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Primary adrenal insufficiency in pregnancy: A review article

Dr. Hussain MOGHARBEL

King Abdul Aziz University, Jeddah, Saudi Arabia
Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

Abstract

Background:

Primary adrenal insufficiency is a rare disease in the general population with an estimated incidence of approximately 144 cases per million.[1,3] Congenital adrenal hyperplasia (CAH) and autoimmune adrenalitis (AA) are the two most common causes for primary adrenal insufficiency in general.[1]

Primary adrenal insufficiency can be congenital or acquired.[2] Congenital types include congenital adrenal hyperplasia (CAH), familial glucocorticoid deficiency (FGD) and congenital adrenal hypoplasia.[2]Autoimmune adrenalitis and tuberculosis account for the majority of acquired primary adrenal insufficiency.[2] In AA, there is autoimmune mediated destruction of the adrenal cortex resulting in cortisol, mineralocorticoid and androgen deficiency.[1]Polyendocrine syndrome (APS) is when this autoimmune process extend to involve the pancreas causing type 1 diabetes and the thyroid gland causing autoimmune thyroid disease.[1]

Addison disease is the term used to describe acquired primary adrenal insufficiency[2] a disease that is more prevalent in women than men with a peak incidence in third and fourth decades of life[3]. This makes good understanding of this disease during pregnancy crucial. The estimated prevalence of adrenal insufficiency during pregnancy is 10 per 100 000.[3] This includes all cases of adrenal insufficiency, primary or secondary congenital or acquired.

As mentioned, Adrenal disorders in pregnancy are not common, the autoimmune nature of the disease leading to chronic anovulation and impaired infertility is one of the reasons [13]. timely diagnosis is imperative because these disorders can lead to significant maternal and fetal morbidity. Making the diagnosis poses a challenge to the clinician because the fetal-placental unit alters the maternal endocrine metabolism and hormonal feedback mechanisms. Pregnancy and its hypermetabolic state may alter the manifestation of disease, making the diagnosis difficult.

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Corresponding Author :
Dr. Hussain MOGHARBEL (MBBS, FRCSC)
Division of Maternal-Fetal Medicine
Obstetrics and Gynecology Department,
King Abdulaziz University, Jeddah, KSA
Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada
dr.hussain.mm@gmail.com

Fertility, rate of miscarriages:

Low fertility rates were observed in patients with classic CAH.[1] As diabetes and thyroid disease are known to impair fertility, patients with APS has significantly reduced fertility.[1] However, recent data showed that patients with isolated AA had normal fertility compared to the general population.[1] This effect is attributed to evolution in treatment of AA as well as hormonal replacement.[4] The rate of miscarriages is shown to be similar to the general population in isolated AA and higher in patients with CAH and APS.[1,4]

Fetal and maternal outcome:

Primary adrenal insufficiency was associated with higher rates of maternal and fetal complications.[1] These findings were based on observational studies from case reports.[3] In the past, maternal mortality associated with AI was as high as 35%. one-third of the fetuses died at term delivery. Diagnosis was proven at autopsy, therapeutic abortions. Nowadays, diagnosis of AI during pregnancy still difficult, especially in the first trimester because some of the symptoms are common in normal pregnancy. A family history of autoimmune disorder should be sought. When accompanied by more specific findings, such as hyperkalemia, hypoglycemia, or skin hyperpigmentation .[12]

Unrecognized AI is still the concern as this often associated with higher rates of maternal or fetal mortality either during pregnancy or in the puerperium [9.] More recent studies have attributed this correlation to poor compliance.[1] However, a large recent retrospective cohort study demonstrated higher risk of preterm delivery, small for gestation age infants, congenital anomalies and maternal mortalities in women with AA[3]. We believe that the result of this study doesn't apply for a patient with known isolated AA. In this study, there was no ICD-9 code for Addison disease in the database used and a diagnosis of corticoadrenal insufficiency was used as a proxy to Addison disease. We believe that this would cause a problem in applying these findings to patients with isolated AA. Firstly, a patient with known AA, is likely to be on appropriate hormonal replacement prior to pregnancy and is more likely to be followed in a tertiary care facility as opposed to another patient who were diagnosed during pregnancy where she was deficient in adrenal hormones for some time during her pregnancy. Secondly, corticoadrenal insufficiency is an umbrella term, under which can fit a group of endocrine diseases that are known to be associated with adverse pregnancy outcomes, for example APS.[1]

The possibility of this assumption is further supported by the fact that diabetes mellitus and thyroid disease were more common in the AA group in this study compared to the non-AA patients. Lastly, information regarding hormonal replacement were not available to the researchers and hence were not reported.

Majority of women with known AI and appropriately treated before conception have uneventful pregnancies without fetal compromise[12]. Another recent cohort study has demonstrated that birth weight and length of children born to women with AA didn't differ from the general population.[1] This is particularly true if the pregnancy occurred after the diagnosis of AA.[1] Most patients with known AA deliver at term, however there was an increase rate of caesarian section.[1]

First trimester Management:

Most cases of adrenal insufficiency in pregnancy are diagnosed before a woman becomes pregnant. AI can be dangerous during pregnancy if undiagnosed specially during the first trimester when symptoms of adrenal crisis can be similar to pregnancy-associated emesis [12]. The diagnosis may be difficult to make because many of the signs and symptoms seen in adrenal insufficiency are also seen in routine pregnancy. These include fatigue, dizziness, syncope, nausea and vomiting, weight loss, increased pigmentation and hyponatremia. Excessive dizziness, syncope, nausea, vomiting and weight loss should warrant further evaluation. Hyperpigmentation in Addison's disease can be differentiated from chloasma of pregnancy by the presence of hyperpigmentation on the non-exposed parts of the skin, creases of the hands, the extensor surfaces and mucous membranes. bluish-black spots on the lips, gums, and mucosal membranes of mouth, rectum, and vagina are more evident in adrenal insufficiency. Severe salt cravings and decrease in Na+ (Sodium) which is greater than the normal 5 mmol/L decrease in pregnancy should also warrant further evaluation. Hyponatremia with metabolic acidosis has been reported to cause poor fetal outcome. In contrast to the classic presentation of primary adrenal insufficiency, reported pregnant patients with the disorder did not present with hyperkalemia. Patients have presented in stress-induced adrenal crisis in the third trimester, triggered by illness or labor. Fetal adrenal production may be protective during pregnancy, hence an adrenal crisis may only present in the post-partum period. Careful attention must be given to the positive history of autoimmune disorders in the patient and her family members as this would make the diagnosis of Addison's disease more likely.

Morning cortisol less than 3 mg/dl or abnormal response to cosyntropin stimulation using pregnancy- specific thresholds are the main stay diagnostic tests in pregnancy. salivary cortisol levels in pregnancy has evolved, but its use for diagnostic purposes need further study to be established and used . [8]

Prednisolone is the preferred synthetic glucocorticoid as it has a very low placental transportability.[2] Fluorinated steroid on the other hand, can possibly cause intrauterine growth restriction as it crosses the placenta easily and should be avoided.[2]The dose for hydrocortisone in pregnant women is 12-15 mg/m$^{2.}$ During first trimester, inappropriate and insufficient dosing of glucocorticoid may increase the risk of miscarriages.[1]At the same time,

unnecessary high doses of glucocorticoids should be avoided during early pregnancy as its associated with increased risk of cleft lip and cleft plalate.[2]

Second, third trimester and Peripartum management:

Undiagnosed cases of AI in pregnancy are critical during the first trimester as mentioned and during the stress associated with labor and delivery[12.] *During normal pregnancy, 90%–95% of fetal cortisol derives from maternal adrenal secretions up to the 33ed week of gestation, when fetal adrenal cortisol production increases and maternal contribution decreases. Transplacental passage of cortisol from the fetus to the mother might have a partial protective effect. When maternal AI is undiagnosed, symptoms may apparat during the stress of labor, delivery, or immediate postpartum period*[12] *. Patients with primary AI are best managed by a multidisciplinary clinic that includes an endocrinologist and an obstetrician, the aim of treatment in pregnancy is to achieve a physiological glucocorticoid replacement dose to maintain good fetal and maternal outcome.*

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

[12] Adrenal insufficiency in pregnancy: challenging issues in diagnosis and management Kevin C. J. Yuen , Lindsay E. Chong, Christian A. Koch

Hydrocortisone is preferred choice at a replacement dose of 12–15 mg/m^2 of body surface area. 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. The thrice a day regimen is the preferred one as this regimen more closely mimics the normal diurnal variation than the twice a day regimen. Hydrocortisone doses are stable initially in most cases, and may need to be increased by 20–40% during the second half of pregnancy, specially in 3rd trimester, based on clinical evaluation [8]. To compensate for the physiologic increase in CBG levels in the last trimester, 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 is recommended.

Mineralocorticoids are required in primary AI and are continued during pregnancy. Mineralocorticoid dosages are usually stable through pregnancy; however, in some cases, dose may need to be increased during the second half of pregnancy, based on clinical evaluation (BP and electrolytes). Andreduced during the third trimester to avoid side effects. 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. Mineralocorticoids should be decreased if hypertension or hypokalemia occurs, and discontinued if Preeclampsia develops [14] .

During labor: Normal vaginal delivery is a reasonable expectation for women with AI. Indications for delivery by C-section are similar to those in a pregnant healthy individual [7] ·Stress-dose glucocorticoid treatment during delivery is required under specific circumstances. Recent studies indicate that higher doses may be needed for vaginal compared with cesarean delivery. Postpartum period adjust the dose according to clinical condition.In a minority of cases, stress doses of glucocorticoids may be necessary after delivery if the patient is in pain, recovering from surgery or having an intercurrent illness followed by preconception doses within 3-7 days. Physiological glucocorticoid replacement can continue during breast feeding, as less than 0.5% of the absorbed dose is excreted per liter of breast milk in women who received adequate glucocorticoid replacement during pregnancy, there is usually no indication to evaluate the HPA axis of their infants. Mothers who had received high doses of glucocorticoids during gestation may have infant affected by adrenal atrophy as glucocorticoids can cross the placenta and inhibit fetal glucocorticoid production.

Adrenal crisis occurring during pregnancy:

Cortisol and aldosterone replacement are the mainstay treatment of primary adrenal insufficiency either in pregnancy or not. In Addison disease, even with appropriate hormonal replacement, the ability to adapt an appropriate increase in cortisol secretion during stressful situation is lost.This can lead to a life threating state known as Addison crisis. Diagnosis of this condition at timely manner is extremely important by both patient and caregivers to avoid complications. Triggers like pregnancy, pneumonia, influenza, hyperemesis, pre-eclampsia, and during labor and delivery can lead to acute deterioration. 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 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 [12] .

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