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The hypothalamic-pituitary-adrenal axis in pregnancy: Challenges in disease detection and treatment

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Abstract

Pregnancy dramatically affects the hypothalamic-pituitary-adrenal (HPA) axis leading to increased circulating cortisol and corticotropin (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 corticotropin-releasing hormone (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 HPA 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 IPSS 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 (AI) that is appropriately treated can expect to have uneventful pregnancies. While a fetal/placental source of cortisol may mitigate crisis during gestation, unrecognized AI may lead to maternal or fetal demise either during gestation or in the puerperium. Appropriate treatment and management of labor are reviewed.

I. Introduction

II. Hypothalamic-pituitary-adrenal (HPA) axis physiology in normal pregnancy

- A. Circulating hormone levels and their origin
  1. Circulating and urinary glucocorticoids and CBG
  2. Plasma ACTH
  3. Plasma CRH and CRH binding protein
  4. Mineralocorticoids
- B. Regulation of the HPA axis
  1. ACTH stimulation of cortisol secretion
  2. Stimulation of ACTH secretion by CRH and vasopressin
  3. The stress response

4. Suppression of the axis by glucocorticoids
5. The HPA Axis during Parturition

III. Cushing's syndrome in pregnancy

A. Frequency

B. Maternal and fetal morbidity and mortality

C. Causes

D. Screening and diagnosis

E. Treatment of Cushing's syndrome

IV. Adrenal insufficiency in pregnancy

A. Overview

B. Frequency

C. Causes

D. Maternal and fetal morbidity and mortality

E. Diagnosis

F. Treatment

V. Summary

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. Plasma corticotropin (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 corticotropin-releasing hormone (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 hypothalamic-pituitary-adrenal 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.

Cushing's syndrome 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 Cushing's syndrome is increased in pregnancy. This poses diagnostic problems, because the increased ACTH levels of normal pregnancy are not suppressed by the hypercortisolism; thus, in contrast to non-pregnant 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 to identify patients with Cushing's disease. 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 that is appropriately treated can expect to have uneventful pregnancies of normal length without fetal compromise. However, if unrecognized, adrenal insufficiency 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 adrenal insufficiency. Excessive emesis, hypoglycemia and hyponatremia are important clues to its presence. Women are at increased risk for adrenal crisis post-partum, 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. Hypothalamic-pituitary-adrenal (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-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 post-partum 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 two- to three-fold elevated compared to non-pregnant 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 (Figure 1) (3). As shown by Mukerjee et al., there is a wide range of normal variation in the third trimester plasma cortisol from 16.3 – 55 μg/dl (450-1518 nmol/l) (14). The circadian rhythm of cortisol is preserved, although it may be partly blunted (3-5, 10, 14, 15).

Plasma free cortisol elevations of two- to four-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 1st and 2nd trimesters, reaching a plateau in the third trimester (7). Salivary cortisol, another measure of plasma free cortisol, is more than 2-fold increased compared to non-pregnant controls in the third trimester (10, 17).

Urine cortisol and its metabolites also increase in parallel with cortisol throughout gestation. In 1953 Gemzell demonstrated that 17-OHCS levels were elevated 4-fold in pregnancy (1); this increase is mainly due to increased cortisol (9). Mean 24h UFC is elevated at least 180% during gestation compared to non-pregnant levels (4). The aforementioned elevations in cortisol and its metabolites are consistent with an 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. demonstrated significant correlations between serum progesterone and salivary cortisol during late pregnancy (17). They suggested that elevated free plasma cortisol levels may result from antiglucocorticoid effects of elevated progesterone concentrations in pregnancy (17). Others 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 (11β-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 11β-HSD 2 is sufficient to ensure that fetal cortisol levels are much lower than maternal levels (19). While fetal cortisol concentrations are affected by 11β-HSD 2 enzyme activity, around three quarters of fetal cortisol originates from fetal adrenal gland production in term infants (21-23). Dexamethasone in contrast is a poor substrate for 11β-HSD 2 and can cross the placenta readily (20). In non-pregnant 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 11β-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 is observed in intrauterine growth retardation, and pre-eclampsia, which are commonly associated with pre-term 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, pro-opiomelanocortin (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 prior to demonstration of ACTH and immunoreactive β-endorphin and lipotropin within placenta in the 1970s (29-31). Demura later showed the presence of equimolar concentrations of ACTH and β-endorphin in trophoblastic tissues consistent with their origin from a common precursor (32). 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 non-pregnant women but became detectable by the 3rd month and then steadily increased towards mid-gestation (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 (Figure 1), in one study increasing almost 3-fold from the end of the first to the third trimester (23 to 59 pg/ml measured by radioimmunoassay (RIA); 5-13 pmol/l) (3). Compared with healthy non-gravid women, basal plasma ACTH levels in pregnancy have been varyingly 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 suggests that a source of ACTH exists that is not subject to normal feedback control (3). Placentally-derived 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 demonstrated that CRH modulates release of placental ACTH (40).

3. Plasma CRH and CRH-binding protein

CRH was isolated from human placenta in 1988 by Sasaki (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 week 7 to 40 of gestation; it increased more than 20-fold in the 5 weeks 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 weeks gestation (50, 51). At the 35^{th} week there is a sharp increase to a peak of 4000 pg/ml at 40 weeks gestation (5, 52) (Figure 2), with normalization to non-pregnant values within 24 hours 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 non-pregnant 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), while 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, non-circadian, and non-pulsatile fashion (15). Placental CRH mRNA is upregulated by glucocorticoids, in contrast to negative feedback effects of cortisol on hypothalamic CRH (61, 62). Robinson suggested that the rise in CRH preceding parturition could result from stimulation by elevated fetal glucocorticoids (61). 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-binding protein (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 non-pregnant levels, suggesting that CRH-BP is not stimulated by elevated estrogen levels in

pregnancy, in contrast to CBG (66). Between weeks 34-35 of gestation CRH-BP concentrations fall by around 60%, leading to elevations in free CRH (66) (Figure 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 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 receptors are located in non-pregnant 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, and these 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-receptors 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.

While 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 FasL, 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 to 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 35-43% 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 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 PGE2 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). While 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 distensability and reduced peripheral vascular resistance (85). While the intravascular volume in gravid subjects increases by around 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 increased in filtered sodium load of 5000-20,000 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 100-300 ng/ml in parallel with increases in plasma estradiol levels (87, 90). Acting as a mineralocorticoid receptor antagonist, progesterone reduces sodium re-absorption; it also contributes to reduced systemic vascular resistance, causing smooth muscle relaxation (91, 92). Conversely, increased estradiol and estriol levels in pregnancy are associated with elevated renin concentrations and upregulation of the renin angiotensin system (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 renin-angiotensin system are of critical importance to fetal growth and development (94).

a. Renin-Angiotensin System (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 (ACE) to the octapeptide angiotensin II, which promotes aldosterone synthesis and secretion. While renin is predominantly produced 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 increases early in the first trimester of normal pregnancy reaching values almost three to seven-fold greater than the normal range by the third trimester (87, 96, 97) (Figure 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 estriol and estradiol supporting a 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 prorenin (102, 103). However other factors influence the plasma renin concentration including changes in salt intake, blood pressure, effects of progesterone, increased renin substrate concentration and the fetoplacental unit (87, 95, 104, 105). The response of plasma renin to posture or saline loading in pregnancy is similar in direction and

magnitude compared with non-pregnant 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), whose exact role 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 fasiculata (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 include the observation of natriuresis following administration of an aldosterone inhibitor (118).

Significantly, aldosterone levels are reduced in pregnancy associated hypertension (96). Women with pregnancy induced hypertension have a two-fold greater increase in plasma aldosterone:plasma renin ratio compared with normal pregnant women (97), whereas in primary hyperaldosteronism, PAC is increased in association with reduced renin (119).

c. Other mineralocorticoids

Corticosterone, deoxycortisol, and cortisone parallel the two to three-fold rise seen in cortisol during gestation (18). Plasma desoxycorticosterone (DOC), a potent mineralocorticoid, increases from two-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 to non-pregnant controls; these observations suggest that DOC represents a substantial non-suppressable source of mineralocorticoid that is relatively independent of the RAS (123). In the third trimester, while total DOC levels are unchanged following 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 it 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). Nolten et al. have speculated that placental progesterone might be converted to DOC by the fetal adrenals (120). Further support for this hypothesis is provided by the observation that DOC sulphate 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 to non-gravid women (126-128). Subsequent studies measuring urinary 17-oxogenic steroids or 11-hydroxycorticosteroids or plasma cortisol after intramuscular tetracosactrin, corticotrophin gel or synthetic ACTH demonstrated 1-2 fold elevations in normal pregnancy compared to non-pregnant subjects (129). There was speculation that the apparent increased responsiveness might in part be due to delayed clearance of cortisol

(126), because of a delayed peak response at 120 minutes. 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 pre-eclampsia (2,3,5 and 7 μg/h for 80 minutes) demonstrating a similar pattern of enhanced responsiveness of cortisol release in the third trimester of pregnancy compared to non-pregnant women (130). The mean maximum cortisol response in pregnancy was 34.9 μg/dl (963 nmol/l) compared to 18.4 μg/dl (507 nmol/l) in a group of non-pregnant controls, despite administration of lower doses (1,2,3 and 5 μg/h) to the control women to account for their lower relative plasma volume (130).

McKenna et al. examined responses to ACTH, 1 μg, of six healthy women during the 24-34th weeks of gestation (131). The mean peak cortisol response was 44 μg/dl (1215 nmol/l) (99% CI 33.2- 55.6 μg/dl; 917-1535 nmol/l) and was attained at a mean of 27 minutes following cortrosyn.

2. Stimulation of ACTH secretion by CRH and vasopressin

Exogenous human CRH (hCRH), 1 μg/kg, failed to increase plasma cortisol or ACTH in seven pregnant women one week prior to their expected delivery date (132). While 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 weeks post-partum, there was a prompt ACTH response to administered CRH. Other investigators using a higher dose (2 μg/kg) during third trimester pregnancies demonstrated ACTH and cortisol increments that were similar to those of non-pregnant women (133). While diminished CRH responsiveness may be due to effects of CRH-BP, i*n vitro* studies of pituitary columns continuously perfused with CRH demonstrated initially brisk responses of β-endorphin secretion that gradually declined to baseline after a period of hours (134). These observations are consistent with a hypothesis proposed by Schulte that blunting of the CRH response may arise due to high endogenous cortisol concentrations with desensitization of the pituitary corticotrophs (132).

As noted earlier, plasma CRH levels are relatively non-variant during the third trimester (17), suggesting that circadian and pulsatile secretion of ACTH from the corticotrope may be driven by another secretagogue (15). AVP has been postulated to fill this role, as it is secreted in a pulsatile fashion with a circadian increase in amplitude (15). Goland 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 (135).

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 around 55% following 4-6 mg dexamethasone (129). Women in the third trimester treated with high dose glucocorticoids (dexamethasone 24 mg) prior to delivery exhibit suppressed ACTH levels within the first 24 hours post-partum compared to untreated controls (137), but these effects are short-lived (138). Following intravenous administration of dexamethasone 4 mg to women in the 2nd trimester with congenital adrenal hyperplasia (CAH), approximately 60% suppression of plasma cortisol was noted within 2 hours that continued for up to 8 hours. Up to 90% suppression was achieved following 12 mg dexamethasone given in a divided dose (139).

Odagiri demonstrated a 40% versus 87% suppression of plasma cortisol and similar effects on UFC following 1 mg dexamethasone in normal 2-3rd trimester pregnancy compared to non-gravid controls (Figure 5) (13). Whereas the majority of non-pregnant 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 following dexamethasone 1 mg (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. While 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 intramuscular route (141). In an other series the bioavailability of an 8 mg oral dose was similar to 6 mg intramuscular dosing (142).

5. The HPA Axis during Parturition

Plasma CRH, ACTH and plasma cortisol concentrations increase several fold with the onset of labor and delivery (3, 45, 143). Peak CRH levels occur within 48 hours prior to delivery and fall during labor consistent with a pre-eminent role for CRH in parturition (73). While 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 to non-pregnant individuals (144). ACTH does not cross the placenta (137) and there is a two-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 C-section (14). A subsequent study demonstrated ACTH, β-endorphin and β-lipotropin levels that were highest immediately after vaginal delivery compared with those following C-section; while both groups fell rapidly to the normal range, ACTH levels were highest in the C-section group at 30 minutes post-delivery reflecting surgical stress (28).

In the immediate post-partum period, plasma CRH, ACTH and cortisol levels fall rapidly toward the non-pregnant range consistent with their biological half-lives (145). Both CRH and ACTH normalize within two hours from delivery whereas normalization of plasma cortisol levels is more protracted (58). In one series mean postpartum 24h plasma cortisol levels were 5.4 μg/dl (149 nmol/l) compared with the 2nd (18.8 μg/dl; 518 nmol/l) and 3rd trimesters (20.3 μg/dl; 560 nmol/l) (4). Diurnal patterns of ACTH are present in the post-partum period (14, 15, 17).

In the immediate post-partum period 82% of women in one series did not have normal cortisol suppression after dexamethasone 1 mg (146). This abnormality may persist for up to 2-3 weeks in a significant proportion of women (147). Owens observed normal responses to dexamethasone by the 5th post-partum week (147).

III. Cushing's Syndrome in pregnancy

a. Frequency

Cushing's syndrome (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 & McConaghey in 1953 (148). Since then at least 136 pregnancies, including one twin pregnancy, 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 around 18 weeks (173).

b. Maternal and fetal morbidity and mortality

CS is associated with significant maternal morbidity and mortality in around 70% of cases. The most common complications in pregnancy are hypertension, 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 was reported in the month following delivery as a result of cerebrovascular disease and disseminated intravascular coagulation caused by pheochromocytoma (177). Another women died due to complications from adrenalectomy and Caesarian 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 8 stillbirths, 6 intrauterine deaths/spontaneous abortions, and one ectopic pregnancy. Six therapeutic abortions were undertaken and in 3 cases the outcome was uncertain. One infant died from respiratory distress and hyaline membrane disease (171). Intraventricular hemorrhage caused another infant death (178). Fetal adrenal insufficiency 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 Cushing's syndrome 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 Cushing's syndrome cases, accounting for approximately 40 - 50% of cases in pregnancy, as compared to about 15% in non-pregnant women (149, 159). Conversely

Cushing's disease (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 Cushing's syndrome in four cases, 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, Cushing's syndrome is often not detected until 12 - 26 weeks gestation (149, 157), possibly partially because changes in physical appearance are ascribed to pregnancy rather than CS (3).

2. Screening Tests

In non-gravid women, screening tests for Cushing's syndrome 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) (Figure 1). As reviewed above, these changes include estrogen-dependent increases in CBG, increases in plasma cortisol and ACTH, and a two to three-fold increase in plasma free cortisol and UFC (3, 133).

The mean morning plasma cortisol levels of 37 μg/dl in pregnant women with Cushing's syndrome is similar to the range observed by Carr in normal pregnancy (Figure 1). Thus, as in the non-pregnant individual, morning plasma cortisol concentrations generally do not establish the diagnosis of CS.

The nocturnal nadir of plasma cortisol is lost in Cushing's syndrome, 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 Cushing's syndrome (185). However, there is only one case report that documents the potential utility of this non-invasive measure in pregnancy (185).

In non-pregnant women, UFC increases above four-fold normal are virtually diagnostic of CS. While 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 – 22-fold)(173). This overlap of UFC values in pregnant women with and without Cushing's syndrome 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 cut-off 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 non-pregnant patients with autonomous adrenal disorders, and are inappropriately normal or increased in those with tumoral

ACTH production. In such patients, a two-site immunometric assay (IRMA) reliably discriminates low (<10 pg/ml; 2.2 pmol/l) or suppressed (< 5 pg/ml; 1.1 pmol/l) 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 non-pregnant 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 cut-off point of plasma cortisol suppression above 80% is used (187, 188). However, some authors advocate abandoning the test altogether; while 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, while 4 of 7 patients with CD did (173).

In non-pregnant individuals with Cushing's disease, 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 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 μg/kg, were reduced in third trimester normal pregnancies (132). While 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 non-pregnant 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 non-pregnant 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 are necessary during pregnancy including a direct jugular approach for catheter insertion and use of additional lead barrier protection. We advocate that IPSS should be only considered during pregnancy following completion of careful non-invasive assessment and only in centers with special expertise using the technique. Also, as 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, while 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 HDST 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

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 post-partum period (196). Despite inadequate tumor definition using these modalitites, several women had successful localization and surgery (148, 170). In more recent reports, about fifty percent 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). MRI and CT have been used effectively, although the former is preferred during pregnancy due to the risk of ionizing radiation (180, 197, 198). Specific precautions for the use of MRI are detailed below.

Pituitary

Pituitary MRI should be obtained in all non-pregnant 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 weeks gestation. Between 12 and 32 weeks, 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 non-pregnant 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 non-pregnant population. The use of the contrast agent gadopentetate dimeglumine (Gd-DPTA, gadolinium) is contraindicated in pregnancy as it is FDA category C. In one series of non-pregnant 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 5 of 8 cases with CD, 3 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 over-represented compared to non-pregnant series (163, 165, 191, 201, 202).

E. Treatment of Cushing's Syndrome

As cited previously, untreated CS is associated with significant maternal morbidity including diabetes, hypertension, heart failure and pre-eclampsia (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 to 50 live births (89%) in women in whom treatment was instituted at a mean gestational age of 20 ± 1 weeks (173). Even in cases with apparent remission following 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 (157, 174, 197). The live birth rate after unilateral or bilateral adrenalectomy is around 87%; while the patient group is heterogeneous, adrenalectomy appears beneficial (149, 157, 158, 173).

Forty women, including 4 that were treated at our institution, have been reported with CD. Around 20% underwent transsphenoidal surgery (164). The remainder received medical therapy, adrenalectomy and one case of unrecognized pregnancy had external pituitary irradiation (148, 158, 206-208). A high proportion either presenting late in pregnancy or prior to modern management were 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). There is most experience with metyrapone, which seems generally well-tolerated (155, 204), with 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 following metyrapone (151). However while metyrapone is effective, there is

the potential for exacerbation of hypertension and progression to pre-eclampsia, which may limit its use (155, 178). Ketoconazole has been used successfully without adverse event in 3 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 weeks (211). In the rat, ketoconazole crosses the placenta and is teratogenic and abortifacient, so that the drug is FDA category C. While 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 Cushing's syndrome 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

While adrenal insufficiency (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 plasma renin activity (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 renin-angiotensin system.

B. Frequency

The prevalence of primary AI in the predominantly Caucasian non-pregnant population is estimated to range between 39 to 117 per million (220-222). Although the majority of cases of primary AI affect women (approximately 92%) (223), the exact prevalence of AI occurring in association with pregnancy is unknown. By 1953, there were around 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-year period between 1976-1987 in Tromso, Norway, 5 women with AI gave birth to 6 children. From this series of 15,700 deliveries the estimated incidence of pregnancy in women with AI was 1:3000 births per 12 year period (225). In 1968 Mason estimated one case of AI in pregnancy per 12,000 gestations (221).

C. Causes

The presentation and causes of adrenal insufficiency 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. While 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 years and although tuberculosis was relatively uncommon (12%) that condition was more prevalent in males who had a mean age of presentation of 53 years (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 DM, 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 over-represented in the literature of AI in pregnancy, as it is a unique multi-system endocrine disease. Three cases with APS presented as a new diagnosis of AI during pregnancy (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 prior to or during pregnancy. In addition to the morbidity associated with AI, untreated hypothyroidism is associated with higher incidence of infertility, 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 adrenal insufficiency in the adult population is administration of exogenous corticosteroids for conditions including asthma, 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 following long-term glucocorticoid replacement in either the non-pregnant 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 weeks (246). In these cases glucocorticoid reserve should be tested formally prior to 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). While chronic oral or high-dose corticosteroid use for asthma in pregnancy is associated with gestational diabetes, pre-term labor and pre-eclampsia, there have been few reports of adrenal crisis in pregnancy (248). Similarly while steroid dependency is common in up to 36% of cases with Crohn's disease, there have been have only been 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 pre-term delivery (131, 250).

Post-partum pituitary necrosis (Sheehan's syndrome) is a well-recognized complication of pregnancy, resulting following obstetric shock and usually presenting with failure to lactate or to resume normal menses in the post-partum period (251). The diagnosis should be considered in post-partum 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). While 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 (LH) has considerable overlap in clinical presentation with Sheehan's syndrome and these two conditions are the primary differential diagnoses for post-partum hypopituitarism (255). LH was first described in 1962 by Goudie and Pinkerton and since then at least 130 cases have been described. Approximately 90% of cases present in the last trimester of pregnancy or in the early post-partum period (256). LH is characterized by inflammatory lesions of the pituitary that 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 UK series of hypopituitarism 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 transsphenoidal 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 reported a 35% mortality rates for AI in pregnancy in the 70 years before 1930, which decreased to 18% between 1940-1947 (261). In one of the largest early series, Brent observed high rates of adrenal crisis and mortality (45%) in 39 cases of AI in pregnancy prior to 1946 (224). In contrast, Hendon and Melick subsequently found only 1 death in 14 cases in 1955 (262). 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 trans-placental 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 only be recognized in the immediate post-partum 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). While maternal hypotension is a presentation of adrenocortical failure, side effects of treatment for AI include hypertension and exacerbation of pre-eclampsia (225, 265). It is also important to recognize that while the early emphasis is on careful antenatal care, follow-up in the distant post-partum period is critical given a report of late maternal death at 8 months post-partum (225).

Intrauterine growth retardation (IUGR) and low birth weight are the most commonly reported adverse effects for the fetus from mothers with untreated AI. Osler demonstrated the association of fetal growth retardation with AI in a series of 15 cases in 1962; His 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 Ronnicke showed no discrepancy in gestational age or fetal weight compared with the general population (268). 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 towards 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 prior to the availability of modern glucocorticoid regimens (265, 270, 271). While 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%, mid-trimester 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 prior to excluding other causes arising in pregnancy, and this symptom may be exacerbated by growth hormone 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 othostasis or hypotension, even in the post-partum 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 adrenal insufficiency 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 are known prior to pregnancy, particularly if they have had previous glucocorticoid treatment as detailed above. Less commonly new onset hypopituitarism may 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 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 non-pregnant women. A failure of lactation or resumption of menses in the post-partum period may be the first sign of hypopituitarism. Involution of normal breast tissue may occur due to loss of prolactin reserve. Symptoms of fatigue, 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 intravenous access immediately prior to emergency treatment. Testing is divided firstly into assessment of the functional integrity of the HPA axis followed by a search for the underlying cause of AI. A variety of approaches are available for confirmation of AI including random plasma cortisol or dynamic testing with ACTH stimulation, the insulin tolerance test (ITT), the metyrapone test and lastly the CRH stimulation test. However, most of these tests of HPA reserve have not been validated in pregnancy.

Random cortisol

In the non-stressed general population and pregnancy, an undetectable early morning plasma cortisol (<3.0 μg/dl; 83 nmol/l) 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 μg/dl (525 nmol/l) (131, 281). While a basal plasma cortisol greater than 19 μg/dl (525 nmol/l) may be adequate for exclusion of AI in the non-stressed non-pregnant population, a normal non-pregnant 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 3rd trimester of normal pregnancy (3, 120, 131, 282). In non-gravid 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 (3-30 μg/dl; 83-828 nmol/l) 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 cut-off points have not been validated during pregnancy.

Standard or high dose Cosyntropin stimulation test

Administration of cosyntropin (1-24 corticotropin) is the most commonly employed test used for the diagnosis of adrenal insufficiency. The standard cosyntropin test (SCT) is performed by administering a supraphysiological dose of 250 μg i.m. or i.v. and measuring plasma cortisol levels after 30 and 60 minutes. The test may be performed at any time of the day and the 30 minute cut-off 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 cut-off 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 non-pregnant population (283). Discrepancies between results from the SCT and the insulin tolerance test (ITT) have also been a recent matter of debate given a number of non-pregnant patients who may pass the SCT but fail an ITT (285-287). Conversely, higher cut-off 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 μg/dl (497 nmol/l) after cosyntropin 250 μg 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 μg ACTH ranging between 60-80% above non-pregnant responses in the 2nd and 3rd 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 prior to an abnormal plasma cortisol following 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 cut-off points during pregnancy. However based on previously reported 8am 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 following SCT are at least 30 μg/dl (828 nmol/l) (131).

Low dose Cosyntropin stimulation test

Whereas the SCT has good reliability for detection of moderate or severe adrenal insufficiency, it has limited utility in early AI, probably because mild adrenal dysfunction can be overcome by the supraphysiological ACTH dose. The 1 μg low dose cosyntropin test (LCT) has been extensively studied in non-pregnant subjects and has sensitivity approaching 93% using cortisol criteria of 18.1-20.0 μg/dl (500-550 nmol/l) (283, 292, 293). The test is conducted by administering 1 μg ACTH (1-24) i.v., with sampling for plasma cortisol at baseline and at intervals until 60 minutes. There has been controversy as to whether the 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 ROC analysis for non-pregnant 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 has however recently been examined in secondary AI in pregnancy (131).

McKenna et al. examined responses to LCT during the 24-34th weeks of gestation (131). This prospective case-control trial enrolled 18 pregnant women at risk of pre-term labor who were receiving antenatal corticosteroids, and 6 healthy controls with low risk pregnancies. The women who had received at least 2 weekly courses of two doses of betamethasone 12 mg 24 hours apart, were assessed after a median of 3 days from betamethasone administration. The 6 normal pregnant woman had a mean peak cortisol response of 44 μg/dl (1215 nmol/l) (99% CI 33.2-55.6 μg/dl; 917-1535 nmol/l), which was attained at 27 minutes following LCT. In the

corticosteroid treated group, the peak cortisol was delayed at 37 minutes and did not exceed the normal unsuppressed response, 30 μg/dl (828 nmol/l). Only one subject had a peak cortisol greater than the non-pregnant cut-off of 18-20 μg/dl (497-552 nmol/l) used for the non-pregnant population (131). These preliminary observations suggest that a diagnosis of AI is confirmed using existing non-pregnant thresholds in the majority of cases. Using a threshold above 30 μg/dl (828 pmol/l) following 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 8am plasma cortisol as only 17% of subjects with a subnormal LCT had basal plasma cortisol greater than 3 μg/dl (82.8 nmol/l) (131).

Insulin tolerance test

The insulin tolerance test (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 post-partum period for more formal assessment of HPA and growth hormone reserve. The test is conducted by administering 0.1-0.15 U/kg i.v. and measuring glucose and cortisol at intervals until 60 minutes. The traditional cut-off point for normal responses in the non-pregnant population is 18 μg/dl (497 nmol/l), in the setting of confirmed hypoglycemia (40 μg/dl; <2.2 mmol/l). However the diagnostic accuracy is not 100% and a range of diagnostic cut-off points have been used (283).

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 8 am the following morning. AI is confirmed in the non-pregnant population with an 11-deoxycortisol level less than 7 μg/dl (193 nmol/l), in the setting

of cortisol levels 2-7.5 μg/dl (55-207 nmol/l) (281). We do not recommend using the metyrapone test in pregnancy due to the risk of precipitating adrenal crisis.

Corticotropin-releasing hormone (CRH) stimulation test

The CRH stimulation test has utility for differentiation of tertiary versus secondary AI in non-pregnant 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 adrenal insufficiency

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 non-pregnant 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 prior to 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/l) 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/l) 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 pre-chilled EDTA tubes, with transport in an ice bath and prompt refrigerated centrifugation and plasma separation.

Around 90% of non-pregnant 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/l) at 30 minutes after cosyntropin supports a diagnosis of primary AI in non-pregnant subjects (283, 303). While plasma aldosterone levels and plasma renin activity are elevated in normal pregnancy, there are no data on these values in patients with AI (87), and cut-off points for AI in pregnancy have not been established.

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

4. Retesting in the Post-partum Period

Formal re-testing 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 re-testing should not be considered in the immediate post-partum period as biochemical values do not usually return to pre-pregnancy levels until at least 7 days 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. While MRI provides excellent soft tissue enhancement and has improved resolution compared with ultrasound (306, 307), we recommend deferment of adrenal

imaging until the post-partum period during the differential diagnosis, 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, since documentation of this diagnosis is not needed for treatment, we recommend that CT scans be deferred to the post-partum 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 post-partum period. The team must decide on the optimal timing for surgical removal of craniopharyngiomas or other large intracranial neoplasms; while surgery may be left to the post-partum period in selected cases, the 2nd 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 8 still births, 15 premature infants and 7 congenital abnormalities, 2 of which were cleft palate (312). Walsh et al. 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 corticosteroids (313). They also demonstrated normal progress and development up to age 6 years during screening of a limited number of children whose mothers were treated with pharmacologic corticosteroids in pregnancy (313). 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 due to the potential for fetal adrenal hypoplasia (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 desoxycorticosterone was subsequently replaced by cortisone (17-hydroxy-11-dehydrocorticosterone) (315, 316). The aim of treatment in pregnancy is to achieve a physiologic 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 over-replacement and the potential for inducing symptoms or signs of Cushing's syndrome (267) and in women with co-existing 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/m^2 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/m^2 per day and present replacement regimens for the non-pregnant population may lead to over-replacement 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 5 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. While 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 hours), prednisone and prednisolone have longer half-lives of 24-72 hours (318). Therefore, although these agents are more useful in pharmacological 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 11β-HSD 2. Glucocorticoids can cross the placenta. In contrast to hydrocortisone, dexamethasone is not degraded by 11β-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 commenced at the time of diagnosis of AI. Prior to the availability of 9-α fluorohydrocortisone, 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 that can range between 0.05 – 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 plasma renin activity 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 non-pregnant population, an individual's adherence to the prescribed treatment regimen may avoid

adrenal crisis, which is a particular challenge given the frequency of first trimester nausea or vomiting. Consequently pre-pregnancy 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 intramuscularly 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 intravenous hydrocortisone. 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 Ave, Turlock, CA 95382; Tel 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 caesarian section are similar to those in a non-pregnant 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). Prior to caesarian section stress doses of hydrocortisone 100 mg i.v. or i.m. are given at the onset and continued at 6-8 hourly intervals after delivery (253). The doses of hydrocortisone then can be tapered over 48 hours 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, pre-eclampsia 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 i.v. as single bolus. Thereafter 50-100 mg boluses are given every 6 to 8 hours during the acute period, based on maximal cortisol production rates of 200-400 mg per day (265). Women with hypoglycemia should receive 5% dextrose influsions (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.

Post-Partum

Following delivery all women should recommence mineralocorticoid and/or corticosteroid replacement, usually at the dose prior to gestation, within the first 24-48 hours 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.

Summary

In conclusion, the hypothalamic-pituitary-axis plays an important physiological role in normal pregnancy, contributing to regulation of maternal fertility, parturition, blood pressure control and sodium balance. While disorders of the HPA axis are rare, Cushing's syndrome 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 Cushing's syndrome and hypoadrenalism occurring in pregnancy.

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Table 1. Reproductive Roles of CRH. Reprinted from Ann N Y Acad Sci. 997: Kalantaridou SN, Makrigiannakis A, Mastorakos G, Chrousos GP. Roles of reproductive corticotropin-releasing hormone: 129-35; Copyright (2003) with permission, New York Academy of Sciences.

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

Table 2. Urocortins and urocortin-related peptides expression, established functions and putative effects in the different reproductive tissues. Reproduced from Peptides 25: Florio P, Vale W, Petraglia F. Urocortins in human reproduction: 1751-7; Copyright (2004) with permission from Elsevier.

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

Table 3. Frequency of maternal and fetal complications arising in Cushing's syndrome during pregnancy. IUGR=intrauterine growth retardation, IUD=intrauterine death. Copyright (2005), The Endocrine Society.

Maternal morbidity	Fetal Morbidity
Hypertension (68%)	Prematurity (43%)
Diabetes or IGT (25%)	Stillbirths (6%)
Pre-eclampsia (14%)	Spontaneous abortion/IUD (5%)
Osteoporosis & fracture (5%)	Infant death in 2 cases (acute hepatitis; sepsis & 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 2 cases post-partum

Table 4. Etiology of Cushing's syndrome in pregnancy

ETIOLOGY	CASES (%)
Cushing's disease	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 Cushing's syndrome	4 (3)
Unspecified	4 (3)

Legend

Fig. 1. Serial increases in serum cortisol (○) and ACTH (●) during pregnancy in normal controls throughout pregnancy. This graph was modified from the series of 5 normal pregnant women from the series by Carr et al. (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 Cushing's syndrome in pregnancy (Diamond: Median and range, n=52); ACTH values for Cushing's disease (Closed triangle: Median and range, n=18) and adrenal Cushing's syndrome (Open triangle: Median and range, n=17). Reprinted and modified from Am J Obstet Gynecol. 139: Carr BR, Parker CR Jr, Madden JD, MacDonald PC, Porter JC. Maternal plasma adrenocorticotropin and cortisol relationships throughout human pregnancy: 416-22; Copyright (1981) with permission from Elsevier.

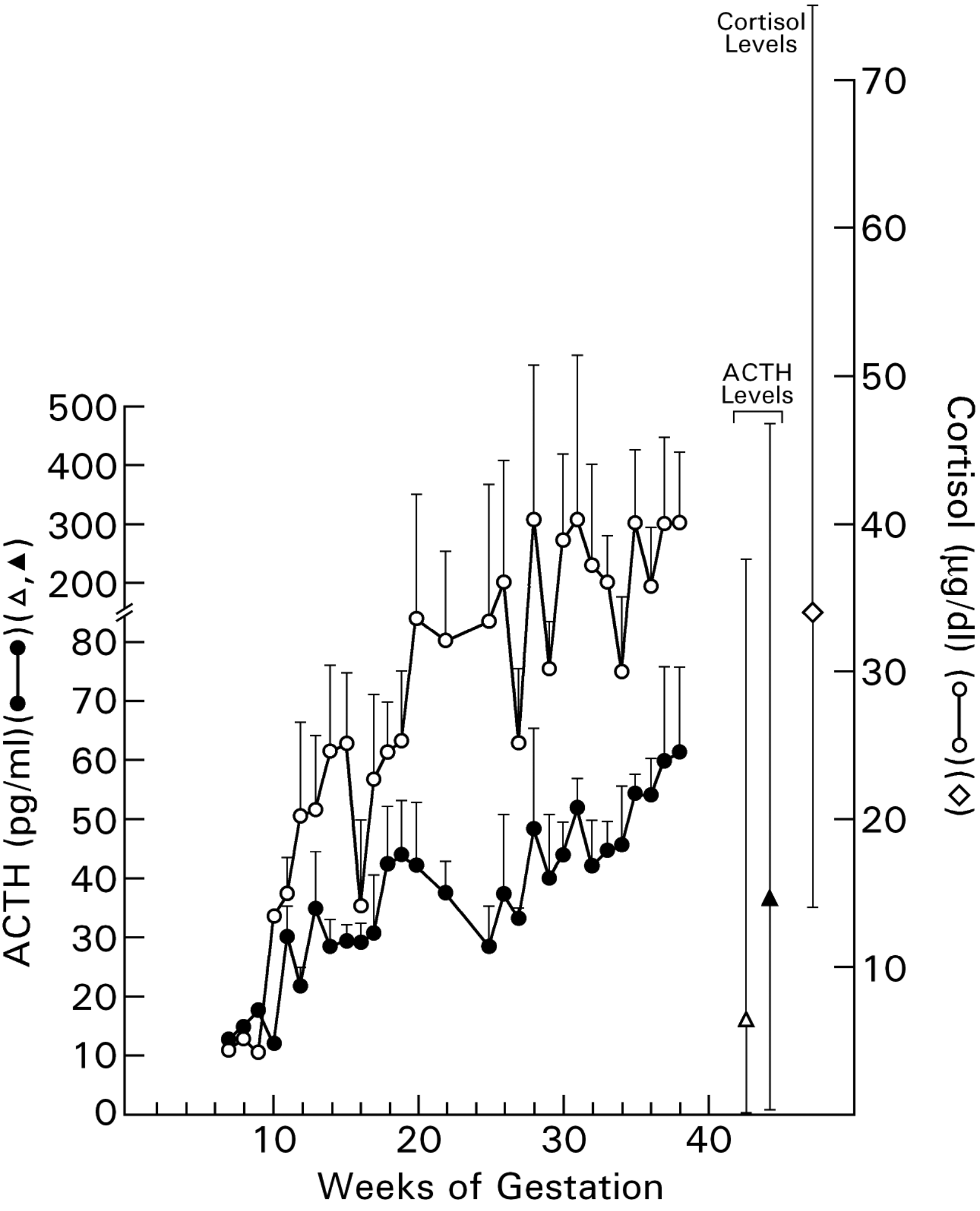
Fig 2. Mean plasma CRH concentrations in seven women throughout pregnancy. Sequential samples were obtained at 1- to 2-week intervals beginning at 12 weeks' gestation. Reprinted from Am J Obstet Gynecol 159: Goland RS, Wardlaw SL, Blum M, Tropper PJ, Stark RI. Biologically active corticotropin-releasing hormone in maternal and fetal plasma during pregnancy: 884-90; Copyright (1988) with permission from Elsevier.

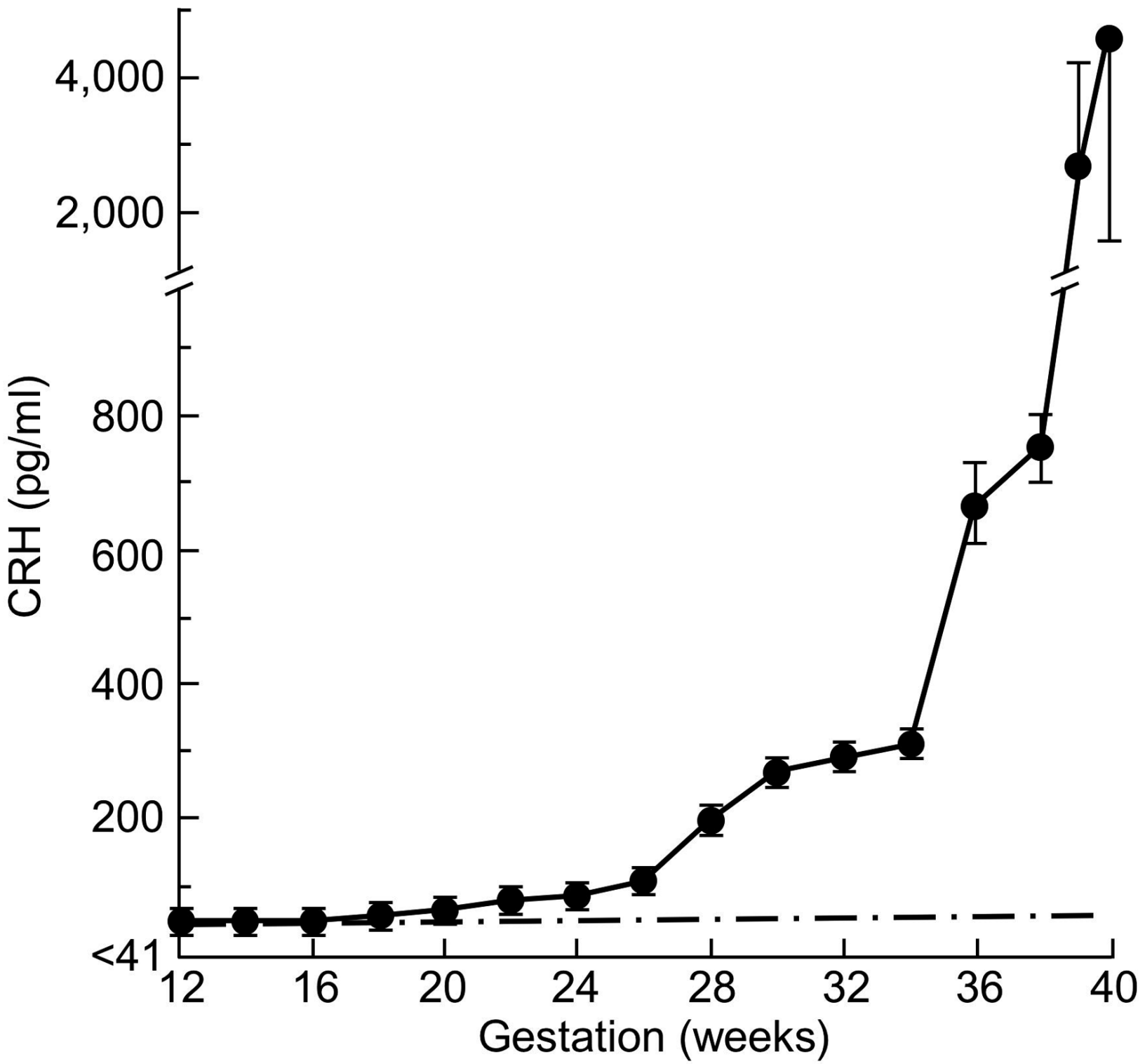
Fig 3. Comparison of the molar concentrations of CRH (■) and CRH-BP (○) in maternal plasma during the final 180 days of gestation in pregnancies ending in spontaneous term labor (37-42 weeks gestation). Each point represents the mean (± s.e.m.) of samples grouped by 10-day intervals calculated retrospectively 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

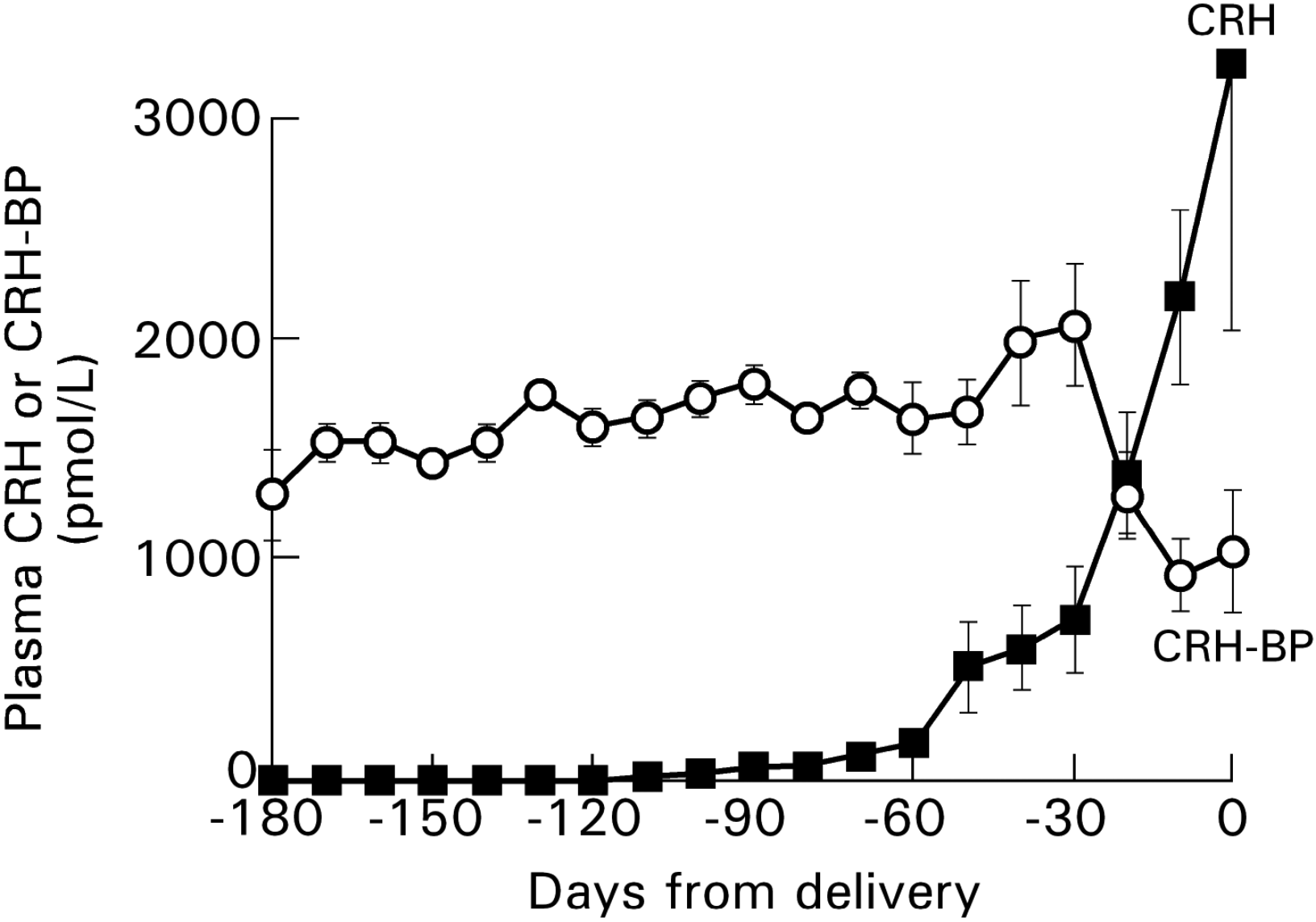
at the intersection of the two curves, 20 days before delivery. Reprinted from Nat Med. 1; 460-3. McLean M, Bisits A, Davies J, Woods R, Lowry P, Smith R: A placental clock controlling the length of human pregnancy; Copyright (1995) with permission from Nature Publishing Group (http://www.nature.com/).

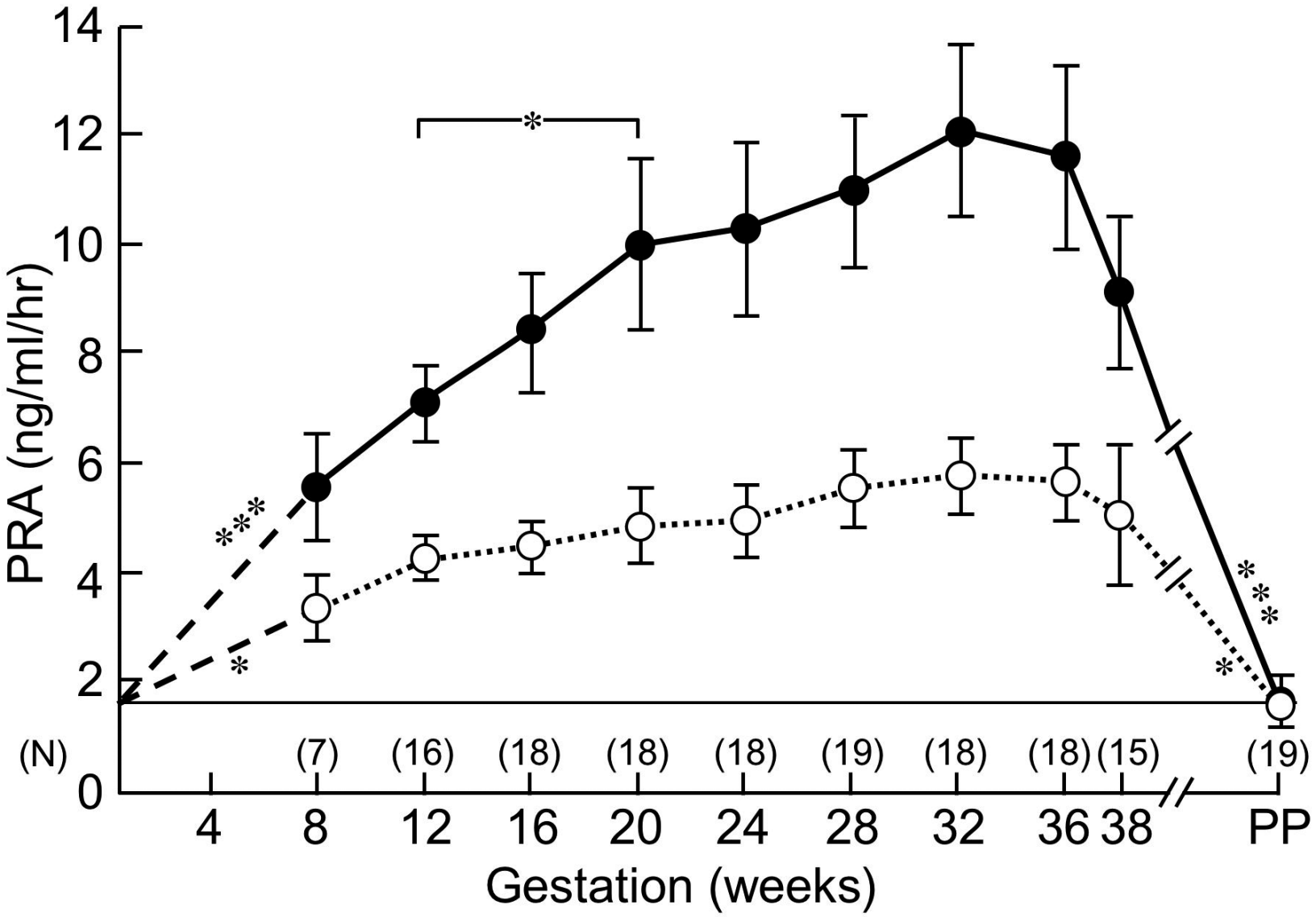
Fig 4. Sequential changes in PRA (●) and in PRA normalized to the postpartum substrate values (○) (mean ± SE) throughout pregnancy (* = $p<0.05$, *** = $p<0.001$). Reprinted from Am J Med 68: Wilson, M, Morganti AA, Zervoudakis I, Letcher RL, Romney BM, Von Oeyon P, Papera S, Sealey JE, Laragh, JH. Blood pressure, the renin-aldosterone system and sex steroids throughout normal pregnancy: 97-104; Copyright (1980) with permission from Elsevier.

Fig 5. Change in plasma cortisol before and after the administration of 1 mg of dexamethasone in pregnant women (●). Blood was drawn at 8 a.m. A single dose of dexamethasone was administered orally at 11 p.m. and blood was drawn at 8 a.m. on the following day. Reprinted from Endocrinol Jpn 35: Odagiri E, Ishiwatari N, Abe Y, et al. Hypercortisolism and the resistance to dexamethasone suppression during gestation: 685-90; Copyright (1988) with permission from Endocrine Soc Japan.


Cortisol Levels
ACTH Levels
ACTH (pg/ml)(●—●)(△,▲)
Cortisol (μg/dl) (○—○)(◇)
Weeks of Gestation
0
10
20
30
40
50
60
70
80
200
300
400
500
10
20
30
40
50


4,000
2,000
800
600
400
200
<41
CRH (pg/ml)
12
16
20
24
28
32
36
40
Gestation (weeks)


CRH
3000
2000
1000
0
Plasma CRH or CRH-BP (pmol/L)
CRH-BP
-180
-150
-120
-90
-60
-30
0
Days from delivery


PRA (ng/ml/hr)
14
12
10
8
6
4
2
0
(N)
(7)
(16)
(18)
(18)
(18)
(19)
(18)
(18)
(15)
(19)
4
8
12
16
20
24
28
32
36
38
PP
Gestation (weeks)
*
**
***
*
*
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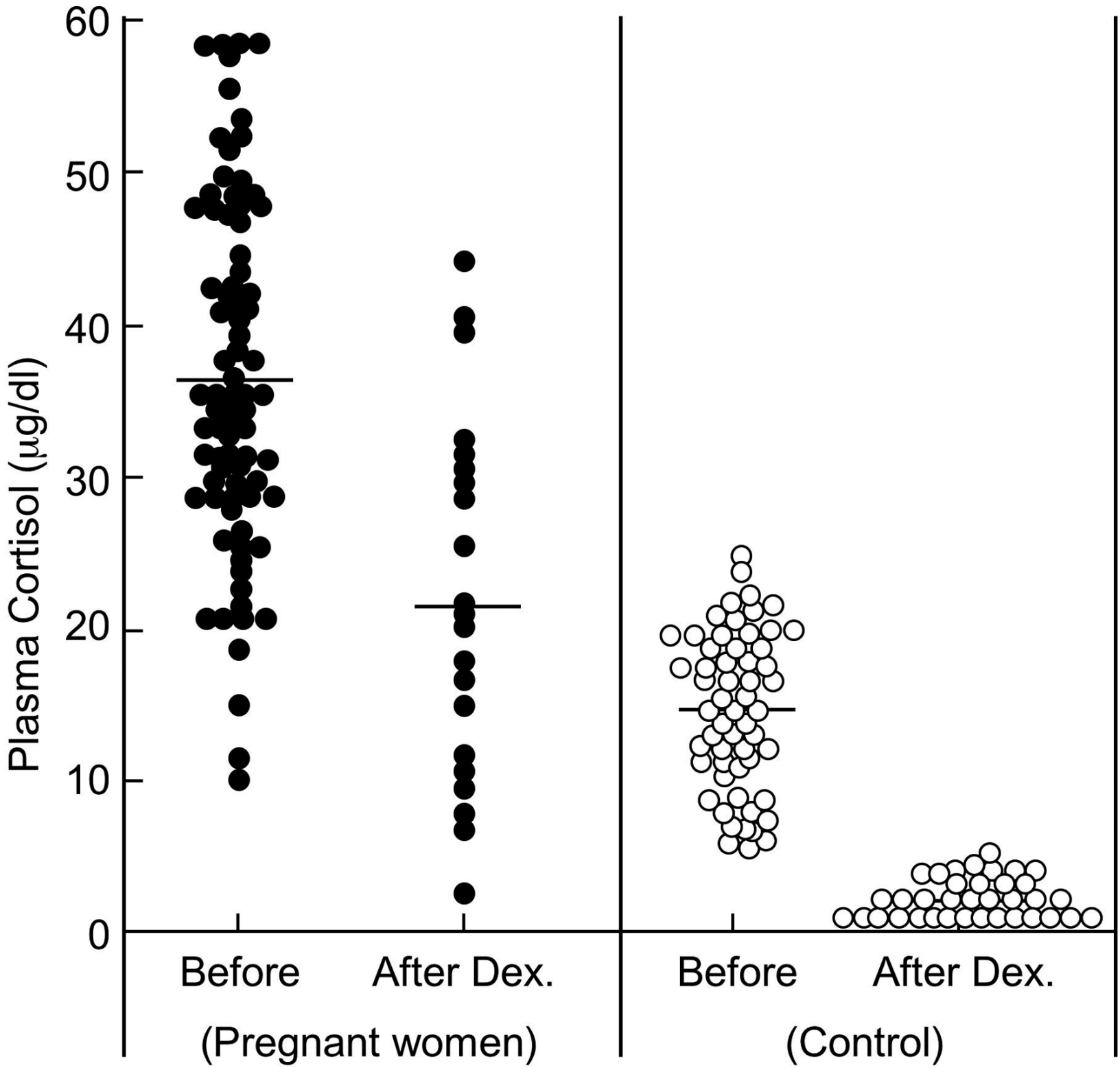
60
50
40
30
20
10
0
Plasma Cortisol (μg/dl)
Before
After Dex.
(Pregnant women)
Before
After Dex.
(Control)