynecol* 162:244–252
159. Pickard J, Jochen AL, Sadur CN, Hofeldt FD 1990 Cushing's syndrome in pregnancy. *Obstet Gynecol Surv* 45:87–93
160. Koerten JM, Morales WJ, Washington III SR, Castaldo TW 1986 Cushing's syndrome in pregnancy: a case report and literature review. *Am J Obstet Gynecol* 154:626–628
161. Ross RJ, Chew SL, Perry L, Erskine K, Medbak S, Afshar F 1995 Diagnosis and selective cure of Cushing's disease during pregnancy by transphenoidal surgery. *Eur J Endocrinol* 132:722–726
162. Nakada T, Koike H, Katayama T 1990 Uneventful delivery following series of successive treatments for virilized Cushing syndrome due to adrenocortical carcinoma. *Urology* 36:359–363
163. Coyne TJ, Atkinson RL, Prins JB 1992 Adrenocorticotrophic hormone-secreting pituitary tumor associated with pregnancy: case report. *Neurosurgery* 31:953–955; discussion 955
164. Mellor A, Harvey RD, Pobereskin LH, Sneyd JR 1998 Cushing's disease treated by trans-sphenoidal selective adenectomy in mid-pregnancy. *Br J Anaesth* 80:850–852
165. Pinette MG, Pan YQ, Oppenheim D, Pinette SG, Blackstone J 1994 Bilateral inferior petrosal sinus corticotropin sampling with corticotropin-releasing hormone stimulation in a pregnant patient with Cushing's syndrome. *Am J Obstet Gynecol* 171:563–564
166. Martin RW, Lucas JA, Martin JN, Morrison JC, Cowan BD 1989 Conservative management of Cushing's syndrome in pregnancy. A case report. *J Reprod Med* 34:493–495
167. Cope O RJ 1955 Cushing's disease: the surgical experience in the care of 46 cases. *N Engl J Med* 253:119–127
168. Birke G, Franksson C, Gemzell CA, Moberger G, Plantin LO 1959 Adrenocortical tumors: a study with special reference to possibilities of correlating histologic appearance with hormonal activity. *Acta Chir Scand* 117:233–246
169. Greenblatt RB, Scarpa-Smith C, Metts JC 1959 Endocrinopathies and infertility. II. Cushing's syndrome and pregnancy. *Fertil Steril* 10:323–339
170. Eisenstein AB, Karsh R, Gall I 1963 Occurrence of pregnancy in Cushing's syndrome. *J Clin Endocrinol Metab* 23:971–974
171. Cabezon C, Bruno OD, Cohen M, Garcia S, Gutman RA 1999 Twin pregnancy in a patient with Cushing's disease. *Fertil Steril* 72:371–372
172. Hana V, Dokoupilova M, Marek J, Plavka R 2001 Recurrent ACTH-independent Cushing's syndrome in multiple pregnancies

- and its treatment with metyrapone. *Clin Endocrinol (Oxf)* 54:277–281
173. Lindsay JR, Jonklaas J, Oldfield EH, Nieman LK 2005 Cushing's syndrome during pregnancy: personal experience and review of the literature. *J Clin Endocrinol Metab* 90:3077–3083
 174. Guilhaume B, Sanson ML, Billaud L, Bertagna X, Laudat MH, Luton JP 1992 Cushing's syndrome and pregnancy: aetiologies and prognosis in twenty-two patients. *Eur J Med* 1:83–89
 175. Kamiya Y, Okada M, Yoneyama A, Jin-no Y, Hibino T, Watanabe O, Kajiura S, Suzuki Y, Iwata H, Kobayashi S 1998 Surgical successful treatment of Cushing's syndrome in a pregnant patient complicated with severe cardiac involvement. *Endocr J* 45:499–504
 176. Bevan JS, Gough MH, Gillmer MD, Burke CW 1987 Cushing's syndrome in pregnancy: the timing of definitive treatment. *Clin Endocrinol (Oxf)* 27:225–233
 177. Oh HC, Koh JM, Kim MS, Park JY, Shong YK, Lee KU, Kim GS, Hong SJ, Koo HL, Kim WB 2003 A case of ACTH-producing pheochromocytoma associated with pregnancy. *Endocr J* 50:739–744
 178. Connell JM, Cordiner J, Davies DL, Fraser R, Frier BM, McPherson SG 1985 Pregnancy complicated by Cushing's syndrome: potential hazard of metyrapone therapy. Case report. *Br J Obstet Gynaecol* 92:1192–1195
 179. Casson IF, Davis JC, Jeffreys RV, Silas JH, Williams J, Belchetz PE 1987 Successful management of Cushing's disease during pregnancy by transsphenoidal adenectomy. *Clin Endocrinol (Oxf)* 27:423–428
 180. Finkenstedt G, Gasser RW, Hofle G, Lhotka K, Kolle D, Gschwendtner A, Janetschek G 1999 Pheochromocytoma and sub-clinical Cushing's syndrome during pregnancy: diagnosis, medical pre-treatment and cure by laparoscopic unilateral adrenalectomy. *J Endocrinol Invest* 22:551–557
 181. Margulies PL, Imperato-McGinley J, Arthur A, Peterson RE 1983 Remission of Cushing's syndrome during pregnancy. *Int J Gynaecol Obstet* 21:77–83
 182. Lado-Abeal J, Rodriguez-Arnan J, Newell-Price JD, Perry LA, Grossman AB, Besser GM, Trainer PJ 1998 Menstrual abnormalities in women with Cushing's disease are correlated with hypercortisolemia rather than raised circulating androgen levels. *J Clin Endocrinol Metab* 83:3083–3088
 183. Avril-Ducarne C, Leclerc P, Thobois B, Messner B, Kuhn J, Wolf L 1990 [Adrenal adenoma disclosing after delivery]. *Rev Med Interne* 11:245–247
 184. Blumsohn D, Munyadziwa EH, Dajie SK, Sher RC, Prajapat DK 1978 Cushing's syndrome and pregnancy: a case report. *S Afr Med J* 53:338–340
 185. Billaud L, Sanson ML, Guilhaume B, Bertagna X, Abecassis JP, Luton JP 1992 [Cushing syndrome during pregnancy. New diagnostic methods used in 3 cases of adrenal cortex carcinoma]. *Presse Med* 21:2041–2045
 186. Lindholm J, Schultz-Moller N 1973 Plasma and urinary cortisol in pregnancy and during estrogen-gestagen treatment. *Scand J Clin Lab Invest* 31:119–122
 187. Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK, Sonino N, Vance ML, Giustina A, Boscaro M 2003 Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 88:5593–5602
 188. Aron DC, Raff H, Findling JW 1997 Effectiveness versus efficacy: the limited value in clinical practice of high dose dexamethasone suppression testing in the differential diagnosis of adrenocorticotropin-dependent Cushing's syndrome. *J Clin Endocrinol Metab* 82:1780–1785
 189. Lim MC, Cheah JS 1990 Cushing's disease in pregnancy. *Ann Acad Med Singapore* 19:848–850
 190. Gormley MJ, Hadden DR, Kennedy TL, Montgomery DA, Murnaghan GA, Sheridan B 1982 Cushing's syndrome in pregnancy—treatment with metyrapone. *Clin Endocrinol (Oxf)* 16:283–293
 191. Kriplani A, Buckshee K, Ammini AC 1993 Cushing syndrome complicating pregnancy. *Aust NZ J Obstet Gynaecol* 33:428–430
 192. Nieman LK, Chrousos GP, Oldfield EH, Avgerinos PC, Cutler Jr GB, Loriaux DL 1986 The ovine corticotropin-releasing hormone stimulation test and the dexamethasone suppression test in the differential diagnosis of Cushing's syndrome. *Ann Intern Med* 105:862–867
 193. Iwase TI, Ohyama N, Umeshita C, Inazawa K, Namiki M, Ikeda Y 1992 Reproductive and developmental toxicity studies of hCRH [corticotrophin releasing hormone (human)] (II): study on intravenous administration of hCRH during the period of organogenesis in rats. *Yakuri to Chiryo* 20(Suppl 5):89–102
 194. Oldfield EH, Doppman JL, Nieman LK, Chrousos GP, Miller DL, Katz DA, Cutler Jr GB, Loriaux DL 1991 Petrosal sinus sampling with and without corticotropin-releasing hormone for the differential diagnosis of Cushing's syndrome. *N Engl J Med* 325:897–905
 195. Mulder WJ, Berghout A, Wiersinga WM 1990 Cushing's syndrome during pregnancy. *Neth J Med* 36:234–241
 196. Murakami S, Saitoh M, Kubo T, Kawakami Y, Yamashita K 1998 A case of mid-trimester intrauterine fetal death with Cushing's syndrome. *J Obstet Gynaecol Res* 24:153–156
 197. Goudie RB, Pinkerton PH 1962 Anterior hypophysitis and Hashimoto's disease in a young woman. *J Pathol Bacteriol* 83:584–585
 198. Shaw JA, Pearson DW, Krukowski ZH, Fisher PM, Bevan JS 2002 Cushing's syndrome during pregnancy: curative adrenalectomy at 31 weeks gestation. *Eur J Obstet Gynecol Reprod Biol* 15:189–191
 199. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH 1994 Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. *Ann Intern Med* 120:817–820
 200. Tabarin A, Laurent F, Catargi B, Olivier-Puel F, Lescene R, Berge J, Galli FS, Drouillard J, Roger P, Guerin J 1998 Comparative evaluation of conventional and dynamic magnetic resonance imaging of the pituitary gland for the diagnosis of Cushing's disease. *Clin Endocrinol (Oxf)* 49:293–300
 201. Mampalam TJ, Tyrrell JB, Wilson CB 1988 Transsphenoidal microsurgery for Cushing disease. A report of 216 cases. *Ann Intern Med* 109:487–493
 202. Leiba S, Weinstein R, Shindel B, Lapidot M, Stern E, Levavi H, Rusecki Y, Abramovici A 1989 The protracted effect of o,p'-DDD in Cushing's disease and its impact on adrenal morphogenesis of young human embryo. *Ann Endocrinol (Paris)* 50:49–53
 203. Lo KW, Lau TK 1998 Cushing's syndrome in pregnancy secondary to adrenal adenoma. A case report and literature review. *Gynecol Obstet Invest* 45:209–212
 204. Close CF, Mann MC, Watts JF, Taylor KG 1993 ACTH-independent Cushing's syndrome in pregnancy with spontaneous resolution after delivery: control of the hypercortisolism with metyrapone. *Clin Endocrinol (Oxf)* 39:375–379
 205. Trainer PJ 2002 Corticosteroids and pregnancy. *Semin Reprod Med* 20:375–380
 206. Bergmann P, Ekman H, Hakansson B, Sjogren B 1960 Adrenalectomy during pregnancy with the appearance of pre-eclampsia at term in a case of Cushing's syndrome. *Acta Endocrinol (Copenh)* 35:293–298
 207. Andreoli C 1962 [Adrenal surgery and its repercussions on pregnancy]. *Minerva Ginecol* 14:139–143
 208. Litowsky D, Ford RV 1962 Adrenalectomy during pregnancy. Case report with observations of adrenocortical function. *Am J Obstet Gynecol* 15:756–758
 209. Chico A, Manzanares JM, Halperin I, Martinez de Osaba MJ, Adelantado J, Webb SM 1996 Cushing's disease and pregnancy: report of six cases. *Eur J Obstet Gynecol Reprod Biol* 64:143–146
 210. Glassford J, Eagle C, McMorland GH 1984 Caesarean section in a patient with Cushing's syndrome. *Can Anaesth Soc J* 31:447–450
 211. Berwaerts J, Verhelst J, Mahler C, Abs R 1999 Cushing's syndrome in pregnancy treated by ketoconazole: case report and review of the literature. *Gynecol Endocrinol* 13:175–182
 212. Amado JA, Pesquera C, Gonzalez EM, Otero M, Freijanes J, Alvarez A 1990 Successful treatment with ketoconazole of Cushing's syndrome in pregnancy. *Postgrad Med J* 66:221–223
 213. Prebtani AP, Donat D, Ezzat S 2000 Worrisome striae in pregnancy. *Lancet* 355:1692
 214. Khir AS, How J, Bewsher PD 1982 Successful pregnancy after cyproheptadine treatment for Cushing's disease. *Eur J Obstet Gynecol Reprod Biol* 13:343–347
 215. Kasperlik-Zaluska A, Migdalska B, Hartwig W, Wilczynska J,

- Marianowski L, Stopinska-Gluszak U, Lozinska D 1980 Two pregnancies in a woman with Cushing's syndrome treated with cyproheptadine. Case report. *Br J Obstet Gynaecol* 87:1171–1173
216. Polli N, Pecori Giraldo F, Cavagnini F 2003 Cushing's syndrome in pregnancy. *J Endocrinol Invest* 26:1045–1050
 217. Hanson TJ, Ballonoff LB, Northcutt RC 1974 Amino-glutethimide and pregnancy. *JAMA* 230:963–964 (letter)
 218. Symonds EM, Craven DJ 1977 Plasma renin and aldosterone in pregnancy complicated by adrenal insufficiency. *Br J Obstet Gynaecol* 84:191–196
 219. Ambrosi B, Barbetta L, Morricone L 2003 Diagnosis and management of Addison's disease during pregnancy. *J Endocrinol Invest* 26:698–702
 220. Lovas K, Husebye ES 2002 High prevalence and increasing incidence of Addison's disease in western Norway. *Clin Endocrinol (Oxf)* 56:787–791
 221. Mason AS, Meade TW, Lee JA, Morris JN 1968 Epidemiological and clinical picture of Addison's disease. *Lancet* 2:744–747
 222. Laureti S, Vecchi L, Santeusano F, Falorni A 1999 Is the prevalence of Addison's disease underestimated? *J Clin Endocrinol Metab* 84:1762
 223. Jacobson DL, Gange SJ, Rose NR, Graham NM 1997 Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol* 84:223–243
 224. Brent F 1950 Addison's disease and pregnancy. *Am J Surg* 79:645–652
 225. Albert E, Dalaker K, Jorde R, Berge LN 1989 Addison's disease and pregnancy. *Acta Obstet Gynecol Scand* 68:185–187
 226. Ten S, New M, Maclaren N 2001 Clinical review 130: Addison's disease 2001. *J Clin Endocrinol Metab* 86:2909–2922
 227. Betterle C, Dal Pra C, Mantero F, Zanchetta R 2002 Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. *Endocr Rev* 23:327–364
 228. Osler M, Pedersen J 1962 Pregnancy in a patient with Addison's disease and diabetes mellitus. *Acta Endocrinol (Copenh)* 41:79–87
 229. Strickland Jr GT, Sode J 1967 Pregnancy with diabetes mellitus and Addison's disease. *NY State J Med* 67:2127–2131
 230. Gurling KJ, Rackow F, Smith MJ 1954 Addison's disease complicated by pregnancy and diabetes mellitus. *Lancet* 267:316–318
 231. Rambert P, Herve R 1960 [Association of Addison's disease and diabetes. Influence of pregnancy]. *Gynecol Obstet (Paris)* 59:223–233
 232. Stechova K, Bartaskova D, Mrstinova M, Cerny M, Snajderova M, Cinek O, Sumnik Z, Vavrinec J 2004 Pregnancy in a woman suffering from type 1 diabetes associated with Addison's disease and Hashimoto's thyroiditis (fully developed autoimmune polyglandular syndrome type 2). *Exp Clin Endocrinol Diabetes* 112:333–337
 233. Gaither K, Wright R, Apuzzio JJ, Gittens L, Ganesh V 1998 Pregnancy complicated by autoimmune polyglandular syndrome type II: a case report. *J Matern Fetal Med* 7:154–156
 234. Roth B, Kribs A, Kribs M, Solbach GH 1990 [Pregnancy in Addison disease and diabetes mellitus]. *Z Geburtshilfe Perinatol* 194:95–97
 235. Mathur G, Fulcher G, Pollock C, Ferry J 1998 Polyglandular autoimmune syndrome type 2 presenting for the first time during pregnancy. *Aust NZ J Obstet Gynaecol* 38:449–451
 236. Drucker D, Shumak S, Angel A 1984 Schmidt's syndrome presenting with intrauterine growth retardation and postpartum Addisonian crisis. *Am J Obstet Gynecol* 149:229–230
 237. Poonai A, Jelercic F, Pop-Lazic B 1977 Pregnancy with diabetes mellitus, Addison's disease, and hypothyroidism. *Obstet Gynecol* 49:86–88
 238. Eisenbarth GS, Gottlieb PA 2004 Autoimmune polyendocrine syndromes. *N Engl J Med* 350:2068–2079
 239. Myllykangas-Luosujarvi R, Aho K, Isomaki H 1995 Death attributed to antirheumatic medication in a nationwide series of 1666 patients with rheumatoid arthritis who have died. *J Rheumatol* 22:2214–2217
 240. Chrisoulidou A, Williamson C, De Swiet M 2003 Assessment of adrenocortical function in women taking exogenous glucocorticoids during pregnancy. *J Obstet Gynaecol* 23:643–644
 241. Newnham JP, Moss TJ, Nitsos I, Sloboda DM 2002 Antenatal corticosteroids: the good, the bad and the unknown. *Curr Opin Obstet Gynecol* 14:607–612
 242. Newnham JP, Evans SF, Godfrey M, Huang W, Ikegami M, Jobe A 1999 Maternal, but not fetal, administration of corticosteroids restricts fetal growth. *J Matern Fetal Med* 8:81–87
 243. French NP, Hagan R, Evans SF, Godfrey M, Newnham JP 1999 Repeated antenatal corticosteroids: size at birth and subsequent development. *Am J Obstet Gynecol* 180:114–121
 244. Challis J, Sloboda D, Matthews S, Holloway A, Alfaidy N, Howe D, Fraser M, Newnham J 2000 Fetal hypothalamic-pituitary-adrenal (HPA) development and activation as a determinant of the timing of birth, and of postnatal disease. *Endocr Res* 26:489–504
 245. Jobe AH, Scott SM, Polk DH, Seidner SR 2003 Adrenal and thyroid axis function in preterm ventilated baboons. *Biol Neonate* 83:208–216
 246. Schlaghecke R, Kornely E, Santen RT, Ridderskamp P 1992 The effect of long-term glucocorticoid therapy on pituitary-adrenal responses to exogenous corticotropin-releasing hormone. *N Engl J Med* 326:226–230
 247. NAE Program 1993 Management of asthma during pregnancy. Bethesda, MD: National Institutes of Health, Publication No. 93–3279
 248. Cydulka RK, Emerman CL, Schreiber D, Molander KH, Wooldruff PG, Camargo Jr CA 1999 Acute asthma among pregnant women presenting to the emergency department. *Am J Respir Crit Care Med* 160:887–892
 249. Barlow AD, Clarke GA, Kelly MJ 2004 Acute adrenal crisis in a patient treated with rectal steroids. *Colorectal Dis* 6:62–64
 250. Helal KJ, Gordon MC, Lightner CR, Barth Jr WH 2000 Adrenal suppression induced by betamethasone in women at risk for premature delivery. *Obstet Gynecol* 96:287–290
 251. Sheehan H 1937 Post-partum necrosis of the anterior pituitary. *J Bact Path* 45:189–214
 252. Zuker N, Bissessor M, Korber M, Conrads M, Margolis J, Massel P, Omar MA 1995 Acute hypoglycaemic coma—a rare, potentially lethal form of early onset Sheehan syndrome. *Aust NZ J Obstet Gynaecol* 35:318–320
 253. van der Spuy ZM, Jacobs HS 1984 Management of endocrine disorders in pregnancy. II. Pituitary, ovarian and adrenal disease. *Postgrad Med J* 60:312–320
 254. Sheehan HL 1961 Atypical hypopituitarism. *Proc R Soc Med* 54:43
 255. Patel MC, Guneratne N, Haq N, West TE, Weetman AP, Clayton RN 1995 Peripartum hypopituitarism and lymphocytic hypophysitis. *QJM* 88:571–580
 256. Vizner B, Talan-Hranilovic J, Gnjdic Z, Sekso M, Berkovic M, Altas V, Rumboldt Z 2002 Lymphocytic adenohypophysitis simulating a pituitary adenoma in a pregnant woman. *Coll Antropol* 26:641–650
 257. Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, Sheppard MC, Stewart PM 2001 Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. *Lancet* 357:425–431
 258. Overton CE, Davis CJ, West C, Davies MC, Conway GS 2002 High risk pregnancies in hypopituitary women. *Hum Reprod* 17:1464–1467
 259. Shearman RP 1957 Acute adreno-cortical insufficiency in obstetrics and gynaecology. *J Obstet Gynaecol Br Emp* 64:14–22
 260. O'Sullivan D 1954 Fatal obstetric shock due to Addison's disease. *J Ir Med Assoc* 35:315–316
 261. Cohen 1948 Addison's disease complicated by toxemia of pregnancy. *Arch Intern Med* 81:879–887
 262. Hendon JR, Melick RA 1955 Pregnancy in Addison's disease. *J Ky State Med Assoc* 53:141–143
 263. Sluder HM 1959 Pregnancy complicated by Addison's disease. Report of 2 cases. *Am J Obstet Gynecol* 78:808–811
 264. George LD, Selvaraju R, Reddy K, Stout TV, Premawardhana LD 2000 Vomiting and hyponatraemia in pregnancy. *Br J Obstet Gynaecol* 107:808–809
 265. Seaward PG, Guidozi F, Sonnendecker EW 1989 Addisonian crisis in pregnancy. Case report. *Br J Obstet Gynaecol* 96:1348–1350

266. O'Shaughnessy RW, Hackett KJ 1984 Maternal Addison's disease and fetal growth retardation. A case report. *J Reprod Med* 29:752–756
267. Khunda S 1972 Pregnancy and Addison's disease. *Obstet Gynecol* 39:431–434
268. Hilden J, Ronnike F 1971 On birth weight and gestation period in infants born to mothers with Addison's disease. *Dan Med Bull* 18:62–65
269. Donnelly JC, O'Connell MP, Keane DP 2003 Addison's disease, with successful pregnancy outcome. *J Obstet Gynaecol* 23:199
270. Gradden C, Lawrence D, Doyle PM, Welch CR 2001 Uses of error: Addison's disease in pregnancy. *Lancet* 357:1197
271. Allemang WH 1961 Pregnancy in the absence of adrenal cortical function. *Can Med Assoc J* 85:118–122
272. Grottolo A, Ferrari V, Mariano M, Zambruni A, Tincani A, Del Bono R 1988 Primary adrenal insufficiency, circulating lupus anticoagulant and anticardiolipin antibodies in a patient with multiple abortions and recurrent thrombotic episodes. *Haematologica* 73:517–519
273. Vengrove MA, Amoroso A 1993 Reversible adrenal insufficiency after adrenal hemorrhage. *Ann Intern Med* 119:439
274. Guibal F, Rybojad M, Cordoliani F, Jaccard A, Sarfaty E, Morel P, Clauvel JP 1996 Melanoderma revealing primary antiphospholipid syndrome. *Dermatology* 192:75–77
275. Perlitz Y, Varkel J, Markovitz J, Ben Ami M, Matilsky M, Oettinger M 1999 Acute adrenal insufficiency during pregnancy and puerperium: case report and literature review. *Obstet Gynecol Surv* 54:717–722
276. Akanji AO, George AO, Olasode BJ, Osotimehin BO 1990 Fasting hypoglycaemia due to insulinoma in pregnancy. *Postgrad Med J* 66:156
277. Ilbery M, Jones AR, Sampson J 1995 Lupus anticoagulant and HELLP syndrome complicated by placental abruption, hepatic, dermal and adrenal infarction. *Aust NZ J Obstet Gynaecol* 35:215–217
278. Ozdemir I, Demirci F, Yucel O, Simsek E, Yildiz I 2004 A case of primary Addison's disease with hyperemesis gravidarum and successful pregnancy. *Eur J Obstet Gynecol Reprod Biol* 113:100–102
279. Hiett AK, Barton JR 1990 Diabetes insipidus associated with craniopharyngioma in pregnancy. *Obstet Gynecol* 76:982–984
280. Kitajima Y, Endo T, Yamazaki K, Hayashi T, Kudo R 2003 Successful twin pregnancy in panhypopituitarism caused by suprasellar germinoma. *Obstet Gynecol* 102:1205–1207
281. Grinspoon SK, Biller BM 1994 Clinical review 62: Laboratory assessment of adrenal insufficiency. *J Clin Endocrinol Metab* 79:923–931
282. Korebits C, Yu DH, Ramirez MM, Marinoni E, Bocking AD, Challis JR 1998 Antenatal glucocorticoid administration increases corticotrophin-releasing hormone in maternal plasma. *Br J Obstet Gynaecol* 105:556–561
283. Nieman LK 2003 Dynamic evaluation of adrenal hypofunction. *J Endocrinol Invest* 26:74–82
284. Dorin RI, Qualls CR, Crapo LM 2003 Diagnosis of adrenal insufficiency. *Ann Intern Med* 139:194–204
285. Courtney CH, McAllister AS, McCance DR, Bell PM, Hadden DR, Leslie H, Sheridan B, Atkinson AB 2000 Comparison of one week 0900 h serum cortisol, low and standard dose synacthen tests with a 4 to 6 week insulin hypoglycaemia test after pituitary surgery in assessing HPA axis. *Clin Endocrinol (Oxf)* 53:431–436
286. Ammari F, Issa BG, Millward E, Scanlon MF 1996 A comparison between short ACTH and insulin stress tests for assessing hypothalamo-pituitary-adrenal function. *Clin Endocrinol (Oxf)* 44:473–476
287. Mukherjee JJ, de Castro JJ, Kaltsas G, Afshar F, Grossman AB, Wass JA, Besser GM 1997 A comparison of the insulin tolerance/glucagon test with the short ACTH stimulation test in the assessment of the hypothalamo-pituitary-adrenal axis in the early postoperative period after hypophysectomy. *Clin Endocrinol (Oxf)* 47:51–60
288. Speckart PF, Nicoloff JT, Bethune JE 1971 Screening for adrenocortical insufficiency with cosyntropin (synthetic ACTH). *Arch Intern Med* 128:761–763
289. Hurel SJ, Thompson CJ, Watson MJ, Harris MM, Baylis PH, Kendall-Taylor P 1996 The short Synacthen and insulin stress tests in the assessment of the hypothalamic-pituitary-adrenal axis. *Clin Endocrinol (Oxf)* 44:141–146
290. Lindholm J, Kehlet H, Blichert-Toft M, Dinesen B, Riishede J 1978 Reliability of the 30-minute ACTH test in assessing hypothalamic-pituitary-adrenal function. *J Clin Endocrinol Metab* 47:272–274
291. Kane KF, Emery P, Sheppard MC, Stewart PM 1995 Assessing the hypothalamo-pituitary-adrenal axis in patients on long-term glucocorticoid therapy: the short synacthen versus the insulin tolerance test. *QJM* 88:263–267
292. Mayenknecht J, Diederich S, Bahr V, Plockinger U, Oelkers W 1998 Comparison of low and high dose corticotropin stimulation tests in patients with pituitary disease. *J Clin Endocrinol Metab* 83:1558–1562
293. Tordjman K, Jaffe A, Trostanetsky Y, Greenman Y, Limor R, Stern N 2000 Low-dose (1 microgram) adrenocorticotrophin (ACTH) stimulation as a screening test for impaired hypothalamo-pituitary-adrenal axis function: sensitivity, specificity and accuracy in comparison with the high-dose (250 microgram) test. *Clin Endocrinol (Oxf)* 52:633–640
294. Dickstein G, Shechner C, Nicholson WE, Rosner I, Shen-Orr Z, Adawi F, Lahav M 1991 Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day, and suggested new sensitive low dose test. *J Clin Endocrinol Metab* 72:773–778
295. Tordjman K, Jaffe A, Grazas N, Apter C, Stern N 1995 The role of the low dose (1 microgram) adrenocorticotropin test in the evaluation of patients with pituitary diseases. *J Clin Endocrinol Metab* 80:1301–1305
296. Spiger M, Jubiz W, Meikle AW, West CD, Tylor FH 1975 Single-dose metyrapone test: review of a four-year experience. *Arch Intern Med* 135:698–700
297. Chaieb L, Chadli M, Jemni L, Chatti N, Hidar N, Zebidi A, Djaidane A 1986 [Sheehan's syndrome followed by spontaneous pregnancy. Apropos of 2 cases]. *J Gynecol Obstet Biol Reprod (Paris)* 15:765–768
298. Rumfitt IW 1977 A case of undiagnosed Addison's disease and successful pregnancy. *Practitioner* 218:553–554
299. Simcock MJ 1966 Addison's disease in pregnancy. *Med J Aust* 1:219–220
300. Falorni A, Laureti S, Nikoshkov A, Picchio ML, Hallengren B, Vandewalle CL, Gorus FK, Tortoioli C, Luthman H, Brunetti P, Santeusano F 1997 21-Hydroxylase autoantibodies in adult patients with endocrine autoimmune diseases are highly specific for Addison's disease. *Belgian Diabetes Registry. Clin Exp Immunol* 107:341–346
301. Nigam R, Bhatia E, Miao D, Yu L, Brozzetti A, Eisenbarth GS, Falorni A 2003 Prevalence of adrenal antibodies in Addison's disease among north Indian Caucasians. *Clin Endocrinol (Oxf)* 59:593–598
302. Bakalov VK, Vanderhoof VH, Bondy CA, Nelson LM 2002 Adrenal antibodies detect asymptomatic auto-immune adrenal insufficiency in young women with spontaneous premature ovarian failure. *Hum Reprod* 17:2096–2100
303. Dluhy RG, Himathongkam T, Greenfield M 1974 Rapid ACTH test with plasma aldosterone levels. Improved diagnostic discrimination. *Ann Intern Med* 80:693–696
304. Kauppila A, Hartikainen AL, Reinila M 1973 Adrenal response to synthetic adrenocorticotrophic hormone during pregnancy and after delivery, with special reference to pre-eclamptic and hypertensive pregnancy. *Scand J Clin Lab Invest* 31:179–185
305. Kelestimur F 2004 The endocrinology of adrenal tuberculosis: the effects of tuberculosis on the hypothalamo-pituitary-adrenal axis and adrenocortical function. *J Endocrinol Invest* 27:380–386
306. Levine D, Edelman RR 1997 Fast MRI and its application in obstetrics. *Abdom Imaging* 22:589–596
307. Carson BJ, Johnson MA, Iwaniuk G 1995 Extra-adrenal pheochromocytoma in pregnancy: ultrasonography and magnetic resonance imaging findings. *Can Assoc Radiol J* 46:122–124
308. Shutter LA, Kline LB, Fisher WS 1993 Visual loss and a suprasellar mass complicated by pregnancy. *Surv Ophthalmol* 38:63–69

309. **Chaiamnuay S, Moster M, Katz MR, Kim YN** 2003 Successful management of a pregnant woman with a TSH secreting pituitary adenoma with surgical and medical therapy. *Pituitary* 6:109–113
310. **Ahmadi J, Meyers GS, Segall HD, Sharma OP, Hinton DR** 1995 Lymphocytic adenohypophysitis: contrast-enhanced MR imaging in five cases. *Radiology* 195:30–34
311. **Sidhu RK, Hawkins DF** 1981 Prescribing in pregnancy. Corticosteroids. *Clin Obstet Gynaecol* 8:383–404
312. **Bongiovanni AM, McPadden AJ** 1960 Steroids during pregnancy and possible fetal consequences. *Fertil Steril* 11:181–186
313. **Walsh SD, Clark FR** 1967 Pregnancy in patients on long-term corticosteroid therapy. *Scott Med J* 12:302–306
314. **Oppenheimer EH** 1964 Lesions in the adrenals of an infant following maternal corticosteroid therapy. *Bull Johns Hopkins Hosp* 114:146–151
315. **Freedman JR, Moore FH** 1956 Addison's disease and pregnancy. *Am J Obstet Gynecol* 72:1340–1342
316. **Richards TA** 1952 Addison's disease and pregnancy. *Br Med J* 1:421
317. **Esteban NV, Loughlin T, Yergey AL, Zawadzki JK, Booth JD, Winterer JC, Loriaux DL** 1991 Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. *J Clin Endocrinol Metab* 72:39–45
318. **Malchoff CD, Carey RM** 1997 Adrenal insufficiency. *Curr Ther Endocrinol Metab* 6:142–147
319. **Normington EA, Davies D** 1972 Hypertension and oedema complicating pregnancy in Addison's disease. *Br Med J* 2:148–149
320. **McFarlane CH, Truelove LH** 1957 Addison's disease in pregnancy. *J Obstet Gynaecol Br Emp* 64:891–897
321. **Sas AM, Meynaar IA, Laven JS, Bakker SL, Feelders RA** 2003 [Irreversible coma following hypoglycemia in Sheehan syndrome with adrenocortical insufficiency]. *Ned Tijdschr Geneesk* 147:1650–1653

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Contact Information:
 Tami Martin
 Medical Education Resources
 Toll-free: 1-800-421-3756
 Local: 303.798.9682
 Fax: 303.798.5731
 E-mail: info@mer.org

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