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REVIEW

Adrenal insufficiency in pregnancy: challenging issues in diagnosis and management

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Abstract Adrenal insufficiency (AI) in pregnancy is relatively rare, but it is associated with significant maternal and fetal morbidity and mortality if untreated during gestation or in the puerperium. Hence, timely diagnosis and decisive treatment by the clinician are critical. However, due to pregnancy-induced metabolic and endocrine changes and the resemblance of symptomatology of AI to those of pregnancy, the diagnosis is often difficult to recognize and challenging to confirm. Normal pregnancy is a state of glucocorticoid excess particularly in the latter stages, and normative values for serum cortisol levels are not well-established. Furthermore, testing the hypothalamic–pituitary–adrenal axis using validated stimulation tests during pregnancy are lacking. Therefore, it is the aim of the present review to discuss and to summarize the current knowledge, focussing on the challenges in recognizing AI in pregnancy and interpreting the diagnostic tests, and to propose a clinical approach for optimizing the management of AI in women diagnosed before or during pregnancy.

Keywords Adrenal insufficiency · ACTH · Cortisol · Glucocorticoid · Pregnancy

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Introduction

Adrenal insufficiency (AI) is a clinical syndrome arising either from the direct destruction of adrenal glands (primary AI) resulting in glucocorticoid and mineralocorticoid deficiency, or atrophy of the adrenal cortex due to decreased stimulation of adrenocorticotropic hormone (ACTH) caused by hypothalamic or pituitary damage, or from prolonged excessive glucocorticoid administration (secondary AI) [1]. The estimated prevalence of primary AI is around 110–140 per million population with an incidence of 4.7–6.2 per million [2]. In contrast, as glucocorticoids are increasingly used for a variety of diseases [3], it is no surprise that the prevalence of secondary AI far exceeds that of primary AI [4]. However, AI remains relatively rare in pregnancy with the reported incidence of 1:3,000 births over a 12-year period from a series of 15,700 deliveries [5]. The rarity of AI during pregnancy stems from the fact that in primary AI such as Addison's disease, the autoimmune nature of the disease is associated with chronic anovulation leading to impaired fertility [6], whereas in secondary AI due to hypopituitarism, growth hormone deficiency has been implicated to play a role in reducing pregnancy rates [7–9].

Previous data demonstrate that mortality is increased in AI [10, 11], with adrenal crisis being a substantial contributor [12]. Therefore, it is important to recognize AI early to optimize maternal and fetal outcomes. The diagnosis can be challenging as the presentation can range from being insidious to acute. The non-specific symptoms that are frequently thought to be due to pregnancy such as nausea, emesis, fatigue, and altered food preferences contribute to the delayed clinical recognition of AI. In contrast, undiagnosed women with AI may acquire cortisol transplacentally from fetus to mother and only come to attention

when adrenal crisis occurs in the postpartum period [13], or can present acutely when an illness or infection precipitates an adrenal crisis. In a survey of patients with Addison's disease, 11 of 25 patients (44 %) reported a history of adrenal crisis [14], whereas in a group of 44 patients who underwent bilateral adrenalectomy for Cushing's disease, Nagesser et al. [15] reported adrenal crisis in 9 patients (20 %). In another analysis of 137 patients with primary and secondary AI, Omori et al. [16] found that 29 % of these patients had experienced at least one adrenal crisis.

The majority of women with known AI before pregnancy that are appropriately treated have uneventful pregnancies without fetal compromise [6, 17]. Problems arise if AI is unrecognized, as this often leads to higher rates of maternal or fetal mortality either during gestation or in the puerperium [17]. In this review, we discuss the physiology of the hypothalamic–pituitary–adrenal (HPA) axis in pregnancy and maternal/fetal risk; highlight the challenges of interpreting the diagnostic tests in pregnancy; and propose a clinical approach for optimizing the management of AI in pregnancy.

Physiology of the HPA axis in pregnancy

During pregnancy, cortisol levels are increased due to multi-factorial mechanisms that alter the sensitivity of the HPA axis. Rises in placental estrogen stimulates hepatic corticosteroid-binding globulin (CBG) production that then decreases free cortisol levels transiently. This causes an increase in pituitary ACTH secretion to maintain normal free cortisol levels. Free cortisol levels then rises by the 11th week of gestation reaching a plateau in the third trimester [18], while plasma ACTH levels continues to increase throughout pregnancy (Fig. 1). As a result, total cortisol levels increases (Fig. 1), and cortisol clearance decreases [18] resulting in a state of physiologic hypercortisolism but lacking specific clinical characteristics of Cushing's syndrome [19]. Despite hyperactivation of the HPA axis, the circadian rhythm is intact during gestation with feedback mechanisms of cortisol being regulated at a higher set point [20] (Fig. 2).

In contrast to the usual negative feedback of cortisol on hypothalamic CRH production, placental CRH production is increased in response to cortisol being the major stimulus for the HPA axis in the third trimester [21], and may have effects on the maturation of the fetal adrenal, fetal-placental unit circulation, and paracrine effects on the placenta. Up until about 33 weeks of gestation, more than 90 % of fetal cortisol is derived from maternal sources but beyond that, fetal adrenal cortisol production takes over and maternal contribution decreases. Serum cortisol levels then rapidly normalize in the postpartum period [22].

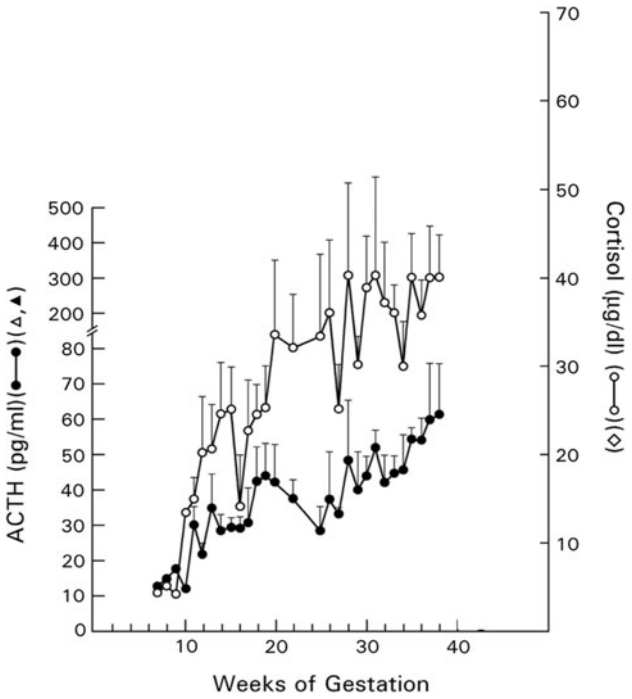

Fig. 1 Changes in serum cortisol (*open circles*) and ACTH (*dark circles*) levels during pregnancy in normal controls during 40 weeks of gestation (reprinted and modified with permission from Carr et al. [80])

The renin–angiotensin system also undergoes adaptation in pregnancy. The ovaries and maternal decidua produce early rises in renin levels causing rises of 5–20 fold of plasma aldosterone levels in the third trimester [23]. Further stimulation of aldosterone production occurs by the increased estrogen and subsequent angiotensin II levels [24]. Progesterone, with its abundant receptors in the placenta [25], also stimulates the production of another potent mineralocorticoid, deoxycorticosterone which rises by 2–3 fold [26, 27], thus explaining much of the increased mineralocorticoid activity during pregnancy.

Etiology

For primary AI, autoimmune adrenalitis accounts for most of the cases in developed countries, whereas tuberculosis is more common in developing countries. In contrast, the most common cause of secondary AI is previous chronic usage of excessive exogenous glucocorticoids for diseases such as asthma, rheumatoid arthritis, and inflammatory diseases [28]. During the postpartum period, Sheehan's syndrome and lymphocytic hypophysitis are the two main differential diagnoses for postpartum hypopituitarism associated with secondary AI. Sheehan's syndrome results after obstetric shock with postpartum pituitary infarction and necrosis, whereas lymphocytic hypophysitis is an

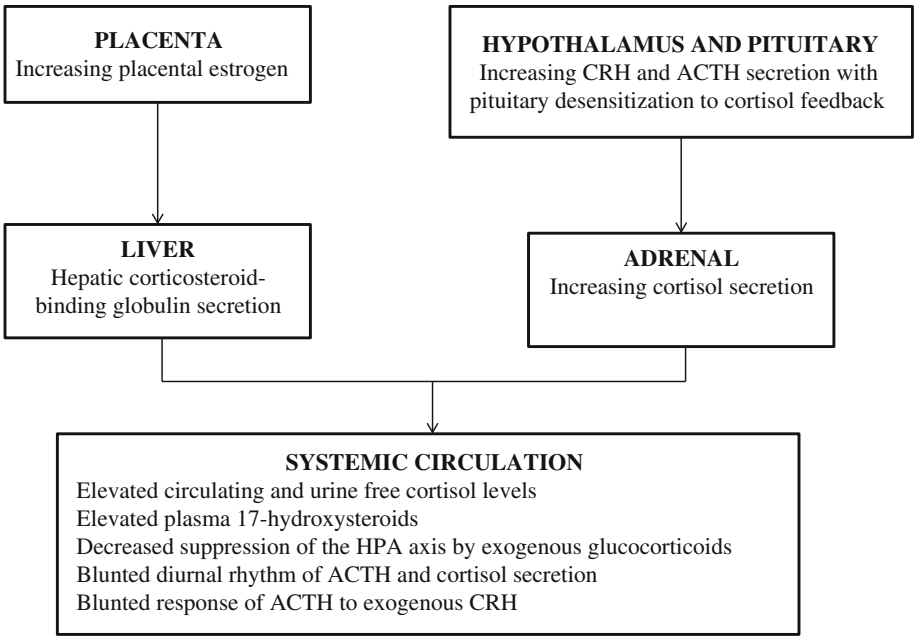

Fig. 2 Changes in the HPA axis during pregnancy

autoimmune inflammatory lesion of the pituitary gland. Other causes of hypopituitarism with resultant secondary AI include hypothalamic and pituitary tumors and their associated treatments of surgery and/or cranial irradiation. In pituitary macroadenomas, ACTH deficiency usually occurs late in association with the progressive decline in growth hormone, gonadotropins, and thyroid-stimulating hormone production. All these may diminish reproductive function, resulting in low fertility rates. However, since the availability of ovulation induction therapy with gonadotropins, women with established hypopituitarism can expect near normal maternal and fetal outcomes, although their pregnancies are still considered high risk [29].

Maternal and fetal risk

Early studies of AI in pregnancy highlighted the potential risks of maternal mortality [30, 31] but the availability of adrenal cortical extracts have seen a reduction in mortality rates from 35 % before 1930 to 18 % between 1940 and 1948 [32], and no maternal deaths since the 1950s [33, 34]. In fact, several subsequent reports have illustrated the potential for safe outcomes for both mother and fetus in previously undiagnosed and untreated cases, probably reflecting earlier detection of AI, less severe AI, and improved obstetric care [5, 33].

Maternal symptoms such as nausea, emesis, fatigue, orthostatic hypotension, and abdominal pains frequently persist beyond the first trimester. If AI is undiagnosed, adrenal crisis can occur during pregnancy especially during the first trimester, the 2 weeks from parturition, during labor and immediate postpartum. While maternal hypotension is a feature of under-treatment with glucocorticoids, the side-effects of excessive glucocorticoid treatment include hypertension, edema, easy bruising, and exacerbation of pre-eclampsia [5, 35].

Intrauterine growth retardation and low birth weight have been previously observed, more severe in untreated mothers [13, 36]. In addition, there have been reported cases of distress [13], oligohydramnios [36], and intrauterine death [37]. Many of these cases occurred in previously unrecognized cases or before the availability of modern glucocorticoid regimens [35, 37]. Although there have been several reports of women with AI presenting during gestation with previous recurrent or subsequent abortions, there does not appear to be an increased risk from AI alone when appropriately treated [38], nor there is evidence of increased prevalence of congenital defects[39]. Thus, careful treatment of AI with optimal glucocorticoid replacement in pregnancy can lead to successful pregnancy outcomes, while follow-up in the distant postpartum period is also important given that late maternal death can still occur at 8 months postpartum [5].

Case scenarios

Pregnant women presenting with diagnosed AI before pregnancy

Most cases of AI in pregnancy are diagnosed before conception, and have established care with an endocrinologist where glucocorticoid and/or mineralocorticoid replacement

regimens are already in place. The majority of patients with secondary AI would have been identified before pregnancy because of a medical history of hypothalamic–pituitary tumors and/or would have undergone treatment with pituitary surgery and/or cranial irradiation. Apart from the preservation of mineralocorticoid secretion, the principal difference in secondary versus primary AI is a history of local effects of a space-occupying lesion at the hypothalamus and pituitary such as headache or visual field disturbance with associated pituitary hormone deficiencies. A presentation with disturbed gonadotropin function resulting in amenorrhea is a frequent initial presentation in non-pregnant women, whereas failure of lactation or resumption of menses may be the first sign of hypopituitarism in the postpartum period. In patients who present with diabetes insipidus, prompt work-up for lymphocytic hypophysitis or craniopharyngiomas should be undertaken.

Pregnant women with undiagnosed AI

In undiagnosed pregnant patients especially in the first trimester, the diagnosis may be difficult to recognize as many of the symptoms of AI such as fatigue, dizziness, syncope, nausea, and vomiting are also frequently seen in routine pregnancy. Only a few cases of AI detected during pregnancy have been reported in the literature [40–43]. As these patients usually present themselves to the obstetrician for management of antenatal care, a high index of clinical suspicion by the obstetrician is required. Clinical features such as excessive dizziness, syncope, nausea, protracted vomiting, weight loss, profound hyponatremia, hypoglycemia, and salt craving should raise the possibility of AI [35, 44]. Skin hyperpigmentation can be present in pregnancy, but hyperpigmentation on the skin creases and mucus membranes should alert to the possibility of primary AI. Some patients present in the 3rd trimester of pregnancy and may be unmasked during illness or the stress of labor [36]. Exclusion of AI should be considered in cases with persistent and unexplained orthostasis or hypotension, even in the postpartum period [38, 44]. Total cortisol levels may be within the normal ranges for non-pregnant women reflecting cortisol bound to CBG, but low morning serum cortisol levels should raise the suspicion of AI. Signs of mineralocorticoid deficiency may signal impending adrenal crisis, with potentially high mortality in unrecognized cases. Patients with secondary AI often do not exhibit orthostasis and hypotension; hence, the absence of these features cannot be reliably used to exclude AI.

Other helpful hints of possible primary AI include a personal or family history of autoimmune disease including polyglandular autoimmune syndromes type 1, 2, and 4 with features such as vitiligo, type 1 diabetes mellitus and primary hypothyroidism [36, 45, 46]. Severe abdominal pain and profound orthostasis may herald the onset of AI secondary to acute adrenal hemorrhage [47]. In some cases, the presentation is associated with persistent vomiting that may be confused with hyperemesis gravidarum [40].

Diagnosis

Laboratory tests

The diagnosis of unrecognized AI in pregnancy, especially in the 1st trimester, can be difficult and requires a high degree of clinical suspicion. Confirmation of the diagnosis is a three-stage process: (1) demonstrating inappropriately low serum cortisol levels, (2) determining whether the cortisol deficiency is dependent on or independent of ACTH deficiency and evaluating mineralocorticoid secretion in patients without ACTH deficiency, and (3) seeking a treatable cause of the primary disorder (e.g., tuberculosis involving the adrenal glands or a pituitary adenoma compromising normal pituitary function). When the clinical suspicion for adrenal crisis is high, samples for serum cortisol and ACTH levels should be obtained for measurement before starting empirical treatment with high dose intravenous glucocorticoids (Table 1).

Because serum cortisol and urine free cortisol levels increase during gestation [48, 49], random serum cortisol and urine free cortisol levels are unreliable markers for the diagnosis. However, in the appropriate clinical context, basal morning serum cortisol of less than 3 μg/dL makes the diagnosis of AI in pregnancy highly likely [50, 51]. Based on the recent results by Jung et al. [49], it has been proposed that basal morning serum cortisol levels of less than 11, 16.3, and 22 μg/dL during the 1st, 2nd, and 3rd trimesters, respectively should prompt further work-up for possible AI [52]. We recommend for patients with basal morning serum cortisol of less than 3 μg/dL to undergo dynamic testing using the standard 250 μg cosyntropin stimulation test (CST) (United States FDA class C drug) [50, 53]. Although this test has high sensitivity and specificity (97 and 95 %, respectively) [54], we acknowledge that the accepted serum cortisol cutpoints of less than 18–20 μg/dL were studied in nonpregnant patients [50, 53, 55]. In pregnancy states, this cutpoint may misdiagnose patients as the peak cortisol responses to 250 μg cosyntropin ranges between 60 and 80 % above the nonpregnant peak responses [56] due to enhanced maternal adrenal responsiveness to ACTH stimulation [57]. Therefore, based on current available data, we and other investigators [51, 52] recommend raising the peak serum cortisol cutpoints to 25, 29, and 32 μg/dL for the 1st, 2nd, and 3rd trimesters of pregnancy, respectively. Nonetheless, others have challenged the reliability of 250 μg CST because this is a

Table 1 Laboratory tests for diagnosing AI in pregnancy

Tests	Comments	References
[a]Basal serum cortisol	Morning basal serum cortisol levels ≤3.0 μg/dL is indicative of AI	[51]
	For patients with morning basal serum cortisol levels >3.0 μg/dL, dynamic testing is required	[79]
[a]Basal plasma ACTH	Usually helpful in determining cause of AI, but may also be useful in diagnosis when measured simultaneously with basal serum cortisol	[61, 80]
[b]Salivary free cortisol	May be more consistent, generalizable, and physiologically rational measure of adrenal function in pregnancy rather than basal serum cortisol, but requires larger longitudinal studies to confirm its utility	[57, 81]
[a]250 μg cosyntropin test	Most widely used test but little data to determine specific cutpoints in pregnant women	[50, 53, 55]
	Cosyntropin is licensed as a FDA class C drug when administered in pregnancy	[82]
	Peak serum cortisol cutpoint <18–20 μg/dL may be inaccurate in pregnancy due to enhanced adrenal responsiveness to synthetic ACTH stimulation	[57]
	Raising peak serum cortisol cutpoints to 25, 29 and 32 μg/dL during the 1st, 2nd and 3rd trimesters of pregnancy, respectively, may improve the sensitivity of the test	[51]
[b]1 μg cosyntropin test	Some investigators have proposed this test because 1 μg is more physiological, but remains debatable if this test improves the sensitivity	[58–60]
[b]Insulin tolerance test	This test is the gold standard test for detection of AI in non-pregnant patients. No studies in pregnancy due to its relative contraindication of severe hypoglycemia for the fetus	[55]
[b]Metyrapone test	Metyrapone, administered 30 mg/kg orally at midnight, inhibits adrenal 11β-hydroxylase, thereby inhibiting the final step of cortisol biosynthesis and promoting pituitary ACTH hypersecretion, but invokes a risk of precipitating adrenal crisis	[83, 84]
	This test is at least as sensitive as the insulin tolerance test for detecting AI	[84]
[b]CRH stimulation test	This test can differentiate secondary versus tertiary AI in non-pregnant patients	[85]
	Limited utility for the diagnosis of AI and lack of validation in non-pregnant and pregnant patients	[86]

[a] We recommend using these tests

[b] We do not recommend using these tests

supraphysiological dose and proposed the use of the more physiological 1 μg CST. However, controversy remains as to whether the 1 μg CST improves the sensitivity for detecting secondary AI [58–60]. By contrast, although the insulin tolerance test (ITT) is considered the gold standard test for assessing the HPA axis in the nonpregnant population, there are no studies that support its use in pregnancy due to the relative contraindication of inducing blood glucose levels to less than 40 mg/dL and its potential harm for the fetus. We do not recommend using the ITT, but the test may be considered in the postpartum period. Other dynamic tests such as the metyrapone and CRH stimulation tests should not be used due to the risk of potentiating adrenal crisis and lack of validation, respectively.

Once the diagnosis of AI is established, the next step is to differentiate whether the patient has primary versus secondary AI. Plasma ACTH levels exceeding 100 pg/mL is generally consistent with primary AI, even in late pregnancy [50, 61]. Conversely, if both the morning serum cortisol and plasma ACTH levels are inappropriately low, then the patient has secondary AI. Other helpful laboratory tests include 21-hydroxylase and 17-hydroxylase antibodies as 90 and 30 %, respectively, of nonpregnant patients with primary AI respectively are positive for these antibodies [62, 63]. Positive adrenal antibodies should raise the suspicion of other autoimmune diseases and a work-up for other autoimmune endocrine deficiencies is recommended. Patients with secondary AI should undergo further testing measuring thyroid-stimulating hormone and free thyroxine levels to avoid missing the diagnosis of secondary hypothyroidism. For these patients, the inability to breastfeed or the lack of resumption of menstrual periods during the postpartum period should raise the suspicion of hypopituitarism.

Radiological tests

Rarely radiological tests are helpful in making the diagnosis of AI. Imaging the adrenal glands is not required in patients with positive adrenal antibodies, but may be useful in detecting large glands associated with tuberculous or fungal infection, bilateral metastases, hemorrhage, or infarction [47, 64, 65]. Magnetic resonance imaging (MRI) without gadolinium administration is preferred to CT in pregnancy. We recommend deferring imaging, especially if the patient is clinically stable, until the postpartum period. The exception is if a pituitary tumor or a cranial space-occupying lesion is suspected. For these patients, a pituitary MRI without gadolinium administration should be considered [66].

Therapy

Patients with AI should be managed by a multidisciplinary team that includes an endocrinologist and an obstetrician, and access to an experienced pituitary neurosurgeon. For pregnant women presenting with diagnosed AI, the obstetrician should work with the endocrinologist in monitoring for the adequacy of glucocorticoid and/or mineralocorticoid replacement therapy in the antenatal period, during crisis and labor, and for continuity during the postpartum period. Because of the changes in the HPA axis during pregnancy and the challenges that underlie the diagnostic process, an obstetrician who suspects that a pregnant woman has AI should consult an endocrinologist to formulate a diagnostic work-up and therapeutic strategy. If the patient has secondary AI with a large pituitary macroadenoma or other large intracranial neoplasms, the team must then decide on the optimal timing for surgical removal. Although surgery could be delayed into the postpartum period in selected cases, the second trimester is thought to be the optimal time for surgery during gestation [67]. Our recommendations for optimal management of pregnant women with AI are displayed in Table 2.

Glucocorticoid replacement

The primary aim of glucocorticoid therapy in pregnancy is to achieve optimal replacement to enhance maternal and fetal outcomes. In this context, one should consider normal cortisol production rates in nonpregnant individuals is less than 10 mg/day [68], the start of fetal adrenocortical function at the 7th week of gestation, and the anti-mineralocorticoid effect of progesterone which may require increasing the dose of fludrocortisone, especially in the last trimester [69]. The most critical period during pregnancy is with 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 [37]. During the first and second trimesters, careful monitoring based on clinical grounds and individualized dosing schemes are required to avoid glucocorticoid over-replacement and the potential of inducing iatrogenic Cushing's syndrome. We do not recommend measuring plasma ACTH levels to guide titration of glucocorticoid therapy due to the large interindividual variation in ACTH levels secondary to the varying sensitivity to cortisol [70].

Glucocorticoid treatment is not associated with teratogenicity, maternal infections, poor wound healing, or increased fetal loss [71, 72]. Prednisone, dexamethasone, and cortisone acetate are several glucocorticoid preparations currently available. We prefer hydrocortisone at a replacement dose of 12–15 mg/m^2 of body surface area or 20–30 mg/day mainly due to its safety profile [73], and most patients typically require a dose of no more than 20 mg a day. The daily dose is usually divided into a twice

Table 2 Proposed recommendations for management of AI in pregnancy

Pregnancy
First trimester[a]
Hydrocortisone 12–15 mg/m^2 of body surface area or 20–30 mg/day in divided doses of twice (two-thirds of the dose on wakening and one-third in the afternoon) or thrice (half the dose on wakening, quarter at lunch and quarter no later than 5 pm) a day
Fludrocortisone 0.05–0.2 mg/day depending on blood pressure and serum potassium levels. If fludrocortisone is unavailable, consider salt tablets 3–6 g orally
Third trimester[a]
Hydrocortisone 20–30 to 40–60 mg/day in divided doses of twice (two-thirds of the dose on wakening and one-third in the afternoon) or thrice (half the dose on wakening, quarter at lunch and quarter no later than 5 pm) a day
Fludrocortisone 0.05–0.2 mg/day depending on blood pressure and serum potassium levels
Labor and delivery
Hydrocortisone dose should be doubled, unless the patient is vomiting, in which IV hydrocortisone of 50–100 mg should be administered. Further dosing to be considered if labor is prolonged. If cesarean section is contemplated, stress doses of 100 mg IV hydrocortisone should be administered every 6–8 hourly or as a continuous infusion in saline over 6–8 h until delivery
Acute adrenal crisis in women undiagnosed with AI: hydrocortisone IV bolus 100–200 mg, followed by 50–100 mg boluses every 6–8 hourly, and intravenous dextrose 5 % and potassium supplementation if hypoglycemia and hypokalemia are present
Postpartum
Women with primary AI: recommence oral hydrocortisone and fludrocortisone 0.05–0.2 mg/day with taper to pre-pregnancy doses within 3 days
Women with secondary AI: recommence oral hydrocortisone 20–30 mg/day without fludrocortisone

IM intramuscular, *IV* intravenous

[a] If not able to tolerate due to nausea and vomiting, administer IM hydrocortisone 50 mg or IM dexamethasone 2 mg with IV saline infusion

or thrice a day regimens (Table 2). We prefer the thrice a day regimen as this regimen more closely mimics the normal diurnal variation than the twice a day regimen [74], but does require an extra dosing. To compensate for the physiologic increase in CBG levels in the last trimester, we recommend increasing the doses of glucocorticoid replacement by 50 %, and the adjustment of other potentially interfering medications such as levothyroxine that can increase the metabolism of hydrocortisone [50]. At delivery, hydrocortisone 50–100 mg administered intravenously during the first 24–48 h is recommended followed by taper to pre-pregnancy doses within 3 days.

However, in contrast to managing hypothyroidism in which serum TSH and free thyroxine levels are helpful in guiding the clinician in monitoring the adequacy of levothyroxine replacement, plasma ACTH and serum cortisol levels cannot be used to adjust the dosing of glucocorticoid replacement therapy in patients with AI. This raises a need for the development of novel glucocorticoid preparations to obtain more physiological serum cortisol time-profiles in patients with AI. In this regard, a dual-release preparation of hydrocortisone (Plenadren®) has been developed as 20 or 5 mg tablets formulated with an external layer for a rapid release of the hormone and an internal core for delayed-release. This dual-release preparation may be administered once daily and fulfils the two major important criteria of glucocorticoid replacement therapy: (1) rapid increase of cortisol levels in the morning, and (2) prolonged slower release of hydrocortisone to mimic the physiological circadian cortisol rhythm [1, 75, 76]. Currently, Plenadren® is not available in the United States yet, but was recently made available in Europe following the approval by the European Medicines Agency for use in non-pregnant patients with primary and secondary AI, and congenital adrenal hyperplasia. However, the use of Plenadren® is not advocated in pregnancy and in children due to the lack of safety data in these groups of patients.

Mineralocorticoid replacement

Presently, there are no studies of mineralocorticoid replacement during pregnancy in women with AI. Mineralocorticoids are required in primary AI and are usually initiated at the time of diagnosis of AI in pre-pregnant patients, and are continued during pregnancy. Because of the anti-mineralocorticoid effect of progesterone, the dose of fludrocortisone may need to be increased depending on serum potassium levels and blood pressure. Patients should be closely monitored throughout pregnancy for changes in blood pressure and electrolytes. Oral fludrocortisone should be administered at daily doses between 0.05 and 0.2 mg, and should not be based on plasma renin levels as these levels are unreliable during pregnancy. The dose of mineralocorticoids should be decreased if hypertension or hypokalemia occurs, and discontinued if toxemia develops [77].

Education

Good management of AI in pregnancy relies upon educating the patient at diagnosis of the basic principles of glucocorticoid replacement and the importance of increasing the dose during periods of stress and intercurrent illness ("sick day rules"). Patient adherence is the cornerstone in the successful outcome of the pregnancy, which may be challenging because of the frequency of anorexia, nausea or vomiting during the first trimester. Pre-pregnancy counseling should be emphasized in women contemplating pregnancy and the awareness of seeking medical evaluation early in gestation. It is important to counsel patients to continue on glucocorticoid replacement despite nausea and if needed, to consider parenteral glucocorticoid administration. In addition, patients should be trained in recognizing stressful situations (e.g., fever, infection, surgery under local anesthesia) and symptoms of AI, and instructed on increasing their glucocorticoid doses in these situations. In cases of minor physical stress (e.g., infectious diseases with fever, stress, surgery under local anesthesia) or major and prolonged psychological stress, the daily hydrocortisone replacement dose should be doubled or tripled. Under conditions of medium or major physical stress (e.g., trauma, surgery with general anesthesia, delivery) and in cases of diarrhea/vomiting, women should be taught to self-administer intramuscular hydrocortisone 100 mg and advised to seek medical attention early for intravenous hydrocortisone treatment and rehydration. As high doses of hydrocortisone have mineralocorticoid effects, adjustment of fludrocortisone doses during these stressful periods is not necessary. All patients should be advised to wear an identification bracelet so that they can be identified promptly in an emergency situation.

Labor and delivery

Labor and delivery are stressful and patients require larger doses of glucocorticoids. As labor approaches, the dose of hydrocortisone should be doubled, unless the patient is vomiting, in which intravenous hydrocortisone of 50–100 mg should be administered around the time of the second stage of labor (Table 2). Further dosing may be considered if labor is prolonged or cesarean section is contemplated [33, 73]. The doses of hydrocortisone then can be tapered to regular maintenance oral replacement doses over 3 days [78]. Physiological glucocorticoid replacement can continue during breast feeding, as very

minimal amount of hydrocortisone is excreted into the breast milk [71].

Adrenal crisis occurring during pregnancy

An undiagnosed patient with AI may tolerate the pregnancy but experience an acute deterioration during an episode of illness such as pneumonia, influenza, hyperemesis, pre-eclampsia, and during labor and delivery. In these circumstances, prompt glucocorticoid therapy should be administered with intravenous bolus of hydrocortisone 100–200 mg followed by 50–100 mg boluses every 6–8 hourly, and intravenous dextrose 5 % and potassium supplementation if hypoglycemia and hypokalemia are present. Fludrocortisone is not indicated in patients with primary or secondary AI in the acute period due to the mineralocorticoid-like properties of high doses of hydrocortisone. Once the patient is able to tolerate oral fluids, intravenous glucocorticoid therapy can be discontinued and oral glucocorticoid therapy recommenced.

Postpartum period

Following delivery, women with primary AI should recommence on glucocorticoid and mineralocorticoid replacement, whereas women with secondary AI should recommence only on glucocorticoid therapy without mineralocorticoid therapy as the zona glomerulosa of the adrenal gland is usually intact in these patients. Patients should recommence on pre-pregnancy glucocorticoid doses once they are able to eat and drink after delivery. In a minority of cases, stress doses of glucocorticoids may be necessary if the patient is in pain, recovering from surgery or having an intercurrent illness. In women who received adequate glucocorticoid replacement during pregnancy, there is usually no indication to evaluate the HPA axis of their infants. In contrast, formal assessment of the HPA axis is recommended in infants born to mothers who had received high doses of glucocorticoids during gestation as they can cross the placenta and inhibit fetal glucocorticoid production causing adrenal atrophy.

Conclusion

Detecting AI during pregnancy remains challenging due to the pregnancy-induced metabolic and endocrine changes, the close resemblance of the symptomatology of AI and pregnancy (particularly in the first trimester), and the lack of well-validated diagnostic tests. The obstetrician needs to have a high index of clinical suspicion of AI when confronted with a pregnant patient with symptoms such as emesis, fatigue, hyperpigmentation, and hyponatremia that are more severe and prolonged. Clinical suspicion, timely diagnosis and decisive treatment are critical because untreated AI in pregnancy can lead to significant maternal and fetal morbidity and mortality. A strategy that includes basal and stimulation laboratory tests, and rarely imaging studies, must be carefully formulated by an experienced endocrinologist working closely with an obstetrician that is tailored for each patient. It must, however, be borne in mind that there are still many gaps in our knowledge in terms of the validity and diagnostic accuracy of stimulation tests, the lack of established normative data for cortisol levels in pregnancy, and clear biochemical criteria to guide optimal glucocorticoid replacement in pregnancy. Therefore, early diagnosis and close clinical supervision during pregnancy remains essential in achieving good maternal and fetal outcomes.

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