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REVIEW ARTICLE

Diagnosis and management of Addison's disease during pregnancy

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ABSTRACT. Although primary adrenal failure is considered a rare condition, recent epidemiological studies indicate a rising incidence of the disease owing to the increase of autoimmune disorders. Addison's disease may be a life-threatening condition and the occurrence of pregnancy has been considered as a dangerous event. Nowadays, adrenal insufficiency during pregnancy is associated with high incidence of serious fetal and maternal complications, as fetal death *in utero* and post-partum adrenal crises, only if the disorder is not recognized and adequately treated. In this article pathophysiological aspects, clinical features and guidelines of management of pregnancy in Addison's disease are reviewed.

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INTRODUCTION

Primary adrenal insufficiency is a rare condition with an estimated prevalence in Western countries of 35-60 per million in initial studies (1, 2) and of about 120-140 per million in more recent reports (3-5). Its prevalence is probably underestimated and the incidence of the disease has been rising over the last year, owing to the increase of autoimmune disorders. In fact, although uncommon, Addison's disease is usually due to autoimmune alterations, whereas infiltrative or hemorrhagic causes are less frequent. Recently, the steroid 21-hydroxylase enzyme has been recognized as the major autoantigen of the adrenal cortex and 21-hydroxylase autoantibodies (21-OHAb) have been found in 80-90% of patients with idiopathic Addison's disease with a positive correlation with the severity of adrenal dysfunction (6, 7). The 21-OHAb levels have been found to be a marker of low progression to clinical adrenal insufficiency in adult patients with organ-specific autoimmune disease and the predictive value is about 20-30% (6, 7). Nevertheless a greater incidence of autoimmune adrenal failure in the puerperium, contrary to the occurrence of autoimmune thyroid disorders, has not been reported.

In Addison's disease, the coexistence of chronic anovulation leading to infertility, unless properly treated, may explain the low rate of conception. Furthermore, associated autoimmune oophoritis may impair fertility and lead to premature ovarian failure; it is of interest that in adult patients with organ specific autoimmune disease the prevalence of adrenal cortex autoantibodies (ACA) was significantly higher in women with premature ovarian failure than in healthy controls (7). To date there are many case reports of pregnancy in primary hypoadrenalism described in the literature, but the actual size of its occurrence is not known, thanks to the more frequent recognition and correct management of the disease. Interestingly, in a multi-institutional survey performed by the Study Group on "Etiology of Addison's Disease" of the Italian Society of Endocrinology, 93 affected women were retrospectively reviewed. Pregnancies occurred in 54 women, 52 of whom delivered children: 20 women had one baby, 29 two children and 3 had 3 babies.

The existence of Addison's disease, especially if unrecognized, may be a life-threatening condition and requires medical attention. However, some life events, potentially dangerous, may be anticipated and then prevented by adapting the substitution therapy. Pregnancy has been considered as a dangerous

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event, at least before glucocorticoid replacement therapy became available. At present Addison's disease is an infrequent complication of pregnancy that gives a high risk of maternal and fetal mortality only if not recognized and treated.
The aim of this review is to briefly summarize the present knowledge on both the pathophysiology and the clinical aspects of pregnancy in Addison's disease. The possibilities of precociously identifying and treating the disorder will also be reported.

PATHOPHYSIOLOGY

During pregnancy there is an activation of the hypothalamic-pituitary-adrenal (HPA) axis, that results in increased corticosteroids secretion, by a not yet completely known mechanism (8). In fact, over the course of gestation, maternal ACTH, cortisol, CBG, urinary free cortisol (UFC), androgens, aldosterone levels and plasma renin activity (PRA) are increased without clinical evidence of hypercortisolism or hyperaldosteronism. Total and unbound cortisol levels progressively augment by 12 weeks until midgestation, about 3-fold above the levels of non-pregnant women. This rise is caused either by the estrogen-induced increase of CBG levels or by the augmented cortisol production rate or by the reduction in cortisol clearance rate. UFC excretion initially remains within normal limits and increases 2-3 fold by the second trimester of gestation. Plasma ACTH levels have been variably reported: in early pregnancy they may be found normal, suppressed or augmented, and they gradually increase up to 2-fold after the third month, similarly to cortisol rise.
Despite the increase in ACTH and cortisol levels, their circadian rhythm is normally maintained during gestation, while feed-back mechanisms of cortisol are regulated at a higher set point with a lower suppressibility by dexamethasone. Interestingly, placental secretion of CRH and ACTH may also be involved in HPA activation. In normal women CRH increases during the second and third trimester of gestation and declines quickly after delivery suggesting that CRH is a "placental clock" for delivery. In humans cortisol, but not ACTH, crosses the placenta and contributes to fetal maturation. The increase in maternal cortisol secretion is of great importance to maintain fetal growth, development and well-being, and for maternal volume expansion and blood pressure. Before delivery, HPA activation results in fetal organ maturation and myometrial activity.
Contrary to normal subjects, addisonian pregnant women are not able to increase their cortisol secretion: cortisolemia may be found normal but inappropriately low for the gestational period (see Diagnosis). The increase in ACTH secretion results in increased skin and mucous membrane pigmentation. In normal pregnancy fetal cortisol levels derives from maternal adrenal secretion for much of the gestation period. In fact the major direction of cortisol transfer through the placenta is from mother to fetus and about 90-95% of fetal cortisol is of maternal adrenal origin. Up to 33 weeks of gestation fetal adrenal cortisol production increases and the maternal contribution slowly decreases. In cases of mild hypocortisolism adrenal crisis may be avoided until delivery by the possible transplacental passage of cortisol from fetus to mother to maintain maternal cortisol levels.
In addition, during normal pregnancy a change in androgen concentration is found with a rise in total testosterone, due to the increase in binding proteins as SHBG, and in androstenedione levels, while DHEA-S and DHEA levels are not increased, as they are used as substrate for maternal estrogen production.
As far as mineralocorticoids are concerned, an activation of renin-angiotensin-aldosterone axis during normal pregnancy is also observed and PRA, angiotensin II and angiotensinogen are variably increased by the first weeks of gestation (9). Also plasma aldosterone levels rises 5-fold by 16 weeks up to 10-fold at the end of pregnancy, while urinary aldosterone rises up to 25-fold at delivery. There is an increase in progesterone concentration, which competes with aldosterone for binding to the type 1 corticosteroid receptor and exerts a natriuretic effect: as a consequence, a reduced responsiveness to the sodium-retaining effect of aldosterone occurs. In healthy women this action of progesterone is compensated by an increase in aldosterone levels, associated with increased plasma renin activity (10), but in addisonian pregnant patients a larger dosage of mineralocorticoids replacement may be indicated. Atrial natriuretic peptide concentrations reach their nadir in the third trimester (11), when plasma renin activity and aldosterone concentration reach their peak. In addisonian pregnancy aldosterone deficiency results in hyperkalemia, hyponatremia and reduced excretion of free water by the kidney.

MATERNAL AND FETAL RISK

In the 1940s the availability of adrenal cortical extracts reduced the very high maternal mortality rate, which greatly dropped after the introduction of synthetic steroids (12, 13). Thereafter, conception is not contraindicated, although several complications have been reported. Indeed, in the absence of adequate corticosteroid replacement therapy, adrenal insufficiency during pregnancy is associated with

high incidence of serious maternal and fetal complications. Maternal symptoms as fatigue, anorexia, weight loss, vomiting, postural hypotension and abdominal pain frequently persist after the first trimester. If hypoadrenalism is not diagnosed in time and adequately treated, adrenal crisis may occur during labor, illness and delivery: the most critical periods are the first trimester and the first 2 weeks from parturition. Maternal mortality rate decreased from 35% before 1930 to 18% between 1940 and 1948 (14) and has been nil since 1956 (13). However, Brent (12) reported that 18 out of 40 women died during gestation and observed postpartum adrenal crises in 12 of the other 22 patients; 7 of them died for inadequate treatment.
Fetal growth retardation and suboptimal birth weight have been frequently observed and are more dramatic in infants born to untreated mothers (13, 15, 16). In addition, some cases of distress (16, 17) and oligohydramnios (15) have been attributed to the lack of rise in maternal cortisol levels. At variance, the newborns at term from treated mothers do not show any increase in morbidity; there is no need for glucocorticoid supplementation, since the fetal adrenal gland matures to secrete corticosteroids during the third trimester. In 1950 Brent in his review (12) reported a high rate of fetal deaths *in utero* (40-50% of cases). In the above mentioned multicenter survey performed by the Study Group on "Etiology of Addison's Disease" of the Italian Society of Endocrinology, abortions were observed in 17 out of 104 pregnancies (16%) occurring in 54 addisonian female patients: however, only 13 women had a miscarriage and in 11 of them other pregnancies reached full term. Therefore, the abortion rate, even if relevant, has been falling in the last few decades.

CLINICAL PICTURE

Clinical features of Addison's disease in pregnancy are similar to those found in non-pregnant patients; but the diagnosis can be missed. In fact, during the first trimester nausea and vomiting due to adrenal failure, that mimic the normal symptoms of pregnancy, could be misleading: if these symptoms are persistent and more severe, adrenal failure should be suspected. In addition, maternal symptoms as fatigue, anorexia, weight loss, postural hypotension and abdominal pain frequently persist after the first trimester. A persistent hyperemesis with electrolyte imbalance not improved by the usual treatments has been recently described as presenting symptoms in a young woman with autoimmune polyglandular syndrome (18).
Hyperpigmentation of skin and mucoses, a typical sign of Addison's disease, also may be seen during normal pregnancy, but bluish-black spots on the lips, gums and the mucosal membranes of mouth, rectum and vagina are more evident; a darkening of the skin in non-exposed regions of the body and lines on the palms of the hands is tipically present. Hypotension is a frequent sign, with a further orthostatic fall of blood pressure. In severe cases syncope may occur: in addition, an addisonian crisis also in the eighth week of pregnancy has been recently reported (19). It is to emphasize that mild cases of Addison's disease may go undetected throughout pregnancy: as a consequence, acute adrenal failure may occur during labor and delivery, with serious clinical picture and neurological complications (16, 20, 21).

DIAGNOSIS

As already mentioned, during gestation serum cortisol and UFC physiologically increase: therefore, in pregnant patients suspected for Addison's disease cortisol concentration is frequently in the normal range, and baseline values of plasma or urinary cortisol are not usually reliable or sufficient for the diagnosis. However, the finding of "inappropriately" normal cortisol levels for the stage of gestation may be suggestive of Addison's disease. It is important to note that plasma cortisol may appear to be normal if time of sampling or increase in CBG concentration are not considered. For example, blood drawn after noon is likely to show a low level of cortisol even in normal subjects, so sampling at that time in patients with Addison's disease would not necessarily identify the problem unless plasma ACTH was also measured. Similarly, since early morning (*e.g.* 08:00 h) cortisolemia in healthy pregnant women is higher than in non-pregnant (CBG effect), a cortisol level that is within the reference range for normal (non-pregnant women) may not be recognized as low. Again, it is the combination of greatly raised plasma ACTH with normal or low plasma cortisol in the same sample that provides the most diagnostic information. The concomitant rise in ACTH concentration (usually between 400 and 2000 pg/ml) confirms the diagnosis of primary adrenal failure. In the absence of plasma corticotropin measurement, a short ACTH stimulation test (250 μg iv) will confirm the diagnosis by the absent or diminished cortisol response after stimulus. Other dynamic tests of HPA function (metyrapone, insulin hypoglycemia, CRH tests) are useless and even contraindicated. Since Addison's disease may occur as part of polyglandular autoimmune syndrome type 2 also in pregnancy (18, 22), thyroid function evaluation with anti-thyroid antibodies measurement is recommended. It is to be noted, however, that profound cortisol deficiency may impair the action of TSH. Thus

elevated TSH levels at the time of presentation of adrenal insufficiency do not necessarily indicate established primary hypothyroidism (23).
The aldosterone secretion rate is increased in normal pregnancy; in primary adrenal failure aldosterone levels are usually reduced and renin values elevated – so that the aldosterone renin ratio is reduced (24).
Other laboratory findings may show hyponatremia and hyperkalemia if adrenal function is severely impaired. In such cases, hypotension and diminished extracellular fluid volume result in reduced glomerular filtration rate with increased blood urea nitrogen. Fasting hypoglycemia may be observed, but this finding is not infrequent also during normal pregnancy. Lymphocytosis and eosinophilia are common.

THERAPY

Before the introduction of glucocorticoid replacement therapy, the maternal mortality rate in pregnant women with primary adrenal failure was exceedingly high. Nowadays, most women are adequately treated and followed, and they uneventfully go through pregnancy, labor and delivery (Table 1).
The usual glucocorticoid (cortisone acetate 25-37.5 mg/day or hydrocortisone 20-30 mg/day in 2 or 3 daily doses) and mineralocorticoid (fludrocortisone 0.05-0.1 mg/day) must be given to pregnant women. Only occasionally more glucocorticoid intake may be needed during the third trimester (25). In the first trimester, patients should be advised that, even if nauseated, their normal daily dosage of hydrocortisone must be administered. However, if severe nausea and vomiting occur, parenteral administration of glucocorticoids (e.g. 50 mg hydrocortisone im or 1 mg dexamethasone) may be needed along with iv saline if poor fluid intake or emesis persists.
As far as mineralocorticoid requirement is concerned, patients should be closely observed throughout pregnancy for changes in blood pressure, possible electrolyte abnormalities and volume depletion. PRA may be considered as a useful tool to evaluate the adequacy of fludrocortisone dosage: its values should not be suppressed below those of normal pregnant women, *i.e.*, 20 to 25 ng/ml/h supine or standing (10, 11). The dose of mineralocorticoids should be reduced if hypertension or hypokalemia occurs and completely discontinued if toxemia develops.
Labor and delivery should be considered as stressful events and need an increased amount of steroids similar to that required at the time of surgical procedures. For example, it would be prudent to administer 50 mg hydrocortisone parenterally around the time of the second stage of labor, and additional therapy if labor is prolonged. The usual daily maintenance doses of glucocorticoid and mineralocorticoid can be recommenced immediately after delivery in uncomplicated cases (15, 17, 19, 26, 27). Recently, Tschupp *et al.* (28) suggested that addisonian women should be hospitalized and an intensive care unit should be available during and after delivery.
In the event of a caesarean delivery, hydrocortisone dosage should be increased (e.g. up to 50 mg every 6 h or as a continuous infusion in saline to maintain hydration). In fact, a post-partum adrenal crisis is to be prevented by continuing steroids and hydration for at least 24 h. On the second day the dosage can be halved and tapered rapidly to oral maintenance dosage within 3 days. After caesarean section a variety of complications in women with unknown Addison's disease have been reported: a pre-term labor with severe hypotension and weakness occurred in one case (21) and acute adrenal failure with neurological features and hypoglycemia took place in another one (20). The treatment of an addisonian crisis needs the administration of large amounts of fluids and corticosteroids in order to normalize the clinical picture. Firstly, 100-200 mg hydrocortisone are injected as a bolus and then added to each liter of saline: a total amount of 400 mg and 3-4 l of saline should be given over a 6-h period. In addition, hy-

Table 1 – *Guidelines for management of pregnant women with Addison's disease.*

Pregnancy
- first trimester: cortisone acetate 25-37.5 mg/day (or hydrocortisone 20-30 mg/day) in 2 or 3 daily doses and fludrocortisone 0.05-0.1 mg/day, as usual. If severe nausea and vomiting, hydrocortisone 50 mg im or dexamethasone 1 mg im plus iv saline administration.
- third trimester: cortisone acetate 25-37.5 mg/day (or hydrocortisone 20-30 mg/day) in 2 or 3 daily doses and fludrocortisone 0.05-0.1 mg/day, as usual. Control blood pressure, electrolyte abnormalities and volume depletion for mineralocorticoid requirement
Labor
- hydrocortisone (50 mg iv) in the second stage of labor is suggested
Delivery
- if vaginal delivery: an extra dose of oral cortisone acetate (25-50 mg) is advisable
- if caesarean delivery: hydrocortisone up to 100 mg every 6 h, plus saline infusion for hydration. After delivery, continue steroids and hydration for at least 24 h. On the 2nd day the dosage can be halved and tapered to oral dose within 3 days
– if acute adrenal failure in women with unknown Addison's disease: 100-200 mg hydrocortisone as iv bolus and then add to each l of saline: give 400 mg and 3-4 l of saline over 6 h Correct hypoglycemia and hypokalemia by 5% glucose infusion and 20-40 mEq of KCl

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CONCLUSIONS

Although Addison's disease is considered a rare condition, recent epidemiological studies indicate an increasing incidence of the disorder. In past years the occurrence of pregnancy in women with primary adrenal insufficiency was considered dangerous, owing to the frequently reported maternal and fetal risks; indeed, a low rate of conception and a high abortion rate have been reported. At present, pregnancy, labor and delivery, if properly managed, can occur without risk for mothers and newborns. The major problem is the early recognition of a pregnant woman in whom Addison's disease recently appeared, because symptoms and signs are easily misleading and resemble the clinical picture of a normal pregnancy. On the basis of a correct diagnosis, the treatment is adequate in nearly all cases, and pregnancy, labor and delivery uneventfully occur. Therefore, we can now conclude that pregnancy and Addison's disease are not incompatible, provided that proper management is ensued.

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